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Orr E. Reynolds, Editor

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CONTRIBUTED ABSTRACTS AND INVITED SESSION INFORMATION FOR

THE 32nd ANNNUAL FALL MEETING OF THE AMERICAN PHYSIOLOGICAL SOCIETY

THE CINCINNATI CONVENTION AND EXPOSITION CENTER

CINCINNATI, OHIO

October 11-16, 1981

For Information on Fall Meeting registration, call the APS Fall Meeting Office (301) 530-7010. For information on the meeting program, call our Membership Services Department (301) 530-7171.

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Regulation of the Renal Circulation by Prostaglandin-dependent Mechanisms, John C. McGiff.

The Renin-angiotensin System and the Brain, Ian A. Reid.

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High Density Lipoproteins: Atherosclerosis from Cradle to Grave, Charles J. Glueck.

Workshop (2:00 - 6:00): Circulatory Regulation of Oxygen Delivery and Uptake in the Small Intestine, D. Neil Granger.

Special Session (4:30): Career Opportunities: Criteria for Employment of Physiologists in Academic Departments, Walter C. Randall.

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Symposium: Maximal Work Tolerance in Hyperbaric Environment, Suk Ki Hong.

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Symposium: Use of Radioisotopes for Quantitative Studies of Metabolism, Especially in the Lung, D. Eugene Rannels.

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Actions of the Renin Pressor System in Hypertension, Carlos M. Ferrario.

Developmental Renal Physiology, Leonard I. Kleinman.

Tubular Reabsorption of Low Molecular Weight Proteins, Ernest C. Foulkes.

SESSIONS OF CONTRIBUTED ABSTRACTS BY DAY

1

INDIRECT BLOOD PRESSURES OBTAINED SIMULTANEOUSLY WITH A PIEZOELECTRIC CRYSTAL AND AN IMPEDANCE PLETHYSMOGRAPH COMPARED TO CAROTID ARTERIAL PRESSURE IN THE AWAKE RAT. Carl F. Schaefer and Michael F. Wilson. U. Okla. Health Sci. Ctr. and VA Med. Ctr., Oklahoma City, OK 73190

Electrical impedance plethysmography (IP) was explored as an alternative to the commonly used piezoelectric crystal (PC) method of tail pulse sensing for indirect blood pressure measurement. Ten adult rats (2 Sprague Dawley, 4 Wistar Kyoto, and 4 Spontaneously Hypertensive rats) were tested using a 2 cm long cuff, a PC, and 4 aluminum strip electrodes for IP attached to their tails. Within individual rats the average difference between PC and IP indirect pressures recorded polygraphically was no more than 4 mm Hg. After implantation of a right carotid cannula using enflurane anesthesia, average pressures ± SEM for the 10 awake restrained rats were IP 127.3 ±14.3 mm Hg, PC 128.2±14.4, carotid systolic 153.8±15.4, diastolic 107.2±12.0, and mean arterial pressure (MAP) 125.8± 13.4. By paired t-test no significant differences were found among PC, IP, and MAP, while both indirect pressures were significantly ($p<.001$) different from carotid systolic and diastolic pressures. Thus, indirect blood pressure measurement by either PC or IP reflected MAP rather than systolic pressure. Although the indirect pressures were equally reliable by PC or IP, the latter were more easily determined since the return of the tail pulse was generally more distinct in the differentiated (dZ/dt) output of the IP than in the PC output. (Supported in part by VA Res. Serv. and Anesth. Res. Fund)

2

A CHANGE IN RESPONSIVENESS TO SODIUM ARACHIDONATE IN AORTAE FROM DEOXYCORTICOSTERONE ACETATE (DOCA) HYPERTENSIVE RATS. Warren E. Lockette, R. Clinton Webb, and David F. Bohr. Univ. of Michigan Medical School, Ann Arbor, MI 48109

Experiments were performed to characterize vascular reactivity to sodium arachidonate (SA) in DOCA hypertension. Thoracic aortae were excised from DOCA hypertensive and control normotensive rats. Isometric contractions were recorded from helically cut aortic strips mounted in a muscle bath. Addition of SA (1 µg/ml) produced contraction only in aortic strips from DOCA hypertensive rats [602±266 mg (approx. 50% of the maximum response to norepinephrine), n=4]. Contractile responses to SA were inhibited by treatment with the prostaglandin cyclooxygenase inhibitor, indomethacin (5 ug/ml). Aortic strips from DOCA rats also showed increased sensitivity to norepinephrine [DOCA ED_{50} = $2x10^{-10}$, control ED_{50} = $6x10^{-10}$ g/ml, n=5, $p < .05$]; serotonin [DOCA ED_{50} = $2x10^{-8}$, control ED_{50} $12x10^{-8}$ g/ml, n=5, $p < .05$], and potassium chloride [DOCA ED_{50} = 6.0 mM, control ED_{50} = 12.0 mM, n=4, $p < .05$]. These results demonstrate a differential increase in vascular responsiveness to SA in DOCA hypertension, and this finding is probably due to an alteration in the metabolism of SA in aortic strips of DOCA hypertensive rats. (Supported by NIH grants HL-18575 and HL-00813 and grants from the Michigan Heart Association and the Michigan Memorial Phoenix Project.)

3

RESTORATION OF PRESSOR HYPERRESPONSIVENESS BY SMALL DOSES OF ANGIOTENSIN IN RABBITS BLOCKED WITH SQ-14,225. D.G. Koivunen*, J.A. Johnson, W.K. Nichols*, D.W. Zeigler*, and C.G. Payne*. H. S Truman Mem. V.A. Hospital, and Depts. of Physiology and Surgery, Univ. of Missouri Sch. of Medicine, Columbia, MO 65201

Previous studies have shown that SQ-14,225, an angiotensin converting enzyme inhibitor, blocks pressor hyperresponsiveness to norepinephrine (NE) in rabbits with renal artery stenosis (RAS), suggesting that angiotensin II (A-II) has an important role in this mechanism. This study examined the effect of A-II in subpressor doses in restoring pressor hyperresponsiveness in RAS rabbits during SQ-14,225. Six 1-kidney rabbits with RAS of 3 days' duration and six 1-kidney control rabbits were infused with NE (400 ng/kg min) before and during infusion of SQ-14225. During the latter NE infusions, A-II was infused at 0.5, 1, and 2 ng/kg min. The RAS rabbits had greater increases in mean arterial pressure (MAP) to NE prior to SQ-14,225 when compared to the controls; this difference was abolished by SQ-14,225. Addition of 0.5, 1, and 2 ng/kg min of A-II during SQ-14,225 caused a restoration of the initial hyperresponse to NE by 75, 83, and 96% respectively. In the control animals the changes in MAP in response to NE before SQ-14225 did not differ from those seen in response to NE after blockade, both with and without the addition of A-II. These results show that the hyperresponse to NE in RAS rabbits can be restored after SQ-14225 by infusing very small doses of A-II, suggesting an increased number or affinity of A-II "hyperresponsiveness" receptors in these RAS rabbits. (Supported by the Medical Res. Service of the V.A.)

4

DIFFERENTIATION OF THE ANGIOTENSIN PRESSOR AND HYPERRESPONSIVE RECEPTORS BY ANGIOTENSIN II ANALOGS IN RABBITS. D.W. Zeigler*, J.A. Johnson, W.L. Fowler, Jr.*, D.G. Koivunen*, and C.G. Payne*. H. S Truman Mem. V.A. Hospital and Depts. of Physiology and Surgery, University of Missouri, Columbia, MO 65201.

Previous studies have shown that rabbits with renal artery stenosis (RAS) of 3 days duration have pressor hyperresponsiveness to norepinephrine (NE), which can be blocked by the angiotensin II (A-II) analog, [Sar^1, Ile^8] A-II, indicating that A-II is involved in the hyperresponsiveness. The present study examined the effect of another A-II analog, [Sar^1, Ala^8] A-II, on pressor hyperresponsiveness in this model. Rabbits were divided into 3 groups. Group 1 was the control 1-kidney rabbits (n=4). Group 2 was the 1-kidney RAS rabbits receiving [Sar^1, Ile^8] A-II (n=4). Group 3 was the 1-kidney RAS rabbits receiving [Sar^1, Ala^8] A-II. A pressor dose of 300 ng A-II was given before and during the infusion of the A-II analogs to confirm the blockade of the pressor action of A-II. The pressor response to NE (400 ng/kg min) was determined before and after 15 min of analog infusion. Pressor responses (mm Hg) to NE were:

	Before analog	During analog
Group 1	9.5 ±3.7	8.0 ±3.1
Group 2	16.7 ±4.3	7.6 ±2.0**
Group 3	17.2 ±2.6	16.0 ±3.7

Both A-II analogs blocked the pressor action of A-II, but their ability to block the pressor hyperresponse to NE was significantly different. These data provided evidence that the A-II hyperresponsive receptors and pressor receptors are different.

5

PRESSOR RESPONSES TO NOREPINEPHRINE IN RABBITS TREATED WITH DEOXYCORTICOSTERONE. J.A. Johnson, P. McMurray*, D.W. Zeigler*, S. Siripaisarnpipat*, D.G. Koivunen*, W.L. Fowler, Jr.*, and C.G. Payne*. H. S Truman Mem. V.A. Hospital, and Depts. of Physiology and Surgery, Univ. of Missouri, Columbia, MO 65201.

Previous studies from this laboratory have shown that prehypertensive rabbits with renal artery stenosis have pressor and vascular hyperresponsiveness to vasoconstrictor agents. The present study examined the possibility that rabbits treated with deoxycorticosterone (DOC) would have pressor hyperresponsiveness. Six rabbits received a subcutaneous implant of a 250 mg pellet of DOC and were given saline to drink. Six control rabbits were sham operated and received water to drink. Two weeks later, the pressor responses to 5 min. infusions of norepinephrine (NE) at doses of 25, 50, 100, 200, 400, 800, and 1200 ng/kg min. were determined in conscious rabbits. The changes in mean arterial pressure ±SEM (in mm Hg) were:

	NE dose (ng/kg per min.)						
	25	50	100	200	400	800	1200
DOC-salt rabbits	+2.3 ±0.4	+4.3 ±0.8	+8.3* ±0.6	+12* ±0.8	+16* ±0.7	+23* ±1.1	+32* ±3.0
Control rabbits	+0.8 ±0.3	+3.0 ±0.5	+4.3 ±0.5	+6.8 ±1.4	+11 ±1.6	+14 ±1.3	+19 ±1.8

These results indicate that 2-week DOC-salt treated rabbits have pressor hyperresponsiveness to NE. (Supported by the Medical Research Service of the Veterans Administration.)

6

RESETTING OF THE BAROREFLEX DURING INTRACAROTID INFUSION OF PGE_2 AND ANGIOTENSIN II. S.S. Hull, Jr.* and J.E. Chimoskey. Michigan State University, East Lansing, MI 48824.

Comparison has been made of baroreflex resetting induced by intracarotid (IC) infusion of prostaglandin E_2 (PGE_2) and angiotensin II (AII). Most of these studies have been performed in conscious male Jersey calves, but reflex resetting by PGE_2 has also been observed in conscious dogs and sheep. Electromagnetic flow detectors have been implanted in the calves on the main pulmonary artery (n=5), renal artery (RA) (n=3), superior mesenteric artery (SMA) (n=2) and iliac artery (IA) (n=2). Catheters have been implanted IC in 4 dogs, 4 sheep and 5 calves and in the right atrium (RA) and distal aortic arch (Ao) of the calves. IC PGE_2, 10 ng/kg/min, increases systemic arterial pressure (Pa) in dogs (17%), sheep (31%) and calves (32%), r.e. control (C), $p<.01$ in each species, without reflex decrease in heart rate (HR). In calves IC PGE_2 increases total peripheral resistance 29%, $p<.01$; HR, 9%; $p<.05$; Cardiac Output, 4%, $p<.01$; and resistance in RA, 37%, $p<.01$; SMA, 12%, n.s.; and IA, 39%, n.s., beds. In calves the Pa and HR responses to IC PGE_2 were compared to IC AII, 10 ng/kg/min; intravenous (IV) phenylephrine (PH), 1 µgm/kg/min; IC AII + IV PH; IC PGE_2 + IV PH by 2 way ANOVA. Pa was distributed in the order C < PGE_2 = PH, +26% < AII, +36% < PGE_2 + PH, +46% < AII + PH, +56%; HR was distributed in the order PH = AII + PH, -9% < C = AII = PGE_2 + PH < PGE_2, +9%, $p<.01$ where different. PGE_2 and AII reset the reflex but HR increases with PGE_2 and does not with AII.

7

CAPTOPRIL AND MK 421 CAUSE A FALL IN BLOOD PRESSURE IN NORMOTENSIVE AND HYPERTENSIVE RATS. M. Ian Phillips and Laurie J. Hoffman, Dept. of Physiology, College of Medicine, University of Florida, Gainesville, FL 32610

Captopril and MK 421 are both angiotensin II converting enzyme inhibitors (ACEI). The physiological role of peripheral and central angiotensin II (AII) in blood pressure and water balance can be further studied by these inhibitors. Normotensive and SH rats were prepared with implanted intracerebroventricular cannula and femoral artery and vein catheters 3-7 days after surgery subjects were tested with a dose range of the ACEI at different times after angiotensin I (AI) injections both centrally and peripherally. Results of 35 mg/kg captopril iv, 35 mg/kg MK 421 iv or 2.5 mg/kg MK diacid one hour after AI is given in Table I.

	Control	AI	Capt	MK 421	AI+Cap	AI+MK
	112.5±2.5	167.5±9.5	93.9±2.1	91.7±3.5	110±4.9	105-3.5
n=	19	19	19	6	6	6

Both ACEIs at doses which inhibited AI, lowered normal blood pressure by 12-16% hr. In SHR the pull in BP was 23% to a much lower dose of 2.5 mg/kg MK 421). Using ACEI the results indicates that normal blood pressure is maintained by AII and in hypertension of SHR. There was spontaneous drinking to both ACEIs which implies that they have an effect of AII central receptors. In conclusions 1. MK 421 is more potent than captopril 2. Both lower normal blood pressure 3. Both induce drinking 4. Both lower BP in SHR.

8

THE EFFECTS OF DIETARY SODIUM AND POTASSIUM ON THE BLOOD PRESSURE IN TWO KIDNEY COLDBLATT HYPERTENSIVE RATS. J.L. Treasure and D.W. Ploth. University of Alabama in Birmingham, AL. 35294

The dietary Na:K ratio has been found to influence blood pressure (BP) in various forms of hypertension. Studies were performed in male Sprague-Dawley rats. After clipping, the rats started on a diet containing Na:K in the following ratios: (1) 1:1 (normal), (2) 1:5, and (3) 5:1. Tail BP was measured 3 X per week. By 9 days post clipping the rats in group (grp) (1) show a rising trend in BP which was not seen in grps (2) and (3). Acute studies have been performed in animals in grps (1) and (2). The plasma K was significantly higher in animals in grp (2) 4.72 ± 0.16 mM compared to grp (1) 3.73 ± 0.13. Captopril was infused into both grps and renal function was studied in both the clipped and the contralateral (C) kidney. The BP fell by 17 ± 0.4 mmHg in grp (2) and by 11 ± 7 mmHg in grp (1). The rats in grp (2) did not show any rise in GFR after Captopril (998 ± 86 to 963 ± 96 ml/min) nor any increase in urine volume (V) (4.06 ± 0.65 to 4.46 ± 0.73 µl/min) or sodium excretion $U_{Na}V$ (21.37 ± 3.68 to 24.4 ± 8.0 µM/min) in the C-kidney. This is in contrast to grp (1) where the C-kidney had an increase in GFR (from 1062 ± 107 to 1387 ± 93 ml/min) and V also increased (2.35 ± 0.3 to 4.55 ± 1.05 ml/min) along with $U_{Na}V$ (19.12 ± 6.74 to 62.7 ± 16 µM/min). The effects of Captopril on the clipped kidney were comparable to our earlier studies ie there was a decrease in renal function secondary to the fall in BP. It can be concluded that a low Na:K ratio alters the response to converting enzyme inhibition.

9

EFFECTS OF HIGH-POTASSIUM INTAKE ON EXPERIMENTAL ANGIOTENSIN II HYPERTENSION. David B. Young and Udom Tipyamontri*. Univ. of Miss. Med. Ctr., Jackson, MS 39216

A high-potassium (K) intake results in an increase in sodium (Na) excretion, and in some circumstances has been shown to reduce arterial pressure in experimental animals and man. To analyze the antihypertensive and natriuretic effect of K, a high K intake was given to several experimental models of hypertension, the first of which was angiotensin II hypertension in the dog. Hypertension was produced by continuous infusion of 10 ng/Kg/min angiotensin II in a group of 8 mongrel dogs weighing an average of 21.5 Kg. Dietary sodium intake was 200 mEq/day, K intake was 30 mEq/day. The angiotensin hypertension was characterized by a 26 percent increase in arterial pressure and complete suppression of endogenous renin activity. Increasing K intake by 200 mEq/day resulted in a natriuresis that persisted for two days, the maximum daily rate of Na excretion exceeding the control rate by 48 percent. The cumulative negative Na balance was approximately 100 mEq. The high level of K intake resulted in 0.8 to 1.0 mEq/l increase in plasma K concentration. No measurable change in arterial pressure was observed during the two week period of high K intake, nor following its termination. In this model of hypertension, K intake does not affect the level of arterial pressure although it does strongly affect renal Na excretion.
(Supported by HL 21435, 11678, and 00373)

10

INCREASED RENAL Na^+-K^+-ATPase ACTIVITY IN WEANLING SPONTANEOUSLY HYPERTENSIVE RATS. Carmen Rodríguez-Sargent*, José L. Cangiano, Susan Opava-Stitzer and Manuel Martínez-Maldonado. Research and Medical Service, Veterans Administration Center, San Juan, Puerto Rico 00936.

Plasma renin activity (PRA), plasma aldosterone concentration (PA) and renal Na^+-K^+-ATPase activity (ATPase) were measured in 8 weanling spontaneously hypertensive rats (SHR) and 8 weanling Wistar-Kyoto rats (WKY). Both groups were housed in metabolism cages throughout the experiment. PRA and PA were higher in SHR than in WKY. ATPase, which paralleled PA in both groups, was also elevated in SHR.

	PRA (ng AI/ml/hr)	PA (ng%)	Mg^{+2}ATPase (uMPO$_4$/mg Pr/hr)	Na^+-K^+-ATPase (uMPO$_4$/mg Pr/hr)
SHR	15.2	36.7	135	137
WKY	9.6	22.2	201	99

Interestingly, PRA, PA and ATPase in weanling SHR were greater than we have previously reported in adult normotensive and spontaneously hypertensive rats. We conclude that ATPase is elevated in weanling SHR and that this elevation may be due to increased mineralocorticoid levels secondary to high plasma renin activity. Although hypertension in SHR has been generally believed to be non-renal in origin, our finding of increased renal Na^+-K^+-ATPase activity in these rats prior elevation of blood pressure suggests that the kidney may play a role in the initiation of hypertension in SHR.

11

VASCULAR SMOOTH MUSCLE MEMBRANE POTENTIALS AND THE INFLUENCE OF A OUABAIN-LIKE HUMORAL FACTOR IN RATS WITH ONE-KIDNEY, ONE CLIP HYPERTENSION. M.B. Pamnani, D.R. Harder, S.J. Huot, H.J. Bryant, F.A. Kutyna*, and F.J. Haddy. Dept. Physiol., USUHS, Bethesda, MD and Univ. of Vermont, Burlington, VT.

We have reported presence of a ouabain-like humoral factor and suppressed vascular Na^+-K^+ pump activity in animals with several forms of low renin experimental hypertension. In the present study, to better understand the mechanism of action of the humoral factor, we recorded intracellular membrane potentials in mV from excised tail arteries of rats with one-kidney, one clip hypertension (1KHT) and their paired one-kidney normotensive (1KNT) controls. We also examined the effect of plasma supernates (SUP) prepared from these animals on the membrane potentials. The findings are summarized below.

		EFFECT OF			
TAIL ARTERY FROM	CONTROL	1KNT SUP	1KHT SUP	OUABAIN	OUABAIN + 1KHT SUP
1KNT Rat	-52±.14	-47±2.4	-40±1.3†	-41±1.7†	-40±1.3†
1KHT Rat	-45±1.4*	-44±1.3	-45±2.3*	-44±1.8	-46±1.7*

* P<0.05 HT vs NT, † P<0.01 compared to control

These findings indicate that plasma from 1KHT animals contains a heat stable factor which like ouabain, significantly depolarizes arteries from 1KNT but not from 1KHT rats. Thus, the humoral Na^+-K^+ pump inhibitor we have found in 1KHT rats may function through voltage dependent vasoconstriction in the genesis and maintenance of hypertension.

12

RENAL VASCULAR POTASSIUM RELAXATION IN TWO-KIDNEY, ONE CLIP HYPERTENSIVE RATS. David M. Cohen and David F. Bohr. Univ. Mich. Medical School, Ann Arbor, MI 48109.

Evidence has been presented indicating that "low renin" forms of hypertension may be associated with a circulating factor which suppresses vascular sodium-potassium pump activity (Haddy, F. J., Pamnani, M. B., Clough, D. L. Cardiovascular Reviews and Reports 1: 376, 1980). To determine if pump activity is altered in a "high renin" hypertensive model, potassium relaxation (a functional index of electrogenic pump activity) was examined in 2-kidney, 1 clip hypertensive (2K,1C) and normotensive (NC) rats. The untouched kidney was isolated and perfused with a potassium-free physiological salt solution under constant flow conditions. Renal vascular resistance was increased by the addition of norepinephrine to the perfusate. Potassium, when added to the potassium-free perfusate, produced concentration-dependent decreases in renal vascular resistance (increases in electrogenic pump activity). Relaxation was greater ($p<0.05$) in the renal vasculature of 2K,1C than in that of NC rats.

	PERCENT DECREASE IN RESISTANCE CAUSED BY POTASSIUM							
	0.25mM		0.50 mM		1.0 mM		10.0 mM	
NC	1.0	0.6	5.8	1.9	9.5	2.7	47.0	2.4
2K,1C	6.0	0.8	14.3	2.0	21.5	3.0	51.0	2.4

Ouabain (10^{-8}-10^{-3}) inhibited potassium relaxation to the same degree in both groups. These results provide no support for the hypothesis that decreased electrogenic pump activity is a feature of 2K,1C hypertension. Supported by NIH grant #HL18575.

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EFFECTS OF ASSYMETRIC WAVEFORMS ON CO_2 ELIMINATION DURING HIGH FREQUENCY VENTILATION. WH Paloski*, PS Barie*, RJ Mullins*, and JC Newell. Center for Biomed. Eng., Rensselaer Poly. Inst. Troy, NY 12181 and Albany Medical College, Albany, NY 12208.

To determine whether convective mixing is greater during inspiration than expiration, we studied the effect of varying inspiratory to expiratory time ratio (I:E) on the efficiency of a high frequency jet ventilator (HFV). Carbon dioxide elimination ($\dot{V}CO_2$) was measured in four mongrel dogs 5-15 sec after onset of HFV at frequencies of 4 and 7 Hz and at I:E = 1:1 and 1:2.7 or 1:1.3. Tidal volume to anatomic deadspace ratio (V_T/V_D) was varied from 0.2 to 0.9. Mixed expired PCO_2 was measured with a capnograph having verified linearity of 0.1% from 0.1 to 5.0 Torr. Airway pressure was measured at the carina, and tidal volume, including that entrained by the jet, was determined by electronically integrating the flow waveform from a pneumotachograph having a flat frequency response from 0 to 40 Hz. Root mean square flow ($\dot{V}$rms) was calculated from the flow waveform. At 4 Hz, the change in $\dot{V}CO_2$ per unit change in $\dot{V}$rms($\Delta\dot{V}CO_2/\Delta\dot{V}$rms) was 4.5 times greater at I:E = 1:2.7 than at I:E = 1:1 ($p<.05$). At 7 Hz, $\Delta\dot{V}CO_2/\Delta\dot{V}$rms was 2.0 times greater at I:E = 1:1.3 than at I:E = 1:1 ($p<.05$). Mean airway pressure varied from 0.5 to 10.0 cm H_2O and was directly related to $\dot{V}$rms ($r = 0.95$) but not to I:E. These data support the hypothesis that during HFV, convective mixing is greater during inspiration than during expiration. (Supported by grants HL18630 and GM15426, USPHS.)

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PERIPHERAL ORGAN BLOOD FLOW CHANGES WITH HIGH FREQUENCY OSCILLATION. Frank R. Gioia*, Andrew P. Harris*, Stephen D. Parker*, Richard J. Traystman and Mark C. Rogers. Johns Hopkins Medical Institutions, Baltimore, Md 21205

We used the radiolabelled microsphere technique to determine whether changes occur in the peripheral distribution of cardiac output with high frequency oscillatory ventilation (HFO) relative to conventional positive pressure ventilation (CV). Blood flow to multiple peripheral organs were compared during HFO and CV. Seven supine anesthetized, paralyzed dogs were ventilated at the same mean airway pressure using CV and HFO ($f = 10$ Hz., $V_t = 2.5$ ml/kg) in random order. FIO_2 was adjusted to maintain $PaO_2 > 75$ torr. Arterial and mixed venous blood gases, heart rate, systemic and pulmonary arterial pressures, cardiac output, and intracranial pressure were unchanged with HFO. Blood flow (ml/min/100g. tissue) to brain, myocardium, kidney cortex and kidney medulla during CV were 36 ± 2.7 (mean $\pm$ S.E.), 99 ± 13, 536 ± 66, and 18 ± 8.6, respectively. The corresponding flows during HFO were 34 ± 2.8, 108 ± 15, 511 ± 47, and 14 ± 4.8. These differences were not significant. In addition, blood flow to skin, skeletal muscle, liver, adrenals, pancreas, and jejunum showed no difference between HFO and CV. Likewise, regional cerebral blood flow to cortex, diencephalon, cerebellum, brain stem, spinal cord, grey matter and white matter were not different between HFO and CV. We conclude that, under conditions of similar overall hemodynamics and respiration, HFO does not independently produce regional circulatory changes compared to CV.

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OXYGENATION ON HIGH FREQUENCY OSCILLATION. C. Cattran*, M. Kolton*, A.B.Froese, & A.C. Bryan, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada.

We have previously reported that at the same mean airway pressure (MAP) the oxygenation is the same on high frequency oscillation (HFO) as on continuous positive pressure ventilation (CPPV)(Physiologist 23;177,1980). However, for any MAP the volume depends on the volume history, lying between the inflation and deflation limbs of the PV curve. If the MAP during HFO and CPPV are matched at values below opening pressure the gases are the same. However, just above this pressure there is a progressive increase in lung volume during HFO. This recruitment can be accelerated by brief inflation to 30 cmH_2O and is maintained on return to the initial MAP. In four rabbits with oleic acid pulmonary edema, lung volumes and blood gases ($FIO_2 = 1$) were compared at matched MAP between 10-20 cmH_2O.

	Volume above FRC(ml)	PaO_2(torr)	$PaCO_2$(torr)
CPPV	32 ± 15	92 ± 58	36 ± 13
HFO	48 ± 18	244 ± 131	32 ± 12
	p <0.005	p <0.001	NS

Equivalent lung volumes and gases can also be achieved using CPPV if PEEP is above opening pressure, but this entails very high peak pressures and hence a MAP substantially higher than on HFO. We conclude that HFO at moderate MAP causes progressive recruitment of lung volume and a marked reduction in shunt. (MRC # MA6342)

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PULMONARY WASHOUT OF HE AND SF_6 DURING HFO IN DOGS. T. J. Knopp, T. Kaethner*, J. Kohl*, M. Meyer* and P. Scheid. Department of Physiology, Max-Planck-Institut fuer exp. Medizin, D-34 Göttingen, FRG

This study,addresses the question as to whether molecular diffusion of gases contributes significantly to intrapulmonary gas transport during HFO. Four anesthetized-paralyzed supine dogs were ventilated through a cuffed endotracheal (ET) tube with a piston pump (stroke volume 1.5-2.5 ml/kg; frequency 20-30 Hz) with a fresh gas flow (room air) of 10 l/min. Adding He and SF_6 in low concentrations (1%) to the fresh gas flow resulted in lung gas equilibration with the test gases. For washout the flow of He and SF_6 was suddenly stopped and the changing test gas concentrations were continuously measured by respiratory mass spectrometry at the mouth and distal ends of the ET and outflow tubes. No differences were observed in the washout pattern between He and SF_6. The washout curves could adequately be described by two exponential components. The amplitude coefficient of the slow component increased progressively as the mass spectrometer sampling site was moved from the outflow tube to the mouth and to the distal end of the ET tube. The results suggest that molecular diffusion is not rate-limiting for intrapulmonary gas transport during HFO and that a series rather than a parallel two-compartment model is appropriate for analysis of test gas washout during HFO. (Supported in part by NIH grant HL-21584.)

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PULMONARY GAS EXCHANGE IN BIRDS DURING HIGH FREQUENCY VENTILATION. F.L. Powell and J.R. Torre-Bueno, Dept. of Med., Univ. of Calif., San Diego, La Jolla, CA 92093 and Duke Univ. Med. Center, Durham, NC 27710.

We investigated gas exchange in three domestic geese (3.6-6.4 kg) during mechanical ventilation with a Harvard respirator with normal fR and VT (MV) and during high frequency ventilation by various means (HFV). Exact VT during HFV is unknown but $\dot{M}CO_2$ and $\dot{M}O_2$ were not maintained when the HFV pump stroke volume (VS) was less than VD calculated from: $VD/VT = (FE'-F\bar{E})CO_2/FE'CO_2$ during MV. With VS > VD, $\dot{M}CO_2$ and $\dot{M}O_2$ remained at MV levels with fR from 5 to 40 sec -1. We found no evidence of molecular weight dependent differences in inert gas exchange suggesting that airway diffusion was not limiting. Excretions and retentions of 6 inert gases infused in a peripheral vein were analyzed for $\dot{V}/\dot{Q}$ distributions with a cross-current model. 2 to 10% of effective $\dot{V}$ (i.e. $\dot{V}$ in units with $\dot{V}/\dot{Q} < 1000$) was in units with $10 \leq \dot{V}/\dot{Q} < 1000$ with MV; this increased to 50 to 70% with HFV. This apparent increase in $\dot{V}$ of high $\dot{V}/\dot{Q}$ units suggests enhanced elimination of soluble gases with HFV as described for alveolar lungs. Most of $\dot{Q}$ was in units with $0.1 \leq \dot{V}/\dot{Q} \leq 1.0$ during MV and HFV. Error in fitting inert gas data with cross-current analysis was less than with alveolar analysis but more experiments are necessary to determine statistical significance.

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VENTILATION-PERFUSION ($\dot{V}/\dot{Q}$) RELATIONSHIP AND ARTERIAL OXYGENATION DURING HIGH FREQUENCY OSCILLATION (HFO). Vito Brusasco*, T. J. Knopp and Kai Rehder. Mayo Clinic and Foundation, Rochester, MN 55905

We examined the $\dot{V}/\dot{Q}$ relationship and the arterial oxygen tension (PaO_2) during conventional mechanical ventilation (CMV) and HFO. Five supine, anesthetized-paralyzed dogs (18-25 kg) were studied; their lungs were ventilated both during CMV and HFO with room air and eucapnia ($PaCO_2 = 40.0 \pm 0.4$ SE mm Hg) was maintained. ^{133}Xe dissolved in saline was infused intravenously at a constant rate and after a steady state (3.5 min) had been achieved, ^{133}Xe concentrations (C_Xe) in a nondependent (ND) and dependent (D) lung region (same vertical axis) were determined. The ratio of the $\dot{V}/\dot{Q}$ ratios in ND and D lung regions was inferred from the ratio of $C_Xe(ND)/C_Xe(D)$; this ratio must be unity when $\dot{V}/\dot{Q}$ along the vertical axis is uniform. We found that 1) $C_Xe(ND)/C_Xe(D)$ during CMV (0.81± 0.04 SE) was significantly smaller ($P=0.02$) than during HFO at 5 to 7 Hz (0.96±0.05), but not different from HFO at 15 Hz (0.84±0.05) or 30 Hz (0.74±0.07), and 2) PaO_2 during CMV (85± 3 mm Hg) was significantly ($P<0.05$) less than during HFO at 5 to 7 Hz (90±4), but not different from HFO at 15 Hz (85±3) or 30 Hz (83±3). We conclude that $\dot{V}/\dot{Q}$ matching along the vertical axis and arterial oxygenation during HFO at low (5 to 7 Hz) but not at high frequencies (15 to 30 Hz) are better than during CMV. (Supported in part by NIH grant HL 21584 and the Parker B. Francis Foundation.)

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A METHOD TO STUDY THE REGIONAL FREQUENCY RESPONSE OF LUNG (RFL) DURING HIGH FREQUENCY OSCILLATION (HFO). Jinhe Wei*, Eric A. Hoffman, and Earl H. Wood. Mayo Med. Sch., Rochester, MN 55905

RFL was measured from movements of percutaneously implanted 1 mm O.D. lead markers using a computer-based biplane video x-ray tracking system and a frequency (F) analysis algorithm. Lungs of three anesthetized, supine dogs were oscillated via an endotracheal tube with Fs from 7 to 37 Hz using a piston pump. Pump stroke volumes (PSV) were 20, 40, 50, and 70 ml. Due to the low video sampling (30/sec) relative to HFO, a reconstruction method was developed to recover the wave form of marker movements (M) assuming that the fundamental F of M follows pump F. Amplitude (A) and phase (P) of M were calculated by a modified FFT program. The heart was paced at 180 bpm to eliminate effects of cardiogenic motion. Sinusoidal wave forms of M and volume change of marker tetrahedra were obtained from all Fs used. The three components of A for the fundamental F were significantly larger than the tracking noise and second harmonics (A_x = .070 ± .041, .062 ± .039, and .075 ± .033; A_y = .034 ± .024, .048 ± .031, and .073 ± .030; A_z = .026 ± .025, .038 ± .018, and .026 ± .013 cm at PSV = 50 ml and F = 11, 19, and 29 Hz, respectively; noise level <.01 ± .01). Total A is proportional to PSV (r>.95, p<.05). The pattern for the distribution of A_x, A_y, A_z and P_x, P_y, P_z for individual markers was the same for each cycle (r>.8, p<.01) at a given F. This method appears to be a highly sensitive means for studying RFL in intact dogs. (Supported in part by NIH Grants HL-04664, 21584B, and RR-00007).

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REGIONAL FREQUENCY RESPONSE OF LUNG (RFL) DURING HIGH FREQUENCY OSCILLATION (HFO). Eric A. Hoffman, Jinhe Wei,* Thomas J. Knopp, and Earl H. Wood. Mayo Med. Sch., Rochester, MN 55905

RFL was studied in three supine dogs by tracking the movement (M) of right lung parenchymal markers during HFO (Wei et al., Physiologist this issue). Measurements were referenced to x, y, z body axes (ventral-dorsal, lateral-medial, and cephalad-caudad). Mean total amplitude ($A_t = \sqrt{A_x^2+A_y^2+A_z^2}$) of M's were proportional to pump stroke volume and at all F's M is smaller in upper than middle and lower lobes (UL, ML, LL). Relative amplitudes (A) of the A_x, A_y, A_z components of M varied with pump F. At low F (7 Hz) A_z and A_x were dominant over A_y. A_x and A_y increased with F while A_z diminished reflecting the lower natural F of the diaphragmatic-abdominal system (-3 dB cutoff F around 11-15 Hz) relative to the rib cage. The dominant components of M were: A_x in ML, A_y in UL, and A_z in LL (especially at 17-23 Hz). A and phase (P) shifts correlated with marker position along a given axis and varied with F. A_y increased medial to lateral while A_z increased apex to base at low F (7 Hz) and base to apex at higher F. P_x was uncorrelated to x axis position at 7 Hz whereas a P_x shift at 17-37 Hz was strongly correlated in the ventral-dorsal direction. P_z increased apex to base at 7 Hz while at 29 Hz this reversed and in the LL this slope (degree/cm) increased implying a change in expansion pattern. (Supported in part by NIH Grants HL-04664, 21584B, and RR-00007)

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MODIFICATION OF PEEP INDUCED HEMODYNAMIC CHANGES BY PROSTAGLANDIN SYNTHETASE INHIBITORS. L. Casey*, J. Fletcher, and P. Ramwell. NMRI, Bethesda, Md 20014; Georgetown University, Washington, D.C. 20007.

Since mechanical hyperinflation causes pulmonary prostaglandin production, we evaluated the ability of selective prostaglandin synthetase inhibitors to modify the hemodynamic changes associated with PEEP. METHODS: The cardiovascular effects of 15 cmH20 PEEP were assessed in 26 baboons (Papio anubis), that were randomly divided into 4 groups: I (n=7) control; II (n=7) pretreated with 10 mg/kg indomethacin; III (n=6) pretreated with 5 mg/kg OKY 1581 (sodium-(E)-3-[4-(3 pyridylmethyl) phenyl]-2-methylacrylate)) a selective thromboxane synthetase inhibitor; and IV (n=6) pretreated with trans-2-phenylcyclopropylamine sulfate (tranylcypromine) (1 mg/kg), a prostacyclin synthetase inhibitor. RESULTS: In comparison to the control group, the thromboxane synthetase inhibitor caused exacerbation of the hemodynamic changes after PEEP with a greater decrease in MAP (p<.05) and cardiac output (p<.05), whereas tranylcypromine blocked the decrease in MAP (p<.025) and attenuated the decrease in cardiac output (p<.025). CONCLUSION: Some of the hemodynamic changes associated with PEEP can be attributed to increased prostacyclin production.

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UNEVEN VENTILATION IN RAT MODELS OF CYSTIC FIBROSIS, R.L. Boyd*, E.M. Francis*, M.T. Fletcher*, and J.A. Mangos. (SPON: M.J. Fisher). University of Florida, Depts. of Pediatrics and Physiology, Gainesville, FL 32610.

Rats exhibiting structural and/or functional changes of airway (Sturgess and Reid, Br J Exp Pathol 54:388-403, 1973) and salivary (Martinez et al., Pediatr Res, 9:463-475, 1975) glands during treatment with isoproterenol (ISO) or reserpine (RES), respectively, have been used as models for the study of cystic fibrosis (CF). We studied the pulmonary function of these models. Rats were injected subcutaneously with ISO (25 mg/kg·day) or with RES (0.5 mg/kg·day) for six days. Plethysmographic measurements were made for airway resistance (Raw) functional residual capacity (FRC), phase difference (PD) between air flow rate and mean alveolar pressure, tidal volume (V_T), and frequency (f). In the ISO and RES studies the FRC and f were not different from controls while the PD was greater and V_T was less ($p < 0.05$) than controls, as was the Raw of the RES rats. The results of both studies indicate uneven ventilation (increased PD) and penduluft (decreased V_T), consistent with maldistribution of resistances and/or compliances of the peripheral airways and alveolar compartments. Since peripheral airways involvement is usually the earliest pulmonary lesion found in CF, these studies present additional physiological evidence that the ISO and RES models may be representative of the early pulmonary involvement of CF. (Supported by CF Foundation Grant #I321B).

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PLEURAL LIQUID PRESSURES MEASURED BY MICROPIPETS IN SUPINE RABBITS. S.J. Lai-Fook, P.A. Southorn* and K.C. Beck.* Mayo Clinic and Foundation, Rochester, MN 55901.

Pleural liquid pressure (Plp) was measured by micropipets (5μ) with a servo-nulling system, used previously to measure interstitial and alveolar liquid pressures (Fed. Proc. 39:486, 1980; 40:448, 1981). Rabbits (4 kg) were anesthetized, paralyzed, and mechanically ventilated with 100% O_2. Two windows (2x4 mm) were made by dissecting away the intercostal muscle layers exposing the parietal pleura over the right lower lung lobe. In 5 animals, the upper window was situated between 4th and 5th ribs, 5.64±.34 (SD) cm above lung base; the lower window was between 7th and 8th rib, 2.36±.64 cm above lung base. Total lung height was 5.92±.28 cm. Heights were measured from radiographs. Repeatable measurements of Plp were made at the windows by puncturing the parietal pleura with micropipets during apnea at FRC. Plp relative to atmospheric pressure at upper window was -3.32±1.22 cm H_2O; at lower window, Plp was -1.64±.79 cm H_2O. Plp at upper window was always more negative than Plp at lower window. Lung static recoil (Pst), obtained by occluding the trachea at FRC and opening the chest after killing the animals, was 2.00±.65 cm H_2O. Plp gradient with height was 0.51±.19 cm H_2O/cm. Conclusions: Plp, measured locally by this relatively noninvasive technique, extrapolated to the mid-point of the lung, reflected pleural surface pressure, Pst. We found no evidence that the intrapleural liquid at two points 3 cm apart in height was coupled by a hydrostatic column. (Supported by HL-21584 from NHLBI).

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HANDLING OF CALCIUM BY THE RAT SUBMANDIBULAR GLAND (RSG), J.A. Mangos, R.L. Boyd, and J. Stiefel, Depts. of Pediatrics and Physiology, University of Florida College of Medicine, Gainesville, FLorida.

In order to improve understanding of calcium handling by salivary glands, the excretion of "total calcium" (Ca) and "ionized calcium" (Ca^{++}) in the rat submandibular saliva was studied during stimulation with either pilocarpine (Pilo) or DL-isoproterenol (Iso) injected intravenously. Ca levels were measured by atomic absorption spectrophotometry; Ca^{++} by a flow-through Ca^{++} electrode. 1) During Pilo infusion (1 mg/kg rat wt.), the salivary [Ca] varied with the flow rate from as low as 0.39 mM/L at 125.0 µl/min·gm wet gland tissue (wgt) to as high as 3.22 mM/L at flow rate of 2.5 µl/min·gm wgt; the mean percent of Ca that was in Ca^{++} form was 59.2%. 2) During Iso perfusion (0.5 mg/min for 30 min), the salivary flow rates varied between 1-20 µl/min ·gm wgt; the salivary [Ca] was between 1-4 mM/L with a mean of 2.45 ± 0.76 mM/L and showed no dependence on the flow rate; the mean percent of Ca that was in Ca^{++} form was 6.7%. These results demonstrate that the handling of Ca and Ca^{++} by the RSG depends on the mode of stimulation of salivation: during Pilo stimulation, these results suggest a primary secretory fluid with low [Ca] and a net transductal influx of Ca or Ca^{++} as the fluid traverses the ductal system; during Iso stimulation the $[Ca^{++}]$ is low in the saliva without any indication for transductal influx of Ca or Ca^{++}.

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EFFECTS OF IONOPHORE A23187 ON CYTOSOLIC Ca^{++} AND PANCREATIC ACINAR SECRETION: STUDIES WITH Ca-SELECTIVE MICROELECTRODES. R. J. Stark* and J. O'Doherty* (SPON: L. K. Knoebel). Dept. Physiol. Indiana Univ. Sch. Med., Indianapolis, IN 46223.

In the exocrine pancreas, the action of the natural secretagogues may be mimicked by A23187. As A23187 is believed to act by increasing cytosolic Ca^{++} ($[Ca]_i$), Ca-selective microelectrodes were employed to examine the effect of A23187 on $[Ca]_i$ and the role of $[Ca]_i$ in acinar secretion. The mean $[Ca]_i$ in acinar cells of the mouse pancreas was determined to be $(4.3 \pm 0.3) \times 10^{-7}$M (n=26). When the ionophore was added to the saline bathing the acinar cells, 10^{-6}M A23187 depolarized the membrane potential (Em) by 5.2 ± 0.3 (SEM) mV (n=17) and the intracellular Ca-electrode potential (E_{Ca}) by 9.8 ± 0.6 mV (n=16), while 10^{-5}M A23187 depolarized Em by 7.8 ± 0.4 mV (n=23) and E_{Ca} by 14.1 ± 0.8 mV (n=16). These changes in potentials reflect a 44% increase in $[Ca]_i$ with 10^{-6}M and a 65% increase with 10^{-5}M A23187. The increase in $[Ca]_i$ observed with 10^{-6}M A23187 was similar to that found with concentrations of acetylcholine (ACh) that produced maximal enzyme secretion, while the increase with 10^{-5}M in $[Ca]_i$ was similar to ACh conc. which inhibited or reduced secretion. Measurements of amylase release during 30 min exposure to A23187 produced a 77% increase in amylase activity over basal levels with 10^{-6}M and little or no change with 10^{-5}M indicating that the ionophore influences secretion through changes in $[Ca]_i$ in a manner analogous to the natural secretagogue acetylcholine. (Supported by USPHS NIH Grant AM 26246.)

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ACETYLCHOLINE-INDUCED REDUCTION OF CYTOCHROMES FOLLOWED BY SECRETORY RESPONSE IN ISOLATED PERFUSED RAT PANCREAS. T. Kanno, A. Saito and N. Ikei. Dept. of Physiology, Fac. of Vet. Med., Hokkaido Univ., Sapporo 060 Japan

Redox states of cytochromes $a(a_3)$, b, and $c + c_1$, were continuously recorded with the aid of a scanning organ spectrophotometer (Tateisi Institute of Life Science, Kyoto, Japan) while pancreatic juice was simultaneously collected in the isolated perfused rat pancreas. Continuous stimulation with 30 nM-acetylcholine (ACh) induced reduction of cytochromes within 30 sec after initiation of the stimulus, and almost no change in NAD(P)H-fluorescence. The stimulation caused a gradual increase in secretory response: pancreatic protein output began to increase 2 min and reached the peak level 6 min after the initiation of the stimulus. Continuous stimulation with 1 µM-ACh induced immediate marked reduction of cytochromes; a small increase in NAD(P)H-fluorescence; and a large rapid increase in secretory response followed by steep descending phase during the stimulation. In contrast to a small or no reduction of NAD(P)H-fluorescence in the presence of ACh, anoxic treatment of the preparation always caused parallel reduction of nicotinamide nucleotides and of cytochromes without inducing the secreotry response. The present experiments show that ACh acts on the respiratory chain in mitochondria of pancreatic acinar cells to induce immediate reduction of cytochromes. We propose that this reduction is the initial event in stimulus-secretion coupling in the cells.

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MID-COLLICULAR DECEREBRATION AND GASTRIC ACID SECRETION, ANTRAL CONTRACTIONS AND GASTRIN RELEASE IN ANESTHETIZED CATS. Dale M. Lombardi, H.S. Feng, and Frank P. Brooks. Dept. of Physiology, University of Pennsylvania, Philadelphia, Pa. 19104

We have previously reported that mid-collicular decerebration in dogs failed to alter acid output in response to electrical stimulation of the vagus nerves but resulted in a 5-fold increase in serum concentrations of immunoreactive gastrin in the basal state and during vagal stimulation. We have repeated similar experiments in 9 cats. Acid output from a gastric cannula was determined in 15 min intervals by electrometric titration and antral contractions were recorded by miniature force transducers sewn to the antral wall. Gastrin determinations were performed by W.Y.Chey, Genesee Hospital, Rochester, N.Y. Basal acid outputs during the first hour after decerebration were 0.35mM±0.11mM/hr. Basal serum gastrin was 73.5±19 pg/ml. Comparable data for 13 cats with intact brains were: acid output 0.15±0.02mM/hr and serum gastrin 18.3±3.0 pg/ml. Acid outputs during vagal stimulation were similar in both groups over 3 hours. Serum gastrin rose to 240-369 pg/ml during vagal stimulation in the decerebrate cats vs 52-62 pg/ml in the intact cats. There were no antral contractions greater than 5 gms force during the basal periods. During vagal stimulation there was a 5 fold increase in the numbers of antral contractions 30 gm force in the decerebrate vs intact cats. Decerebration has little effect on vagally stimulated acid secretion but increases gastrin levels.

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CHOLINERGIC-LIKE EFFECT OF RANITIDINE ON LOWER ESOPHAGEAL SPHINCTER PRESSURE (LESP) IN MAN. G. Bertaccini* , E. Foggi* and E. Molina. Institute of Pharmacology and Surgical Clinic, University of Parma, Parma, Italy.

Seven healthy volunteers (age 20-35) were studied by esophageal manometry. No difference was found on basal LESP when saline was injected, whereas after an i.v. bolus of ranitidine (RAN) at doses of 0.5 and 1.0 mg/kg a significant ($p < 0.01$) increase was observed

	BASAL	SALINE	RAN 0.5	RAN 1.0
mm Hg	21.7 ± 2.2	21.5 ± 2.1	31.3 ± 2.4	37.3 ± 0.7

The effect was probably due to this particular molecule and was independent of the H_2-receptor blockade since other H_2--blockers were completely inactive. In a second set of experiments RAN (1.0 mg/kg) was injected 30 min after administration of atropine (0.5 mg s.c.):

	BASAL	ATROPINE	RAN 1.0
mm Hg	23.6 ± 2.0	22.4 ± 1.1	20.0 ± 0.9

The complete inhibition after atropine and the potentiation of a subthreshold dose of urecholine (1.25 mg s.c.) observed in preliminary experiments supported the hypothesis of a cholinergic mechanism of RAN on human LES. These results emphasize the importance of RAN in the treatment of gastroesophageal reflux in addition to the well documented inhibitory effect on gastric secretion.

Supported by a grant from the C.N.R., Rome.

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(^{3}H)QNB Binding and Acetylcholine(ACh)-induced Contractions in Isolated Guinea Pig Gastric Fundus Smooth Muscle Cells. E.R. Seidel* and L.R. Johnson, Univ. Texas Health Sci. Ctr., Houston, TX 77025

Studies were undertaken to compare (^{3}H)QNB binding and the ACh concentration required to induce isolated smooth muscle cell contraction. Cells were isolated by successive incubations with collagenase. They were then incubated with various concentrations of QNB(30min,30°C) followed by centrifugation for 45 sec at 15,000 xg. Specific binding of QNB, 90% of total, was calculated as the difference in the amount of (^{3}H) QNB remaining in the pellet after incubation in the absence or presence of 100µm oxotremorine(Oxo). The receptor/ligand interaction displayed a K_d of 0.19nM with a Hill coefficient of 0.98. The Bmax was 8.3×10^{-19} moles of QNB/cell. Assuming one molecule of QNB binds per receptor, this value suggests a concentration of about 500,000 muscarinic cholinergic receptors per cell. Displacement assays provided the following Ki's:ACh 8µm, Oxo 0.8µm and atropine 0.3nM. An image shearing microscope was used to measure contraction in isolated cells. The ED_{50} for ACh-induced contractions was approximately 0.1nM. This value is in excellent agreement with the binding constants for the antagonists atropine and QNB but not with those for the agonists ACh and Oxo. Comparison of the binding and contraction data indicate an 80,000-fold difference between the ACh Ki for displacement and the ED_{50} for contraction. These data suggest the existence of a large population of spare receptors for ACh-mediated contraction.

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COMPARISON OF THE INHIBITORY EFFECTS OF SPERMINE, PAPAVERINE AND EPINEPHRINE ON ISOLATED INTESTINAL PREPARATIONS.
J.S. Martin and M.F. Tansy. Dept. of Physiol. and Biophys., Temple Univ. Hlth. Sci. Ctr., Philadelphia, PA 19140.

Previous reports from this laboratory have indicated that spermine and spermidine inhibit the spontaneous contractile activity of the canine small intestine (Fed. Proc. 40: 576, 1981). Those experiments were performed with fixed dosages of the agents. The purpose of these experiments was to determine median effective inhibitory dosages for spermine, papaverine and epinephrine upon isolated segments of rat small intestine. Male rats weighing 300 to 500 g were used. Sacrifice was effected by cervical dislocation and segments of duodenum and ileum were removed. The segments were immersed in Tyrodes solution, gassed with 95% O_2 and 5% CO_2 at 37°, and longitudinal contractile force was measured. Initial tension was equilibrated for 30 min prior to administration of any agent. Contractions of rat intestine were measured isometrically with a strain gauge transducer and recorded on a polygraph. Responses were quantitated in terms of percentage of inhibition of spontaneous contractile frequency. Regardless of whether ileal or duodenal segments were tested the 50% inhibitory concentration (C) always adhered to the order $C_S > C_P > C_E$. Also, the duodenum was always more sensitive to papaverine and epinephrine, but the relative sensitivities were about equal for spermine.

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INDUCTION IN VITRO OF PROGRAMMED PATTERNS OF INTESTINAL PROPULSIVE BEHAVIOR.
W.A. Weems. University of Texas Medical School (Houston, Texas, 77030)

In vitro segments of cat ileum spontaneously and periodically produce propulsive complexes when hydrostatic work is required of a segment to expel fluid from the lumen. Duodenal and jejunal segments do not produce similar propulsive behavior. Experiments were conducted to determine if the propulsive behavior of jejunal segments was altered by arterial infusion of pentagastrin and by various modes of transmural stimulation. The oral and aboral ends of jejunal segments were connected to a propulsion evaluation system that imposed input-output conditions of constant capacitance (0.025 ml cm^{-1} of H_2O) and negligible resistance on both ends of a segment. Arterial perfusion of 10^{-10} to 10^{-8} M pentagastrin into jejunal segments induced ileal type propulsive behavior in 31 percent of the segments tested. In 22 percent of the segments tested, a single propulsive complex resulting in the net, aboral transport of fluid was produced within 2 minutes after the onset of pentagastrin infusion. Arterial infusion of acetylcholine chloride at 10^{-8} to 10^{-6} M produced a chronic reduction in the average volume of luminal content but did not induce propulsive complexes. These and other data indicate that (1) net propulsive behavior intrinsic to jejunal segments, unlike ileal segments, must be triggered by external control systems, and (2) hormonal input to in vitro segments of intestine can trigger a precise sequence of neural events that produce stereotyped patterns of propulsive behavior. (Supported by NIH Grant AM 23038.)

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BINDING AND DEGRADATION OF PANCREATIC POLYPEPTIDE FRAGMENTS BY AVIAN TISSUE MEMBRANES.
Martin L. Adamo*, Robert L. Hazelwood and Douglas F. Dyckes.* Depts. of Biology and Chemistry, Univ. of Houston, Houston, Tx. 77004

Avian Pancreatic Polypeptide (APP) has been shown to be an effective gastrointestinal agent in vivo. In vitro tests have failed to confirm many of the metabolic actions which APP possesses in vivo. The pattern of binding and degradation by brain, liver, proventriculus, kidney and pancreas was evaluated. Steady state binding of ^{125}I-APP to liver membrane was highly specific, but of a low affinity (Kd = $8x10^{-8}M$). Brain membranes possessed both high affinity (Kd = $3.9x10^{-10}M$) and low affinity binding sites, but were less specific in that Bovine Pancreatic Polypeptide (BPP) was almost as effective as APP in inhibiting binding, while extremely high levels of insulin ($4x10^{-7}M$) and synthetic C-terminal pentapeptides of APP and BPP ($3x10^{-6}M$) produced 40% inhibition of APP binding. Steady state binding to renal membranes was difficult to observe owing to the high degradation of APP by this tissue. Renal membrane degradation of APP was 2-3 times higher than that observed with brain or liver membranes. It is concluded that the liver and kidney are probably organs of APP clearance, while the brain may possess true biological receptors for APP. (Supported in part by NSF-PCM 80-03688 and NIH-PGM-AM09090)

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EFFECT OF CORTICOSTERONE (B) ON THE DEVELOPMENTAL ACTIVITIES OF GASTROINTESTINAL TRACT (GIT) NEUROTRANSMITTER ENZYMES.
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Steroids have been shown to modulate neurotransmitter enzyme activity in various tissues such as brain, heart, liver, etc.; however, little is known concerning the effects of B on GIT neurotransmitter enzyme activity. This study investigated the activities of choline acetyltransferase (ChAT), acetylcholine esterase (AChE), and monoamine oxidase (MAO) in 7 anatomical GIT segments, as well as adrenal and plasma B levels, in 1, 3, 7, 14, 21, 35, and 50d B-treated and non-treated rats subjected to no stress, acute (2h) or repeated (2h/d x 7d) restraint stress. Pregnant rats (14d) were given B (50 µg/ml or ≃ 2 mg/d) in the drinking water. After weaning, the pups also were maintained on this B regime. The GIT of both B-treated and non-treated rats showed segmental differences in all enzymatic activities. There were no consistent differences between B-treated and non-treated ChAT, AChE, and MAO activities on days 1 to 7; however on days 14 to 50 there were segmental elevations in AChE and MAO activities of B rats. Decreases in adrenal B levels were present in the B-treated animals on all days. Acute or repeated restraint elevated plasma B levels but did not alter the segmental variations of AChE, ChAT, or MAO in both treated and non-treated rats. These data suggest that rats maintained on B for prolonged periods exhibit increased AChE and MAO activities in specific GIT segments. (Supported in part by USPHS NU-05304-02)

SALT AND WATER METABOLISM

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EFFERENT ROLE OF ADH IN CNS-INDUCED NATRIURESIS.
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Previous work showed that ventriculocisternal perfusion (VCP) with CSF containing 300 mM [Na] (Hi-Na) causes a natriuresis (180% of control) and an increase in plasma ADH (176% of control). In the present study, changes in ADH which occur during Hi-Na VCP were mimicked by intravenous (IV) infusion of ADH. VCP was performed in two groups of pentobarbital-anesthetized dogs for three hours with simultaneous measurements of renal and cardiovascular function; 1-hour of either Hi-Na VCP or IV ADH bracketed by two 1-hour control periods. The IV ADH animals received VCP of normal CSF throughout the protocol. Plasma ADH increased gradually throughout Hi-Na VCP reaching maximum values which ranged from 21 to 62 pg/ml. It was possible to achieve virtually identical patterns of ADH elevation by constant infusion of ADH at rates of between 3 and 50 mU/Kg/hr. The dose-response relationships between absolute log ADH and $U_{Na}V$ for individual animals were identical in the two groups. The average changes in log ADH and $U_{Na}V$ for the two groups were the same. We conclude that ADH causes most, if not all, of the natriuresis induced by Hi-Na VCP. (Supported by NIH 5 RO1 NS12825-06 and a grant from the Kidney Foundation of Michigan.)

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ACUTE NATRIURESIS FOLLOWING LESIONS OF THE PERIVENTRICULAR TISSUE IN THE PREOPTIC RECESS IN RATS.
Steven L. Bealer Univ. Tenn. Ctr. Hlth. Sci., Memphis, TN 38163

Electrolytic lesions of the periventricular tissue surrounding the anteroventral third ventricle (AV3V) have chronic effects on fluid regulation and sodium metabolism. The present experiment was designed to determine if AV3V ablation also results in acute post lesion changes in sodium excretion. Mean rates of sodium excretion were measured for three days prior to surgery. Animals then received either electrolytic lesions of the AV3V region, lesions in the cortex, or underwent control surgery. Urine collected at hourly intervals for six hours and overnight was analyzed for sodium content. Sodium excretion by rats with lesions in the AV3V region was significantly higher (300 ± 75 µEq/hr) during hr two and three post surgery than control animals (75 ± 30 µEq/hr) and rats with cortical lesions (100 ± 60 µEq/hr), and higher than their own mean presurgery control levels of sodium excretion. This natriuresis was not reduced by administration of deoxycorticosterone. Following this acute natriuresis, animals with AV3V lesions excreted significantly smaller amounts of sodium than control rats for several days. These data indicate that AV3V periventricular tissue contains neural substrates critical for normal regulation of renal sodium excretion. (Supported by USPHS Grant HL-25877 and a grant from the American Heart Association, Tenn. Affiliate).

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ATRIAL NATRIURETIC FACTOR IN RATS: MOLECULAR WEIGHT. Nick C. Trippodo, Allan A. MacPhee,* Francis E. Cole,* and Howard L. Blakesley.* Ochsner Medical Institutions, New Orleans, LA 70121.

To help characterize the nature of atrial natriuretic factor (Fed Proc 40:534 and 554, 1981), atrial homogenates (Brinkman Polytron) from Sprague-Dawley (SD) rats were extracted with 1.0 M acetic acid (10 ml/g tissue wet weight). After centrifugation (12,000 xg, 10 min) aliquots of the supernatant were lyophilized before or after filtering through Diaflo ultrafilters with different nominal molecular weight cut-offs (molecular weights at which filters exhibit approximately 90% retention). Some non-filtered lyophilizates were reconstituted and fractionated on Sephadex G-75 (equilibrated in 0.5 M acetic acid) and the fractions were lyophilized. To determine natriuretic activity the filtered, non-filtered and fractionated samples were dissolved in Dulbecco's phosphate buffered saline (pH 7.3) and injected (4 ml/kg, IV) into anesthetized SD rats. Baseline sodium excretion was measured in the assay rats during three 10-min periods and the percent increase in sodium excretion during the 10-min period following injection (% ΔNa) was determined. After chromatography the greatest natriuretic activity was found in the fractionation range between 15 and 25 (x 10^3 daltons). Results from the filtration experiments were confirmatory. The mean ± SE of % ΔNa for the non-filtered samples was 1233 ± 348. For the samples that passed through ultrafilters with nominal cut-offs of 10, 30, 50 and 100 (x 10^3 daltons) the means ± SE of % ΔNa were 21 ± 10, 902 ±213, 1001 ± 287 and 1027 ± 276, respectively. The results suggest that the molecular weight of atrial natriuretic factor is between 15,000 and 25,000 daltons.

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PROLACTIN-ADRENAL INTERACTION IN THE MODULATION OF RENAL SOLUTE HANDLING IN THE RAT. David E. Mills*, Maire T. Buckman*, and Glenn T. Peake* (SPON: A. Ratner). Dept. Res. and Med., VAMC, and Dept. Med., Univ. of NM Sch. of Med., Albuquerque, NM 87131

The role of prolactin(PRL) in mammalian renal function is not understood. PRL may interact with mineralocorticoids to alter Na^+ and K^+ excretion, as was reported in ewes. In this study, effects of oPRL on renal solute and water handling were studied in 1)intact, 2)adrenalectomized(adx), 3)adx + dexamethasone(10 µg/100 g BW), 4)adx + corticosterone(133 µg/100 g BW), and 5) salt-loaded(7 ml 5% NaCl ip) male rats. After 7 days of treatment rats received a water load(3% BW ip) prior to a 4h urine collection and blood sample for clearance determinations. Groups 2, 3, and 5 received 0.9% NaCl in place of drinking water. Rats also received 0.9% NaCl(controls,n=8/group) or 1.0 mg oPRL(NIH PS 14,n=8/group)im days 4-7. Treatments were continued day 8 for GFR determination by C_{Inulin}. In intact rats, oPRL ↓C_{Na} 42% (p<.05), ↓C_K 25%(p<.05), and ↑C_{H_2O}(p<.01) vs controls. In adx rats oPRL ↑C_K 145%(p<.005) vs controls, with no change in C_{Na} or C_{H_2O}. oPRL had no effect on C_{Na}, C_K, or C_{H_2O} in adx + dexamethasone rats. However, in adx + corticosterone rats, oPRL ↓ C_{Na} 67%(p<.05), ↓C_K 53%(p<.05), and ↑C_{H_2O}(p<.01). In salt-loaded rats oPRL ↑C_{Na} 87%(p<.05), and ↑C_K 53%(p<.05) vs controls. oPRL did not alter GFR at any time. These data suggest that 1) corticosterone reverses the renal actions of oPRL, 2) oPRL requires mineralocorticoids for an effect on Na^+, but not K^+, excretion, and 3) glucocorticoids may suppress effects of oPRL on the kidney. (Supported by a grant from the VA)

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NATRIURETIC EFFECT OF CAROTID OCCLUSION IN VOLUME EXPANDED NEWBORN AND ADULT DOGS L.I. Kleinman, R.O. Banks, T.A. Disney, University of Cincinnati College of Medicine

The newborn animal has an attenuated natriuretic response to saline volume expansion (VE) compared to the adult. Since bilateral carotid occlusion (CO) has been shown to induce a natriuresis, the renal effects of CO on anesthetized saline expanded newborn and adult dogs were studied. Eleven neonatal dogs 4-20 d old, were VE by 31% and 7 adult dogs were similarly expanded (26%). Fractional sodium excretion (FE Na) in the puppies was 1.9%, significantly less (p<.01) than in the adult (9.4%). In 5 puppies following CO, blood pressure rose 25 mmHg and FE Na increased to 7.5% (p<.05) a value not different from the VE non-CO adult. Distal blockade (DB) with ethacrynic acid and amiloride resulted in FE Na=55% in VE puppies and 36% in VE adults (p<.01). Since results under DB approximate proximal tubule function these n results demonstrate that with VE, newborns reabsorb less Na proximally than do adults although total Na reabsorption is greater. When CO was added to DB and VE, blood pressure rose 16 mmHg in puppies (p<.01) and 29 mmHg in adults (p<.01), FE Na increased to 65% in puppies (p<.01) and to 40% in adults (p<.01). The mean increase in FE Na was larger in the newborn (9.4%) than in the adult (3.9%, p<.05). These results indicate that the natriuretic effect of CO is in the proximal tubule and is greater in the immature than in the mature kidney. Supported by HD 12160.

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RENAL RESPONSE TO NaCl and $NaHCO_3$ LOADING IN NEWBORN DOGS J.M. Lorenz, L.I. Kleinman, T.A. Disney, U. of Cincinnati

Newborn dogs 2-20 days of age were volume expanded (VE) with either NaCl (n=11) or $NaHCO_3$ (n=12) to determine the effect of the anion on the renal response to acute VE with isotonic sodium solutions. Extracellular volume was expanded 31.6% in the NaCl group and 29.7% in the $NaHCO_3$ group (p>0.5). Reabsorption is expressed as µEq/min/GFR and p values compare the NaCl to the $NaHCO_3$ group. In VE with NaCl, reabsorption of sodium (RNa)=127.1, RK=2.2, RCl=108.3, $RHCO_3$=27.2. In VE with $NaHCO_3$, RNa=123.9 (p>0.4), RK=0.1 (p<0.001), RCl=96.9 (p< 0.001), $RHCO_3$=34.8 (p<0.025). In VE with NaCl in 6 puppies receiving ethacrynic acid and amiloride to block Henle's loop (HL) and distal tubular function, RNa=50.5, RK=1.4, RCl 42.6, $RHCO_3$ 23.4. However, in VE with $NaHCO_3$ in 8 puppies receiving these diuretics RNa=59.5 (0.05<p<0.10), RK=1.9 (0.05< p<0.10), RCl=43.1 (p>0.90), $RHCO_3$=26.0 (p= 0.10). Thus VE with either NaCl or $NaHCO_3$ inhibits proximal tubule Na reabsorption resulting in increased loads of Na, HCO_3 and Cl to HL. However, in VE with NaCl relatively more Cl and less HCO_3 is delivered to HL than in VE with $NaHCO_3$. Consequently in the NaCl expanded group HL reabsorbs more Na (as Cl) than in the $NaHCO_3$ expanded group; therefore in the $NaHCO_3$ expanded group more Na is presented to the distal tubule (as HCO_3), resulting in greater distal K secretion and HCO_3 reabsorption. This accounts for Na excretion being the same, K and HCO_3 excretion greater, and Cl excretion less in VE with $NaHCO_3$ than with NaCl.

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EFFECT OF ACUTE VOLUME EXPANSION (AVE) ON CHLORIDE ABSORPTION IN THE LOOP SEGMENT (LS) OF SUPERFICIAL NEPHRONS (SN). B. Booker*, R.H. Williams*, and R.G. Luke. Nephrology Research & Training Center, Univ. of Alabama in Birmingham, B'ham, AL.

To determine the role of AVE on net chloride movement from the LS in the rat at a constant fluid & chloride load, SN were perfused from the late proximal tubule to the early distal tubule at 22 nl/min (PR) with a perfusate consisting of Na 145; ^{36}Cl 130 and HCO_3 15 meq/L. In vivo perfusion rate was calculated using ^3H inulin. Analyses were done before(') & after m (") AVE. AVE was at 10% rat body weight over 1 hour with both 0.15M NaCl and 0.15M $NaHCO_3$. Eight time control rats were studied without AVE: calculated PR (20.2±1.5' → 21.3±0.6" nl/min) (mean±SEM), early distal Cl (95±3'→ 94±5" meq/L), fractional Cl absorption (FCl) (0.44±0.03' → 0.47±0.03") and $F^{36}Cl$ (0.63±0.03' →0.65±0.03") did not change (n=rats). Seven AVE-Cl rats yielded respectively 23.7±1.3' →22.0±1.9" (p=NS); 100 ±7' →83±9" (p<0.05), 0.41±0.07' →0.53±0.08" (p<0.05) and 0.58 ±0.02' →0.61±0.02" (p=NS). Six AVE-HCO_3 rats yielded respectively: 19.5±0.6' →19.5±0.7" (p=NS), 94±1.8' →64±3.0" (p< 0.001), 0.39±0.02' →0.59±0.03" (p<0.005), and 0.66±0.03' → 0.79±0.03" (p<0.025). Absolute Cl absorption changed significantly only in the AVE-HCO_3 rats (1001±63' →1508±96" peq/min, p<0.005). Although FCl increased in both AVE-HCO_3 and AVE-Cl (plasma Cl 93±3 and 122±2 meq/L respectively), the increased unidirectional $F^{36}Cl$ efflux in AVE-HCO_3, but not in AVE-Cl, suggests diminished Cl backflux in both AVE groups but increased Cl efflux in only the hypochloremic group.

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NEUROHYPOPHYSEAL PEPTIDES IN THE CEREBROSPINAL FLUID. Ralph R. Barnard, Jr.* and Mariana Morris Bowman Gray School of Medicine, Winston-Salem, NC 27103

There is increasing interest in the presence of the neurohypophyseal hormones vasopressin (VP) and oxytocin (OT) in the central nervous system. Since the cerebrospinal fluid (CSF) may provide a window for investigating central peptidergic activity, a push/pull technique was used to sample third ventricular CSF. Conscious rats were perfused with artificial CSF (10 µl/min) for 3 hrs. They were then decapitated and trunk blood collected. VP and OT were measured by radioimmunoassay. VP was found to be higher in the perfusate than in plasma; conversely, OT was higher in plasma than perfusate. Moreover, peptide levels in the perfusate were stable over time.

	plasma (pg/ml)	perfusate (pg/ml)	
Vasopressin	3.6 ± 0.3	13.1 ± 0.9	mean ± SEM
Oxytocin	23.2 ± 1.9	4.5 ± 0.4	n = 10

In a second experiment a control perfusion (150 mEq/L Na) was followed by a perfusion with a hypertonic solution (300 mEq/L Na). Hypertonic saline elicited a 3 to 4 fold rise in perfusate VP. These results suggest that CSF VP and OT are of central origin, and that a central stimulus is capable of increasing VP release into the CSF. Studies are in progress to further evaluate the dynamic changes in response to various physiological stimuli.

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EFFECT OF INTRACEREBROVENTRICULAR (ICV) INFUSION OF VASOPRESSIN (ADH) ON PLASMA ADH CONCENTRATION (P_{ADH}) IN ANESTHETIZED DOGS. B.C. Wang, L. Share, and J.T. Crofton. Univ. of Tenn. Center for the Health Sciences, Memphis, Tennessee 38163

Previous investigators have shown that centrally administered ADH caused water diuresis and decreased P_{ADH}. Since they did not measure the cerebrospinal fluid ADH concentration (CSF_{ADH}), it is not known whether this finding has any physiological significance. We determined whether P_{ADH} could be altered by increasing CSF_{ADH} to levels similar to those seen after physiological stimuli. Four groups of dogs were anesthetized with a chloralose-urethane solution. Each group received an icv infusion of artificial CSF, alone or with ADH, at a rate of 10 µl/min for 90 min. Arterial blood and CSF samples were taken just prior to infusion and at 30 min intervals for 210 min. P_{ADH} and CSF_{ADH} did not change in control experiments. Infusion of ADH at rates of 10, 20, and 50 µU/min resulted in increases in CSF_{ADH} of 26 ± 6, 75 ± 5, and 125 ± 8 µU/ml and reductions in P_{ADH} to levels which were 68 ± 7, 43 ± 6, and 49 ± 8% of control ($p < 0.05$-0.01), respectively. Plasma and CSF osmolalities were unchanged in all groups. Since the peak increase in CSF_{ADH} observed when ADH was infused icv at 10 µU/min was similar to CSF_{ADH} after severe hemorrhage and icv infusion of hypertonic saline, it appears that centrally acting ADH may play a physiological role in the control of ADH secretion. (Supported by USPHS grants HL-12990 and HL-19209 and UTCHS grant H-00053.)

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EFFECT OF THE ANGIOTENSIN I CONVERTING ENZYME INHIBITOR, MK-421 ON EXPERIMENTALLY INDUCED DRINKING. Melvin J. Fregly and Dennis C. Fater, Univ. Florida, College of Med., Gainesville 32610.

MK-421, the ethyl ester maleate salt of N-[(S)-]-(ethoxycarbonyl)-3-phenylpropyl-L-Ala-L-Pro, is an angiotensin I converting enzyme inhibitor. An initial objective was to determine whether MK-421, administered at 0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg/kg i.p. to 96 female Sprague Dawley rats 15 min prior to administration of the adrenergic agonist, isoproterenol (I)(25ug/kg, i.p.), would inhibit the drink induced by I. Water intakes of all rats were measured hourly for 2 hr after administration of I. The water intake induced by I was inhibited significantly by 2.5 mg MK-421/kg. When a similar experiment was performed using angiotensin I (200 ug/kg, i.p.) as the dipsogenic agent, MK-421 (5 mg/kg, i.p.) administered 15 min prior to AI inhibited significantly the dipsogenic effect of AI. However, administration of angiotensin II (200 ug/kg,i.p.) 15 min after MK-421 (5 mg/kg) was accompanied by water intake that did not differ from AII alone. The drink induced by i.p. administration of 1.0 M NaCl soln (1% of b.w., i.p.) was not inhibited by administration of MK-421 (5 mg/kg) 15 min prior to allowing access to water while the drink induced by a 24 hr dehydration was partially inhibited. Thus, the drinks induced by administration of either I or AI are dependent on formation of AII. That induced by dehydration is partially dependent, while that induced by hypertonic saline is independent of AII. (Supported by grant NCA2-OR204-101 from NASA).

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WATER DEPRIVATION INDUCED DRINKING IN RATS: ROLE OF EXTRACELLULAR VS. INTRACELLULAR COMPONENTS. C. C. Barney, R.M. Threatte* and M. J. Fregly. Dept. of Biology, Hope College, Holland, MI 49423 and Dept. of Physiology, University of Florida, Gainesville, FL 32610.

The relative importance of extracellular (renin-angiotensin system) and intracellular ($[Na^+]$ and osmolality) components of thirst in the control of drinking in rats deprived of water for varying lengths of time was studied. Male rats were deprived of water for 0, 12, 24, 36 or 48 h and measurements were made of water intake with and without pretreatment with the ACE inhibitor captopril (50 mg/kg, i.p.) plasma renin activity (PRA) and serum osmolality, $[Na^+]$ and $[K^+]$. Water intake increased with the duration of water deprivation (WD) and was significantly increased above control levels from 12-48 h of WD. Captopril significantly decreased water intake at 24-48 h of WD. The captopril-induced decrease in water intake increased with the length of WD. PRA tended to increase with the length of WD and was significantly elevated from 24-48 h of WD. Plasma osmolality and $[Na^+]$ but not $[K^+]$ were significantly increased from 12-48 h of WD but showed no further changes after the initial increase from 0-12 h. These data support the concept of a dual control of water intake in water deprived rats and indicate that as the duration of water deprivation increases the magnitude of the intracellular component remains constant while that of the extracellular component increases. (Supported by a Hope College Faculty Development Award and NASA Grant NCA2-OR204-101.)

TEMPERATURE REGULATION

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EFFECTS OF THYROXINE AND OF THIOUREA ON THERMOREGULATION IN FISHES. William W. Reynolds, Martha E. Casterlin and Richard E. Spieler. University of New England, Biddeford, ME 04005, and (R.E.S.) Milwaukee Public Museum, WI 53233

Acute or chronic administration of thyroxine via the ambient water significantly lowered the preferred temperatures of goldfish (Carassius auratus) and of bluegill sunfish (Lepomis macrochirus) thermoregulating in electronic shuttleboxes. Addition of thyroxine to the ambient water, to yield a final concentration of 20 micrograms of T_4 per liter, lowered the mean preferred temperature during the ensuing 24 hours by 2.1 ± 0.2°C for goldfish, and 2.0 ± 0.2°C for bluegill. Chronic (14 day) exposure to the same T_4 concentration lowered the mean PT by 7.7 ± 1.1°C (to 20.3°C) and 10.2 ± 1.1°C (to 20.8°C), respectively. Chronic (14 day) exposure of goldfish to thiourea (0.33 g/liter ambient water) increased PT by 2.6 ± 0.8°C above the normothermic mean final thermal preferendum of 28.0°C for this species. These results suggest an early evolutionary role of thyroid hormones in theregulatory behavior of ectothermic vertebrates. (Supported in part by NIH Grant AM 25919).

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TEMPERATURE REGULATION IN THE NINE-BANDED ARMADILLO Martha E. Heath* and H. T. Hammel, Physiological Research Laboratory, Scripps Institution of Oceanography, La Jolla, CA 92093

Johansen (1961) reported that armadillos increase their core temperature in response to decreases in ambient temperature (T_a). The present study was conducted to further characterize the thermoregulatory response of the armadillo to changes in T_a. The rate of O_2 consumption and the rectal (T_{re}), hypothalamic (T_{hy}) and skin (T_{sk}) temperatures were measured in armadillos during exposure to environments of 5-35°C both when T_a was altered and when it was held constant. T_a and T_{re} were found to correlate ($r = 0.83$) inversely such that at T_a = 30°C T_{re} was 34.5°C ($\bar{x}$) while at T_a = 10°C T_{re} was 36.4°C ($\bar{x}$). The amount by which T_{re} changed was affected by the magnitude but relatively unaffected by the rate of change in T_a. The change in core temperature in response to altered T_a was most closely associated with changes in T_{sk}. Using thermodes it was also demonstrated that the hypothalamus of armadillos has thermosensitivity and that changing T_{hy} alters thermoregulatory responses. Since changes in both T_{sk} and in T_{re} were observed before any change in O_2 consumption was noted, it appears that the rate of heat exchange with the environment is altered before metabolic changes are stimulated. Presumably this occurs via changes in peripheral blood flow.

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INTERACTION OF EFFECT OF THYROXINE AND NOREPINEPHRINE IN THE ACUTELY COLD-STRESSED RAT. Bruce Powell Douglass* and Eugene Evonuk. Dept. Physiol., U. South Dakota Sch. Med. Vermillion, SD 57069* and Applied Physiol. Lab. U. of Oregon Eugene, Or. 97403.

The interaction of effects of thyroxine and norepinephrine was investigated. Two groups of rats were thyroidectomized and injected daily with differing amounts of thyroxine for a period of three weeks. These rats, along with a control group, were reserpinized and subjected to acute cold stress while receiving increasing doses of infused norepinephrine. Core temperature, heart rate, blood pressure and oxygen consumption were measured at five minute intervals for a period of sixty minutes. No significant interaction of the effects between thyroxine and norepinephrine was found for any of the parameters measured. The groups were found to differ in their ability to maintain resting levels in the measured parameters. The findings in the present study indicated that the ability of the rat to withstand acute cold stress was primarily the result of circulating thyroxine and not by catecholamines.

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MONOCYTIC PYROGEN FEVER: EFFECT OF PROTEIN DEFICIENCY L. Hoffman-Goetz and R. Bell*. Department of Health Studies University of Waterloo, Waterloo, Ontario, Canada N2L 3G1.

In continuing studies on the effects of protein malnutrition on endogenous pyrogen mediated fever, we have investigated pyrogen production by rabbit blood monocytes. Although monocytes are known to be an excellent source of endogenous pyrogen (Bodel, J. Exp. Med. 140:954, 1974), it is not clear how, or if, protein malnutrition affects monocytic pyrogen production. Young male rabbits were fed a protein-free diet for 8 weeks; control rabbits were pair-fed a 21% protein diet. Venous blood samples were collected sequentially at t= 1, 21, 35 and 56 days on the diets. Monocytes were isolated by centrifugation over Ficoll-Hypaque and incubated in HBSS with killed S. albus (40 bact.:leuk.) for 18 hrs. at 37°C. The average yield was $1x10^6$ leukocytes (24.0±.4% monocytes). Sterile, endotoxin-free crude monocytic pyrogen supernatants (1 ml) were injected i.v. into recipient rabbits and rectal temperatures were recorded. The results were as follows:

	Average 4-Hour ΔT (°C)		
	21 days	35 days	56 days
Protein=free	0.72±.18	0.05+.10*	-0.04±.14*(n=4)
Control	0.57±.05	0.65±.11	0.53±.05 (n=4)

($\bar{x}$ ±SEM; *= p <.05 when compared with day 21 fever, ANOVA)

These data suggest that: 1) chronic dietary protein deficiency results in an attenuated monocytic pyrogen fever and 2) reduced pyrogen production is a threshold phenomenon. (Supported by NSERC of Canada #A7645 & Hum. Nutr.Res.Coun. of Ont.)

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RAPID HYPERTHERMIA WITHOUT DEHYDRATION: A COMPARISON OF METHODS IN RATS. R.W. Hubbard and C. B. Kelly*. US ARMY RES. INST. OF ENVIRON. MED., NATICK, MA., 01760

Thermally stressed, rats thermoregulate behaviorally by spreading saliva on body surfaces and thus lose body water (wt). Prior to exploring the role of dehydration in our rat heatstroke model, we sought to compare the capacity of physical restraint, surgical desalivation (desal) and atropine, i.v. to inhibit body water loss and to stimulate heat gain during progressive hyperthermia. Sprague-Dawley rats (n = 41; 521 ± 14 g) were assigned to one of six experimental groups and heat-stressed in an environmental chamber (41.5°C) until a Tre of 42.6°C was reached. The following results were obtained:

Group	n	Wt loss (g)	Exposure time (min)
1) Unrestrained (Un R)	6	42 ± 7	258 ± 40
2) Restrained (R)	8	13 ± 3	62 ± 14
3) Desal-Un R	7	10 ± 5	75 ± 17
4) Atropine (25 µ g)-Un R	6	10 ± 2	84 ± 12
5) Desal-R	8	4 ± 2	32 ± 3
6) Atropine (500 µ g) Un R	6	4 ± 1	42 ± 7

Significant ($p < .05$) reductions in both weight loss and heating time (Group 1 vs 2, 3 or 4) were obtained by either physical restraint, surgical desalivation or 25 u g's of atropine, respectively. Maximal inhibition of weight loss to less than 10 percent of control values, maximal reduction in heating time and, therefore, maximal stimulation of the rate of heat gain was achieved by either physical restraint plus desalivation or a 20 fold increase in the dose of atropine.

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HEAT EXPOSURE AND EXERCISE: EFFECTS ON PLASMA LEVELS OF RENIN, ALDOSTERONE, AND VASOPRESSIN. R. Francesconi and M. Mager. US Army Res. Inst. Environ. Med., Natick, MA 01760.

Adult, male rats were exposed sedentarily to a hot environmental temperature (35°C) or exercised (9.14 m/min, level treadmill) also at 35°C to compare the responses of several fluid regulatory hormones. In exercising animals blood samples were taken as follows: control (time 0, 22°C ambient); when Tre reached 40°C (10-15 min exercise); at hyperthermic exhaustion (Tre = 43°C); and when Tre cooled to 40°C. In sedentary rats, blood samples were taken at 0, 6, 24, 48, and 72 hours of heat exposure. While the animals were exercising, no changes occurred in plasma renin activity (PRA), but following exercise in the heat and when Tre had returned to 40°C, there was observed a significant ($p < .001$) increment in levels of PRA. Alternatively, plasma levels of aldosterone were significantly ($p < .001$) increased shortly after the start of exercise in the heat (Tre = 40°C) and remained elevated at all other sampling times. Vasopressin was elevated ($p < .05$) by the completion of the treadmill run (Tre = 43°C) and remained so during the cooling interval (Tre = 40°C). In contrast, animals exposed sedentarily to more prolonged heat stress displayed much more variability in hormonal responses, and, of the three hormones tested, only aldosterone displayed a pattern of increasing levels with a significant increment ($p < .05$) at 72 h. We concluded from these studies that levels of fluid regulatory hormones are extremely responsive to acute heat exposure combined with exercise stress and concomitant with increments in Tre, while sedentary heat exposure for more prolonged intervals had inconsistent and minor effects on these levels.

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AEROBIC AND THERMOREGULATORY BENEFITS DURING INTERVAL TRAINING ON A BIOKINETIC SWIM BENCH. A. Reino* and R.R. Gonzalez, J.B. Pierce Foundation and Yale School of Medicine, New Haven, Ct. 06519

A 9 day training period with a biokinetic swim bench was done on 5 female subjects (age 19-22) who trained 10 min per day at submaximal and maximal levels (bench MAP=65% cycle ergometer MAP). Three subjects were highly trained swimmers (AS, athletic swimmers, cycle MAP=56ml·kg^{-1}·min^{-1}) and two were non-athletes (NA, cycle MAP=43ml·kg^{-1}·min^{-1}). Ta(=$\bar{T}$r) was 19C and dew point (T_{dp}) was 10C. The training was: (1) 4 min butterfly style pulling (80 rev·min^{-1}), 1 min rest; (2) 3 min pulling as in (1); and (3) 3-1 min bouts separated by 30 sec rest in which 1st and 3rd min were at 70% bench MAP and 2nd min was at 100% bench MAP. Heart rate, body weight (BW) were recorded before and after each regimen. T_{es} and T_{sk}, back sweating ($\dot{m}_s$, automatic dewpoint sensors) and upper torso net flux (net radiometer) were continuously taken. In NA, heart rate increased as a function of power output but in AS it was constant each day after bouts. Total power output (W) increased 9% in AS but 22% in NA; post bench MAP was increased by 16% in AS and by 19% in NA. After the 9th day, $\dot{m}_s$ occurred earlier and at lower T_{es} in both AS & NA; the gain ($\dot{m}_s$ to T_{es}) was greater ($P<0.01$) in AS with higher cycle and bench MAP. Significant improvement in both aerobic and thermoregulatory responses can be elicited by swim bench training. (Supported by NIH OH-00836 to R.G.)

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THE EVALUATION OF HEAT TOLERANCE. Nick B. Strydom, Willie H. van der Walt* and Johan A. Kielblock*. I.H.B., Chamber of Mines of S.A., Johannesburg, 2001, South Africa.

In an effort to decrease the burden of heat acclimatization usually required from returning miners prior to going underground a heat tolerance test was developed. This involves a four-hour stepping routine the positive part of which equals 54 W in conditions where Twb is controlled at either 29, 30, 31 or 31,7 °C with Ta always 1,5 °C higher and V = 0,5 m/s. Those men registering body temperatures of < 38,5 °C are considered as hyper heat tolerant (HHT) and are exempted from further artificial acclimatization procedures. As men are sometimes required to work in hotter areas it was necessary to evaluate the performance of HHT's at Twb = 32,5 °C and 70 W by comparing their responses to those of normally acclimatized men. Although average 4th hour body temperatures did not differ between these groups and even though the HHT's had significantly higher heart rates, a statistical projection, based on results obtained on 200 subjects, indicates that the chances of developing heat stroke levels of body temperature are far less in the HHT's than in normally acclimatized men. The HHT's distinguish themselves by having significantly higher sweat rates.

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THERMOREGULATORY RESPONSES OF PATIENTS RECOVERED FROM EXTENSIVE BURNS. *Y. Shapiro, H. Zur*, Y. Epstein*, G. Keren* and H. Ben-Simchon*. Heller Inst. of Med. Res.& Tel-Aviv Univ.Med. School; Sheba Medical Center,Tel-Hashomer 52621,Israel.*

Two groups (A,n=4; B,n=6) of patients with 2nd and 3rd degree burns and a group of healthy controls (C,n=10) underwent 3 hours of exercising at 40°C, 50% RH ($\dot{V}O_2$=1.051±0.061 l/min). The burned area (A_B) of A was 48.6±3.6% of total skin surface area (A_D) and of B 23.7±3.1%. Rectal temperature (T_{re}), skin temperature (T_{sk}) and heart rate (HR) of A were significantly higher than those of B and C,i.e. at the end of the 1st hour T_{re} was: 38.7, 37.9, 37.7°C; T_{sk}: 37.3, 36.4, 37.0°C; HR: 151, 105, 110 b/min in A,B and C respectively. Total sweat loss ($\dot{m}_{sw}$) was: 594±25, 602±71, 485±107 g/h respectively. $\dot{m}_{sw}$ normalized to healthy skin area: $\dot{m}_{sw}/(A_D-AB)$ was:671±151, 449±70, 280±49 g/h.m² respectively. Maximal evaporative cooling capacity (E_{max}) which is proportional to the area of healthy skin available for sweating and evaporation was lowest in A (4.9± 0.1 W/kg),average in B (7.2±0.5) and highest in C (10.2±0.4). The required evaporation capacity for thermoequilibrium (E_{req}) was: 6.7, 6.8, 6.6 W/kg. Similarity between group B and controls can be explained by the compensatory sweat rate from the normal skin of group B, which was sufficient in this case when $E_{max} > E_{req}$. In group A $E_{max} < E_{req}$, therefore thermoequilibrium could not be maintained despite high compensatory sweat rate from the normal skin.

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COMBINED EFFECTS OF LOCAL CHOLINERGIC STIMULATION AND BETA-ADRENERGIC BLOCKADE ON SWEAT GLAND RECRUITMENT. Kenneth Kraning, Dermatology & Environmental Health, University of Washington, Seattle, WA 98195

As part of a study on differences between normal and atopic human subjects sweat glands responding (SGR) was measured in response to Mecholyl (MC) and Pilocarpine (PC) following pretreatment with either Saline (S) or Propranolol (PR). All drugs were 0.01 M, applied by iontophoresis to 8 randomly paired 1.25 sq cm areas on the volar surfaces of both forearms with a constant current of 0.2 mA, a duration of 240 sec for S or PR pretreatment, and a duration of 30 sec for MC or PC treatment. SGR was determined by counting sweat impressions made on iodized paper sampled at 10, 15, & 20 min after treatment. In all subjects SGR was greater for MC than for PC. In 5 normal male subjects the PR pretreatment always increased the SGR to MC ($p<.01$) and always decreased the SGR to PC ($p<.01$). It is concluded that PR pretreatment in normal subjects increases SGR to mild MC stimulation, perhaps by increasing the sensitivity of a normally less active subpopulation of glands. The observation that MC & PC give opposite responses with PR is paradoxical, as both are parasympathomimetics. This could be due to an unidentified difference in the sudorific mechanisms of MC and PC. Interestingly, in 2 subjects with active allergic disease, PR pretreatment decreased the SGR to MC. In one, an atopic female, PR pretreatment increased the SGR to PC. The other, a male with inhalant allergies, showed the same response to PC as normals. (Supported by NIH Grant No. 5 ROI AI 16636-02)

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SWEAT RATE AND SKIN TEMPERATURE IN DESERT WALKS; BLACKS AND WHITES, YOUNG AND OLD. S.D. Hillyard and D.B. Dill. Univ. of Nevada, Las Vegas, NV. 89154

In a study of thermoregulation by blacks and whites, the sweat rate (SR, ml/m²·min) of both males and females was measured during one hour desert walks at 80 m/min. Skin temperature (T_{sk}, °C) was measured four times during the hour's walk with a thermocouple applied to the skin on the forehead, neck, upper arm and thigh. The average temperature of the four readings of the four sites was used for comparison between groups. The mean values for SR and T_{sk}, ± 1 S.D., were as follows: white women, 6.2 ± 2.3 and 33.7 ± 1.7, respectively; white men, 7.6 ± 1.3 and 32.2 ± 5, respectively; black women, 6.9 ± 2.1 and 32.6 ± 1.1 respectively; black men 7.4 ± 1.7 and 31.5 ± 1.4, respectively. The difference in SR between all men and women was significant at the $P < 0.025$ level while the difference in T_{sk} between these groups was significant at the $P < 0.01$ level. Since rectal temperature of men and women was not different ($P > 0.05$) at the end of the walks, equality in thermoregulation was achieved despite the lower SR and higher T_{sk} in women. It is suggested that this difference is due to the presence of more subcutaneous fat in women than men.

PERIPHERAL CIRCULATION

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HYPOTENSIVE EFFECT OF TWEEN 80 IN DOGS. Paul E. Newton, Stanley D. Erk*, Chris Pfledderer*. University of California, Irvine, Toxic Hazards Research Unit, Dayton, Ohio 45431

Tween 80 (polyoxyethylene(20)sorbitan monooleate) has been frequently used in toxicologic studies as a vehicle for IV drug injections. However, in a control study, 1 drop of Tween 80 in 10 ml of heparinized saline produced hypotension and tachycardia. Subsequently 4 beagle dogs (8.8-12.7 kg) were injected over a 5 minute period with 10 ml of heparinized (10 IU/ml) saline containing either 0, 2, 4 or 6 mg/kg of Tween 80. The following changes in cardiovascular parameters relative to control values were measured 30 minutes after injection and these parameters had not returned to normal after 180 minutes.

Tween 80 mg/kg	Δ Pressure, mmHg Systolic	Diastolic	Δ Heart Rate, min⁻¹
0	0	0	0
2	-60	0	+115
4	-80	-20	+125
6	-120	-30	+115

At the 2 mg/kg dose there was an initial transitory rise in both pressures due to an increase in heart rate but then the pressures fell despite a continued increase in the heart rate. Conclusion: Tween 80 should not be considered inert and any use as a drug solvent should be very carefully considered. (Supported by U. S. Air Force Contract: F33615-80-C-0512).

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HISTOCHEMICAL FIBER TYPE AND CAPILLARITY OF THE HAMSTER RETRACTOR MUSCLE. Sharon M. Sullivan and Roland N. Pittman. Dept. of Physiology, Medical College of Virginia, Richmond, VA 23298

Prior to the initiation of microcirculatory oxygen transport studies, the retractor muscle of the golden hamster was characterized histochemically. 12 μm thick serial sections were cut and stained for NADH-tetrazolium reductase and myofibrillar ATPase (pH 9.4) to determine muscle fiber type. Sections were also incubated for alkaline phosphatase to demonstrate the presence of capillaries. Fibers were classified as slow-twitch-oxidative (SO), fast-twitch-oxidative-glycolytic (FOG) and fast-twitch-glycolytic (FG). The retractor consists primarily of FG fibers (69.2%), with the balance made up of FOG (16.5%) and SO (14.3%) fibers. Fiber areas (mean ± SE in μm²) were 1345 ±75, 913 ±70 and 672 ± 30 for FG, FOG and SO fibers, respectively. FG fibers had an average of 2.0 ±.3 capillaries surrounding each fiber, with SO having 2.4 ±.4 and FOG fibers having 2.9 ± .6. The number of capillaries per FG fiber was related to its proximity to either FOG or SO fibers being higher if it was in contact with either fiber type. The number of capillaries around FG fibers which were adjacent only to other FG fibers was significantly ($p \leq .01$) lower at 1.5 ±.1. A significant ($p \leq .01$) correlation between fiber cross-sectional area and number of capillaries was found for FG fibers but not for SO or FOG fibers. These results indicate that FG fiber capillarity is dependent on the neighboring fiber types and is also correlated to fiber cross-sectional area. (Supported by AHA grant 78 915 and NIH grants HL 18292 and HL 26901).

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IS INTESTINAL CAPILLARY FILTRATION RATE AUTOREGULATED?
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It is generally considered that intestinal capillary pressure remains relatively constant when arterial pressure is reduced. In order to determine if intestinal capillary filtration rate is autoregulated, we measured lymph flow (LF) capillary pressure (Pc), capillary filtration coefficient (KFC) and the transcapillary oncotic pressure gradient ($\Delta\pi$) under isovolumetric conditions in the cat ileum. Interstitial fluid pressure (Pt) was then calculated from measured parameters in the Starling equation. Local arterial pressure was reduced in 25 mmHg increments from 125 mmHg to 25 mmHg. Venous pressure was held constant (5 mmHg) at each arterial pressure. As arterial pressure was reduced, Pc, Pt, and $\Delta\pi$ decreased while KFC increased. Lymph flow decreased progressively as arterial pressure was reduced. At 25 mmHg arterial pressure lymph flow consistently ceased. The results of this study indicate that capillary pressure and capillary filtration rate in the intestine are poorly autoregulated when arterial pressure is reduced.

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CHANGES IN THE SOURCES OF HEPATIC PORTAL BLOOD FLOW WITH FEEDING IN THE SHEEP.
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Blood flow was measured with 15μ diameter radioactive microspheres before, during and at two times following the ingestion of a daily meal of hay and concentrates. Flow was enhanced in the muscle of the ruminoreticulum and in the parotid and submandibular salivary glands only during eating. The flow to the epithelium of the ruminoreticulum also rose during feeding, but the major increase was observed 2hr after feeding began when food had been withdrawn. Flow had not declined to prefeeding levels by the fourth hour. This peak epithelial flow accounted for the increase in portal flow at 2hr. By contrast, omasal blood flow was steady except for a marked depression during eating. In the other organs contributing to the portal flow, the blood flow either remained steady throughout, as in the large intestine, jejunum, pancreas and spleen, or decreased during the period of observation, as in abomasum, duodenum, ileum and gut fat. The fraction of portal blood flow supplied by the foregut varied with feeding from 0.18 to 0.43. The corresponding fractions for gut fat in these fat sheep were 0.12 to 0.04.

The distribution of blood flow thus shows marked changes with feeding both between and within the organs examined. Any diversion of blood within the portal drainage area to the epithelium of the ruminoreticulum at the height of ruminal fermentation can only be minor.

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THE MEASUREMENT OF CANINE GASTRIC MUSOCAL BLOOD FLOW WITH A LASER DOPPLER VELOCIMETER.
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In recent years some 30 techniques have been developed with the hope of achieving an ideal method of measuring splanchnic blood flow. Yet, this ideal remains elusive. Disadvantages include: invasiveness, expense, difficult procedures, complex apparatus, and hazardous radioactivity. The Laser Doppler Velocimeter uses safe, low energy laser light to measure the Doppler shift caused by moving particles (red blood cells) in a cubic millimeter of tissue. It is noninvasive, easy to apply, gives instant or continuous values, and can be applied to the gastric mucosa through an endoscope. We compared the Laser Doppler technique with mucosal flow estimated by radioactive microspheres in five chambered canine stomachs. Mucosal flow was stimulated with different doses of a vasoactive PGE_1 analog (SC-29333). The Laser Doppler numbers showed a high linear correlation with total venous outflow ($r=0.80$, $P<.001$) and with microsphere estimated mucosal flow ($r=0.77$, $p<.01$). We conclude that the Laser Doppler Velocimeter is a quantitatively accurate tool for the estimation of mucosal flow/volume of tissue, and should be considered in clinical experimental studies of mucosal blood flow. (Supported in part by NIH Grant #GM 23095-05.)

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THE EFFECTS OF BLOOD VOLUME EXPANSION ON RENAL FUNCTION IN THE RHESUS MONKEY.
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The blood volume in 7 male rhesus monkeys (6-9 kg) anethetized with ketamine was determined using R ^{125}ISA - ^{51}CR-tagged red cells. Blood volume was found to be 6.0±0.58% of body weight. After two 20 min control urine collections, the animals received 15% (n=7) and, 4 weeks later, 25% (n=6) blood volume expansion (BVE) with iso-osmotic Dextran 75. Twenty minute collections of urine began 20 min after initiation BVE and continued until 1 hr post-BVE. Blood samples were drawn at the midpoint of each urine collection; this volume was replaced with Dextran. Creatinine clearance, (Ccr) PAH clearance (Cpah), sodium excretion (UNa^+V), potassium excretion (UK^+V), filtered Na^+ (FNa^+), and urine flow ($\dot{V}$) were determined. The data were then analyzed using an ANOVA for repeated measures and the Newman-Keul's multiple range test. *P <.05, **P <.01.

	15% BVE		25% BVE	
	30 min	50 min	30 min	50 min
$\dot{V}$	NS	NS	**	**
Ccr	NS	NS	*	NS
Cpah	*	*	**	*
$UNa^+\dot{V}$	NS	*	**	**
$UK^+\dot{V}$	*	*	*	NS
FNa	NS	*	*	**

Thus, 15% BVE does not appear to activate the complete renal compensatory mechanisms, indicating that a threshold exists between 15% and 25% BVE. Supported by NASA Grant #2282.

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INDOCYANINE GREEN (ICG) AND EVANS BLUE: A COMPARATIVE STUDY OF PLASMA VOLUME MEASUREMENT.
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Plasma volumes (PV) were measured in two groups of rats by injection of ICG (n = 213) or Evans Blue (n = 100) via indwelling jugular cannulae. Both groups had similar ($p > 0.05$) body weights, core temperatures, plasma protein concentrations, and corrected venous hematocrits. Serial blood samples were obtained over 10 min (8 samples, ICG) or 60 min (6 samples, Evans Blue). PV's were assessed directly by dye dilution, and blood (BV) and cell volumes (CV) were calculated. The coefficients of determination (r^2, $\bar{X} \pm SD$) of ICG and Evans Blue plasma dye disappearance curves were 0.995 ± 0.008 ($p < 0.01$) and 0.677 ± 0.215 ($p < 0.01$), respectively. The half-lives ($t_{½}$) were 3.1 ± 0.5 and 256 ± 139 min ($p < 0.01$) for the ICG and Evans Blue groups, respectively, and corresponding disappearance constants (K, fraction of dye disappearing/min) were 0.23 ± 0.04 and 0.0034 ± 0.0017 min^{-1} ($p < 0.01$). The PV, BV, and CV values (ml, $\bar{X} \pm SD$) for ICG were 21.7 ± 4.3, 36.0 ± 5.2, and 14.3 ± 2.0 and were not significantly different ($p > 0.05$) from corresponding values for Evans Blue. In additional experiments (n = 12), PV was quantitated (21.9 ± 3.2 ml) followed by injection of known volumes of 0.9% saline (6.1 ± 0.5 ml). One hour later, the predicted volume (28.0 ± 3.6 ml) was not significantly different ($p > 0.05$) from the estimated volume (28.2 ± 4.1 ml), and the correlation ($r = 0.858$) was significant ($p < 0.01$). The data indicate that ICG can be used to measure PV in rats and simultaneously assess changes in liver function (i.e. clearance rate). Because of its short $t_{½}$, PV can be reestimated within an hour.

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THE EFFECTS OF ENDOGENOUS VERSUS EXOGENOUS MICROEMBOLI ON LUNG FLUID FILTRATION. A. Johnson*, M.V. Tahamont* and A.B. Malik, Dept. Physiology, Albany Medical College, Albany, NY 12208.

We examined the effects of fibrin microaggregates (FM) on lung fluid and protein exchange in the sheep lung lymph preparation to determine if exogenous fibrin mediates lung vascular injury. FM (diameter ~100 μm) were produced in vitro from citrated sheep plasma after precipitation with glycine. The response to exogenous fibrin was compared to the effects of endogenous intravascular coagulation induced by i.v. thrombin (120 U/kg). Pulmonary vascular resistance (PVR), lung lymph flow ($\dot{Q}_{lym}$) and lymph/plasma protein conc. ratio (L/P) were determined. Baseline and postembolization (PE) values are shown:

	FM (n=7)		Thrombin (n=8)	
	Baseline	PE	Baseline	PE
PVR,mmHg/l/min	5.8±1.0	20.4±5.6*	6.5±1.1	18.4±2.5*
$\dot{Q}_{lym}$,ml/hr	6.7±1.6	14.1±3.7*	5.8±1.5	11.9±2.9*
L/P	0.84±0.02	0.64±0.09*	0.79±0.04	0.81±0.04

*$p < 0.05$

While PVR increased similarly in both cases, lung vascular permeability increased only after thrombin-induced intravascular coagulation. The increase in filtration after embolization with FM was due to increased filtration pressure and not to increased permeability. Therefore, in vivo activation of coagulation is required to produce an increase in vascular permeability. (HL-12355, HL-26651, HL-00363, and Parker B. Francis Foundation)

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THEORETICAL EFFECTS OF PLASMA PROTEIN CONCENTRATION ON LUNG LYMPH FLOW AND L/P RATIO. R. J. Roselli, Department of Chemical Engineering, Vanderbilt University, Nashville, TN 37235

Transvascular fluid and protein transport in the lung was simulated at various plasma protein concentrations (C_p) and transvascular pressure differences (ΔP) using the multiple pore model of Harris and Roselli (J. Appl. Physiol. 50:1-14, 1981). The membrane structure and baseline ΔP were assumed to remain unchanged as C_p was altered. Results indicate that C_p and the percentage of albumin in the plasma can influence lymph flow (Q_L) and total lymph to plasma protein concentration ratio (L/P). The predicted baseline protein L/P is considerably higher for a C_p of 8g/dl(.78) than 4g/dl(.55). Although the L/P becomes independent of C_p at very high lymph flows, a noticeable discrepancy in the L/P vs. Q_L relation persists between C_p of 4g/dl and 8g/dl at lymph flows below 2 ml/min. Several important consequences may arise from the theoretical dependence of L/P on C_p. First, variations among sheep may be due to differences in baseline C_p or albumin content. Generally, higher flows and lower L/P ratios are expected with decreasing C_p. Second, since no universal relation between L/P and Q_L exists, one may need to account for C_p when comparing L/P vs. Q_L from altered permeability studies to differences expected from ΔP alone. Finally, reflection coefficient estimates, obtained by extrapolating L/P vs. Q_L to higher flows, are subject to larger errors at high C_p.

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"Lung vessel leak in monocrotaline treated rats may relate to their subsequent pulmonary hypertension." J.T. Reeves, T. Sugita,* T. Hyers, and W. Wagner, Univ. of Colorado, Denver, and A. Tucker and A. Alexander* Colorado St. Univ., Ft. Collins

One injection of monocrotaline (40mg/kg) causes pulmonary hypertension in rats weighing less than 200 gm. Two of us (AT, JTR) independently observed that lungs from monocrotaline treated rats easily develop edema when perfused. We considered that lung vessel leak might somehow cause the hypertension. If so an increase in lung wet/dry weights (a marker of lung water) would precede right ventricular hypertrophy (a marker of pulmonary hypertension). The results below suggest that wet/dry ratios increased before right ventricular hypertrophy developed. Lung dry weight increased with right ventricular hypertrophy. Possibly lung vessel leak relates to pulmonary hypertension and lung hyperplasia with monocrotaline.

TIME AFTER MONOCROTALINE	BODY WT.(GM)	WET/ DRY	LUNG DRY WT. BODY WT.	RV LVTS
Control (5)	226	5.17	.00107	.33
8 Hrs. (5)	200	5.28	.00107	.33
72 Hrs. (5)	234	5.35	.00114	.34
1 Week (5)	237	5.50	.00116	.39
2 Weeks (5)	271	5.24	.00156	.48
3 Weeks (3)	249	5.07	.00280	.77

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PHORBOL MYRISTATE ACETATE INFUSION CAUSES LEUKOPENIA, PULMONARY HYPERTENSION AND INCREASED LUNG VASCULAR PERMEABILITY IN AWAKE SHEEP. J.E. Loyd,* J.H. Newman, D. English,* and K.L. Brigham. Pulmonary Circulation Center, Vanderbilt University School of Medicine, Nashville, TN 37232.

Phorbol myristate acetate (PMA) is a potent in vitro activator of polymorphonuclear leukocyte (PMN) respiratory burst. In isolated rabbit lungs, PMA causes PMN dependent lung injury. We find in vitro that PMA stimulates respiratory burst but not lysozymal enzyme release in sheep PMN's. To study effects on lung hemodynamics and fluid balance we infused 5 mcg/kg PMA i.v. into 6 unanesthetized sheep chronically instrumented with lung lymphatic and vascular catheters, and made observations for 6 hours. PMA caused blood leukocyte count to fall from 5250±363 S.E. cells/mm^3 to 2450±224 at 1 hour. Pulmonary artery pressure rose from 14±1 S.E. cmH_2O to 51±3 within 5 minutes and slowly decreased to baseline by 4 hrs. PaO_2 decreased from 90±3 S.E. torr to 59±6 by 15 minutes after PMA. Lung lymph flow tripled initially and remained more than twice baseline for 6 hours while lymph/plasma protein concentration was 0.63±0.02 S.E. at 4-6 hrs. (baseline = 0.64±0.10) suggesting increased permeability. PMA causes initial pulmonary vasoconstriction and later increased lung vascular permeability perhaps by stimulating PMN's to produce superoxide.

(Supported by NHLBI Grant No. HL 19153, SCOR in Pulmonary Vascular Diseases, and NHLBI 00702.)

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HYDROSTATIC PRESSURE ESTIMATES OF PULMONARY CAPILLARY FILTRATION COEFFICIENTS CORRECTED FOR VASCULAR VOLUME CHANGES AND TISSUE ELASTICITY. L. E. Wittmers, Jr.* and J. A. Johnson. Departments of Physiology, University of Minnesota School of Medicine, Duluth, MN 55812 and The Medical School, Minneapolis, MN 55455.

Capillary filtration coefficients, K_f, are measured by an alteration in either capillary hydrostatic pressure or colloid osmotic pressure of the perfusing fluid. Most modern theories dealing with solvent flow across capillary membranes indicate that the K_f determined by alterations in either osmotic driving forces should be the same. However, they are usually not: osmotic changes yield values smaller than those obtained by hydrostatic methods. The experiments presented here were done on isolated Ringer-perfused, rabbit lungs in which a change in capillary hydrostatic pressure was induced to estimate K_f. The organ weight gain and an independent measure of vascular volume (indicator-dilution) were obtained. The results indicate that there is a time-dependent increase in vascular volume, "creep", during the entire period of the elevated capillary hydrostatic pressure. Returning this pressure to control values resulted in a residual organ weight gain associated with a vascular volume that returns to control levels almost immediately. If corrections are made for the increase in vascular volume as well as for changes in the tissue pressure resulting from a finite tissue elasticity, the K_f values obtained from osmotic and hydrostatic methods are equivalent.

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EFFECT OF INFLATION VOLUME ON PROTEIN LEAKAGE ACROSS THE ALVEOLAR BARRIER IN FLUID-FILLED, ISOLATED DOG LUNG. R.L. Conhaim* and N.C. Staub, Cardiovascular Research Institute and Department of Physiology, University of California, San Francisco, CA 94143.

At what lung volume does the alveolar barrier become permeable to protein? We inflated degassed, isolated dog lung lobes with an isosmotic solution of 5% albumin labeled with .02% Evan's blue dye. We inflated two lobes each to a transpulmonary pressure (P_{tp}) of 4, 7, 10 or 14 cmH_2O, corresponding to 25, 50, 75 or 100% of total lung capacity (TLC). We maintained each lobe at constant pressure for 1h, then froze the lobes in liquid nitrogen. We measured perivascular cuff and vascular diameter (100/lobe) from photomicrographs of frozen lungs, and measured cuff protein concentration relative to airway concentration by spectrophotometry (5/lobe). The data are summarized in the table (average only).

TLC (%)	25	50	75	100
P_{tp} (cmH_2O)	4	7	10	14
Cuff Size (relative to TLC)	.04	.08	.36	1.0
Prot Conc (relative to instillate)	.1	.2	.2	.8

Small cuffs with low protein concentration occurred even at the lowest volume and pressure, but significant protein leakage across the alveolar barrier occurred only when P_{tp} was greater than 10 cmH_2O. [Supported by HL25816 (Program Project)].

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TOTAL LYMPH FLOW IN NORMALLY HYDRATED DOG LUNGS.
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The plexiform nature of the pulmonary lymphatics prohibits collection of total lung lymph in a particular experiment. In the present experiment, we calculated the weight of lung tissue drained by cannulated afferent lymph vessels to the left tracheobronchial (subaortic) lymph nodes in 5 dogs. These lymphatics have been shown to contain essentially pure pre-nodal lung lymph. Lymph and plasma samples were collected at half hour intervals for 4 hours after injection of a bolus of ^{125}I-albumin. The volume of tissue fluid drained by the lymphatics was calculated based on the equilibration rate constants for ^{125}I-albumin (b) using relationships in the linear solute flux equation. Tissue blood weight measured using ^{51}Cr labelled red cells was .20±.02 (mean±SE), and extravascular ^{99m}Tc-DTPA (diethylene triamine penacetic acid) space was 2.35±.09 ml/g LFDW (blood free dry weight). Extravascular lung water was 3.92 ±.04 g/g BFDW, and extravascular albumin space was 1.35±.08 ml/g BFDW. Albumin equilibration b values were .352±.059 hrs^{-1}, or a half-time of 1.97 hrs. A volume of 11.6±3.1 ml of tissue fluid, or .32±.04 percent of the post-mortem lung weight was drained by the cannulated lymphatics. This represented a lung lymph flow of .105±.023 ml/min, or .068±.014 ml/min/100g wet weight of lung. Use of these normalized lymph flows permits a comparison of absolute PS products, lymph protein fluxes, protein clearances, and lung protein turnover rates between animals. (Supported by NIH 22549 and 24571.)

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PULMONARY PHOSPHOLIPID CHANGES FROM MECHANICAL HEAD INJURY
David L. Beckman and Daniel J. Crittenden*. Dept. Physiology, School of Medicine, East Carolina Univ., Greenville, NC 27834

The alveolar surface lining may be adversely affected by mechanical head injury with subsequent development of pulmonary edema. Lung injury and associated convulsive seizures from head injury were ameliorated by prior treatment with sympathetic blocking agents. In the present study adult cats were exposed to sudden lethal blow by captive-bolt; controls were given lethal succinyl choline. Excised lungs were rinsed with saline (JAP 43:39, 1977). Minimum surface tension as measured on a surfactometer increased from 5.0±1.1 dynes/cm in 6 controls (C) to 11.6±1.5 in 5 head injury (HI) cats with seizures ($P<0.001$) but was only 6.5±0.9 in HI cats without seizures after HI. Cholesterol values were 0.26±.02 mg/g lung in 8C, 0.45±0.08 in 4 HI cats ($P<0.01$) but only 0.23±0.03 in HI cats without seizures. Total phospholipids were 3.6±0.4 in 8C, 4.7±0.6 in 6 HI cats and 4.1±0.5 in HI cats without seizures. Disaturated phosphatidyl choline was 0.85±0.20 in 5C and 0.97±0.08 in 2 HI cats. The ratios of cholesterol to total phospholipids were 0.09±0.01 in 5 C, 0.11±0.03 in 4 HI cats and 0.06±0.01 in 6 HI cats without seizures. Our results show that cholesterol and surface tension increased only in HI cats with seizures and suggest that the surface tension and phospholipid changes associated with convulsive seizures in head injury may be important factors in the subsequent development of neurogenic pulmonary edema. (Supported by N.C. United Way)

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HETEROPORE POPULATIONS IN NORMAL BULLFROG ALVEOLAR EPITHELIUM.
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Diffusional fluxes of a large number of hydrophilic solutes and water across the alveolar epithelial barrier were measured using the hollow bullfrog (Rana catesbeiana) lung mounted in the Ussing chamber. Lungs were isolated from double-pithed animals and studied as flat sheets. Tracer amounts of radiolabeled solutes and water were added to the upstream reservoir and the rate of change of downstream reservoir radioactivity was monitored. A permeability coefficient was estimated for each substance from a linear relationship between radiotracer concentration in the downstream reservoir and time. These permeability data were used to analyze the equivalent water-filled pore characteristics of the alveolar epithelial barrier using both the Renkin and Levitt approaches. The data reveal that the alveolar epithelium is best characterized by two distinct pore populations (rather than by a single homogeneous population). The large pore population consists of pores with ∿9 nm radius and occupies 3% of available pore area. The small pore population consists of pores with ∿0.45 nm radius and occupies 97% of available pore area. These results confirm an earlier suggestion by Gatzy (Fed Proc 38:2234, 1979). The ratio, number of small pores/number of large pores, is ∿ 10^4. These findings have important implications for interpretation of bulk flow measurements across biological tissue barriers, since hydrostatically- and osmotically-driven water fluxes probably take place largely via separate pathways. (Supported in part by NIH HL26223 and AHA GLAA 654F-2.)

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SUBSTANCE "P" STIMULATES Cl SECRETION BY CANINE TRACHEAL MUCOSA.
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We investigated the effect of the neurotransmitter, substance P, on the electrical and ion transport properties of dog trachea. Posterior mucosal tissues were mounted in Ussing chambers and perfused with Krebs-Henseleit solution, pH 7.4, at 37°C. The solution was gassed with 95% O_2, 5% CO_2. ^{36}Cl and ^{22}Na fluxes were measured under short circuit conditions. Substance P (10^{-7}M) added to the mucosal bath elicited within seconds a rapid rise in short circuit current (SCC) and tissue conductance. Net Cl secretion increased from 1.46 ± 0.41 to 2.85 ± 0.57 μeq/cm².h ($\bar{x}$ ± SE. n=6 P < 0.005). This increase was brought about by enhancement of unidirectional submucosa to lumen flux. Sodium transport of 0.63 ± 0.04 did not change significantly (0.59 ± 0.16). SCC increased from 50 μA/cm² to 63 μA/cm² (P < 0.02), and tissue conductance rose from 1.58 to 2.11 mS/cm² (P < 0.05). These findings suggest that nerve fibers containing substance P might play a role in regulation of ion transport across the trachea. Further, these observations lend support to the recent report of finding substance P-containing nerve fibers adjacent to dog airways and pulmonary vessels (Fed Proceedings 40 (3): 595, 1981) (Supported by the American Heart Association and VA Medical Research grants).

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^{99m}Tc Fibrinogen Imaging and ^{125}I Albumin Distribution Following Canine Lung Contusion.
E. Geller*, A. Carvalho*, B. Khaw*, B.Rajagopalan*, H. W. Strauss*, R.Jones*, L.Reid and W.M.Zapol. Mass. General Hospital, Boston, MA 02114.

To analyse the role of fibrinogen (F) deposition in acute lung injury we I.V. injected 2 to 4mg of ^{99m}Tc human F into 10 anesthetized dogs 15 mins after producing unilateral contusion with a 0.30 "calibre blank. 50 μCi of ^{125}I labelled human serum albumin was injected simultaneously with the F. A second contralateral contusion was produced 105 mins later (90 mins after F injection). Animals were scanned serially with a γ camera for 6 hours and again after 20 hours prior to sacrifice. Excised lungs were scanned, sectioned and counted in a well counter. Only the second contusion was consistently visualized by scanning, not the first. In the central area of the second contusion we found the tissue F counts/g lung to be increased to a ratio of 10.1±5.5 (n=8, mean ± SD) as compared to normal lung. In the first contusion the ratio only increased to 2.3±1 (n=4). ^{99m}Tc counts/g lung were maximal to the center of the contusion and high in the pericontused area as compared to normal lung. The ^{125}I counts/g were lower in the contusion center and normal lung and maximal in the pericontused area. ^{99m}Tc F from the blood stream accumulates rapidly in subsequently contused lung and can be readily located by scanning. The ^{99m}Tc remains in the contusion site for at least 20 hours. Supported by Grant HL23591.

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INFLUENCE OF ADENOSINE TRIPHOSPHATE ON LUNG FLUID BALANCE.
Mary I. Townsley* and W. Jeffrey Weidner. Dept. of Animal Physiology, UC Davis, Davis, CA 95616.

Adenosine triphosphate (ATP) is known to be a potent vasodilator in many vascular beds. Its effect on pulmonary hemodynamics has not been well substantiated and its influence on pulmonary fluid balance has not been examined. In acutely prepared sheep anesthetized with halothane, we studied the effects of ATP (dose range 2.04-3209.1 μg/min, i.v.) on pulmonary vascular resistance (PVR), lung lymph flow ($\dot{Q}_L$), and lung lymph to plasma protein concentration ratio (L/P). Administration of ATP, irrespective of initial dose, produced an initial increase in PVR, concomitant with an increase in $\dot{Q}_L$ and a slight increase in L/P. Subsequent increases in ATP dosage were accompanied by decreases in PVR, slight decreases in L/P while $\dot{Q}_L$ remained elevated. Over the course of a 4 h administration of ATP, $\dot{Q}_L$ increased by a mean of 93% while L/P fell by 5.7% on the average. The doubling of $\dot{Q}_L$ concomitant with slight decreases in L/P suggest that the effect of ATP on pulmonary fluid balance is due to recruitment of the pulmonary microvasculature rather than a change in permeability. (Supported in part by AHA, CA Affiliate No. 80-N105.)

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EFFECT OF AIR EMBOLISM ON THE MEASUREMENT OF EXTRAVASCULAR LUNG THERMAL VOLUME. R.C. Allison*, J.C. Parker, A.E. Taylor. Dept. Physiology, Univ. of South Alabama College of Medicine, Mobile, AL, 36688.

The effect of air embolism on the measurement of extravascular lung thermal volume (ETV) using a double indicator dilution technique was investigated in 10 closed chest dogs. Five ml of iced (0°C) D5W containing 1.5 mg indocyanine green dye was injected into the right atrium. Thermal (t) and dye (d) outflow curves were measured simultaneously in the aorta and used to calculate cardiac output (CO) and mean transit time (MTT). ETV was calculated by: ETV=CO x (MTTt-MTTd). After a control period, two successive right atrial air infusions (E1, E2) were used to maintain constant and increased pulmonary artery pressure (Ppa) and pulmonary vascular resistance (PVR). After the second air infusion, Ppa was allowed to return to control.

	Control	E1	E2	Recovery
PVR (cmH_2O/L/min)	2.0	8.0	15.0	6.0
ETV (ml)	100	37	20	88

In 5 of these dogs, extravascular lung mass (ELM) was determined gravimetrically and closely approximated the final ETV measurement: EVLM=0.93 ETV+35.9 ml (r=0.83). We conclude that measurements of ETV will significantly underestimate ELM under conditions of embolism in which Ppa and PVR are significantly increased above control. (Supported by NIH 22549 and 24571.)

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EFFECT OF CARDIAC OUTPUT ON LUNG FLUID BALANCE IN ALVEOLAR HYPOXIA. A. Jeanneret-Grosjean,* M. Julien,* M.-C. Michoud,* J. Lelorier * and R. Amyot.* (SPON: M. King) Hôtel-Dieu de Montréal, Université de Montréal, Québec, Canada. H2W 1T8.

High altitude pulmonary edema may involve alveolar hypoxia and overperfusion. In a dog model of unilateral hypoxia, we tested the effect of different cardiac outputs (C.O.) on the formation of pulmonary edema. 15 dogs were intubated with a tracheal divider, one lung was ventilated with 100% N_2 and the other with 100% O_2, the PCO_2 maintained at 25 ± 4 mmHg. In group 1 (n = 4) C.O. was not altered. In group 2 (n = 7) C.O. was increased 60% by femoral and carotid arterio-venous fistulae, and expending the vascular volume with saline to obtain a capillary wedge pressure of 12 ± 1 mmHg. In group 3 (n = 4) C.O. was increased 170% by creating a fistula between the aorta and the inferior vena cava. These C.O. were maintained during 4 hours of split ventilation. The shunt fraction was over 50% in each dog indicating that there was no significant hypoxic vasoconstriction in the N_2 lung. The dogs were sacrificed by exanguination. The wet weight-dry weight ratio of individual lobes was not statistically different between the N_2 and the O_2 lungs in either of the groups:

	Group 1:O_2/N_2	Group 2:O_2/N_2	Group 3:O_2/N_2
upper lobes	4.7±0.3/4.8±0.3	5.2±0.3/5.2±0.2	5.1±0.3/5.1±0.2
lower lobes	4.8±0.3/4.7±0.1	5.3±0.4/5.3±0.4	5.2±0.4/5.1±0.3

We conclude that increasing the C.O. by 170% during 4 hours has no effect on lung fluid accumulation in alveolar hypoxia in dogs. Supported by MRC of Canada (#MA-7400).

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ABSENCE OF GRAVITY-DEPENDENT GRADIENT IN ALVEOLAR LIQUID PRESSURES IN ISOLATED EDEMATOUS DOG LUNG. Kenneth C. Beck* and Stephen J. Lai-Fook, Mayo Clinic, Rochester, MN, 55901.

Micropipets were used in conjunction with a servo-nulling system to measure pressures (Pliq) in "free" liquid spaces .1-.5 mm beneath the pleural surfaces of excised dog lung lobes. Lobes were mounted with long axis vertical, held at constant transpulmonary pressure (Ptp), perfused with plasma, and made edematous by raising vascular pressures. Pliq was measured at two sites, near the top and bottom surfaces, and wet (W) and dry (D) weights for the top and bottom thirds of lobes were obtained in two groups of 5 lobes, one at Ptp=5 and the other at Ptp=15 cm H_2O. Means ± SD for Pliq (cmH_2O), the ratios W/D, vertical distance between sites (Δh, cm) and pressure gradient with height (ΔPliq/Δh) were:

		Pliq	W/D	Δh	ΔPliq/Δh
Ptp=5	top	2.4±0.5	6.6±0.9	8.4±0.6	-0.03±0.15
	bottom	2.2±0.9	8.2±0.9		
Ptp=15	top	2.0±1.6	6.3±0.7	10.6±0.7	0.18±0.20
	bottom	3.9±1.4	7.5±0.8		

The ratio W/D was always greater at the bottom than at the top, though Pliq was consistently greater at the bottom only at Ptp=15, reflecting the greater dependence of Pliq on lung liquid at high Ptp. If Pliq reflects pericapillary interstitial fluid pressure (Pi), then there is no significant vertical gradient in Pi due to gravity. (Supported by HL-21584, HL-00674 and HL-06244A from the NHLBI)

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DENSITY OF DOMES IN MONOLAYER CULTURES OF ALVEOLAR EPITHELIAL CELLS. Barbara E. Goodman and Edward D. Crandall. Department of Medicine, University of California, Los Angeles, CA 90024.

Domes formed by isolated epithelial cells from several organs when cultured on plastic or glass have been assumed to indicate active transport of solutes from medium to substratum, with water following passively. We have analyzed the formation of domes by Type II alveolar epithelial cells harvested from rat lungs. The cells were isolated and purified using elastase and differential plating. The culture medium contained gentamycin, penicillin, insulin, thyroxine, and hydrocortisone. No fungicide was used. By 3 days, cells had formed an almost completely confluent monolayer with a large number of domes. The area covered by a dome was variable, ranging from $2x10^3$ μm^2 to $100x10^3$ μm^2. The density of domes at 3 days was 237±49/cm^2. At 4 days, the density had dropped to 147±25/cm^2, with 56±16/cm^2 at 5 days, 72±14/cm^2 at 6 days, and 20±15 at 7 days. No domes and some sloughing of cells were seen at 8 days. When hormones were omitted from the culture medium, domes were observed for up to 14 days. To date, we have not seen domes in similar preparations when trypsin was used to isolate the cells. Domes have been observed previously in monolayer cultures of Type II alveolar epithelial cells grown on plastic and conditioned plastic surfaces (Mason & Williams, ARRD 123:216, 1981). We suggest that primary culture of alveolar epithelial cells may be a useful model for studying the transport characteristics of intact mammalian alveolar epithelium. (Supported in part by HL 26223.)

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OLEIC ACID INDUCED EDEMA IN THE DEXTRAN-SERUM PERFUSED LUNG LOBE. W.F. Hofman and I.C. Ehrhart. Med. Coll. of Ga., Augusta, Ga. 30912.

Various blood components have been implicated in lung permeability edema. We embolized isolated dog lung lobes with oleic acid (OA) during perfusion with a solution nearly devoid of normal blood components. The perfusate consisted of a balanced salt solution containing 6% Dextran and approximately 10% serum by volume from the lobe donor. The ventilated lower left lobe was perfused at constant pressure with the Dextran-serum solution. Each lobe was washed-out with 600 ml of perfusate before recirculation started. Lobe weight changes were continuously monitored as an index of edema formation. Control lobes (n=6) were perfused over a 3 hr. period and averaged a 25% increase in weight with a small decline in perfusate P_{O_2} (134±10 to 124±16 mm Hg) and dynamic lobe compliance (3.6±1.9 to 2.9±1.2 ml/cm H_2O). A second group of lobes (n=5), administered 45 µl/Kg body wt. OA showed a massive weight gain that averaged 125% by 0.5 hr. after OA. Lobe compliance decreased from 4.5±3.3 to 0.5± 0.2 ml/cm H_2O and perfusate P_{O_2} declined from 130±8.0 to 71.4 ±4.0 mm Hg by 1 hr. after OA. We conclude that increased lung vascular permeability associated with oleic acid is not dependent upon normal concentrations of blood cellular and protein components. OA appears to injure the lung directly or release mediators endogenous to lung tissue that enhance vascular permeability. (Supported by American Heart Assoc.-Georgia Affiliate).

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EFFECTS OF PROPRANOLOL-HISTAMINE INFUSION ON PULMONARY HEMODYNAMICS AND LUNG WATER. N.C. Olson*, N.E. Robinson, D.L. Anderson*, and J.B. Scott, Michigan State University, E. Lansing, MI 48824

Local intraarterial administration of histamine is reported to increase microvascular permeability and cause edema in the canine forelimb. During intravenous (IV) infusion of histamine these effects are not seen unless there is concomitant β blockade. Thus, increased blood levels of β agonists during IV histamine antagonize the increased water efflux. In the present study we tested the possibility that this also accounts for the fact that IV histamine causes little or no increase in lung water. In anesthetized dogs cold 3% NaCl was used as the indicator to determine cardiac output (CO), central blood volume (CBV) and lung extravascular thermal volume (ETV_L). Following β blockade with propranolol, histamine (10 µg/kg/min) was administered IV for 90 min. Propranolol decreased CO, increased CBV, mean pulmonary artery pressure ($P_{\overline{PA}}$), pulmonary artery wedge pressure (P_{PAW}), and total peripheral resistance (TPR) but did not change pulmonary vascular resistance (PVR), ETV_L, or mean arterial pressure. Histamine with propranolol further reduced CO whereas $P_{\overline{PA}}$, and P_{PAW} returned to control values. Mean arterial pressure, CBV and TPR decreased, PVR increased, and ETV_L remained unchanged. Postmortem extravascular lung water/dry weight ratio was unchanged. We conclude that the inability of IV histamine to markedly increase lung water is not due to reflex β-receptor stimulation on the microvascular membrane as proposed for the canine forelimb.

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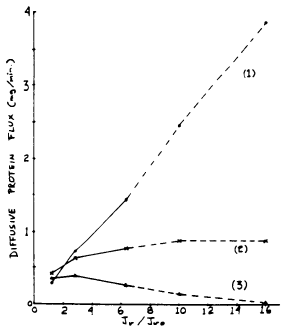
ESTIMATION OF TOTAL PROTEIN DIFFUSIVE FLUX ACROSS PULMONARY CAPILLARIES. A.E. Taylor, R.C. Allison*, and J.C. Parker. Dept. Physiology, Univ. South Alabama, Mobile, AL, 36688.

The diffusive component of transcapillary total protein flux (J_d) was calculated using protein concentrations obtained in plasma and pulmonary lymph at different pulmonary lymph flows (Parker et al, Circ. Res. 48:549-561, 1981). Two estimates were derived from the linear solute flux equation: (1) $J_d=J_p-J_v(1-\sigma)\bar{C}_p$; $\bar{C}_p=(C_p+C_L)/2$ and (2) $J_d=PS\Delta C$. A third was derived from the non-linear flux equation (3) $J_d=J_v(1-\sigma)\Delta C/(e^x-1)$; $x=(1-\sigma)J_v/PS$. Solid lines show calculations using experimentally obtained data, and dashed lines show extrapolation of fluxes to higher lymph flows than obtained experimentally, where PS=.022, σ=0.7, J_{vo}=.02. Only the non-linear equation predicts the expected diffusive flux at high filtration rates where lymph should represent an ultrafiltrate of plasma. Supported by NIH 22549 and 24571.



FEEDING, DIGESTION, NUTRITION

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SELF-SELECTION FROM THREE EQUICALORIC DIETS IN WEANLING RATS WITH HYPOTHALAMIC OBESITY. Lee L. Bernardis, Rafael Luboshitzky* and Larry L. Bellinger.

Weanling male Sprague-Dawley rats received electrolytic lesions in the ventromedial hypothalamus (VMNL rats); sham-operated rats served as controls. For 28 days after the operation VMNL rats selected more ($p<0.05$) from a high-carbohydrate and high-fat ($p<0.01$) but similar amounts from a high-protein diet. Total intake from all three diets, Lee Index (both $p<0.001$) and Lee Index gain/kcal ($p<0.05$) were greater and linear growth and body weight gain/kcal ($p<0.001$) were smaller in VMNL rats. Body weight gains were normal, however. For 14 days, half of the VMNL and control rats were switched to lab chow. Analysis of variance showed a lesion effect for Lee Index ($p<0.001$) and Lee Index gain/kcal ($p<0.01$), for white and brown fat per cent protein (both $p<0.001$), carcass lipid ($p<0.001$) and protein ($p<0.01$) and plasma insulin ($p<0.001$). However, energy intake and body weight gains were similar in all groups. There were also no differences among the groups in plasma glucose, glycerol, total protein and free fatty acids. Availability of a palatable diet immediately after VMN lesion placement in weanling rats will cause hyperphagia that eventually recedes to normophagia. Availability of a less palatable diet (chow) following a palatable diet will not result in a decrease of caloric intake, body weight, obesity and plasma insulin levels.

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WEIGHT, FOOD CONSUMPTION AND BODY LIPID CHANGES IN YOUNG MICE TREATED WITH MONOSODIUM GLUTAMATE AND GOLD THIOGLUCOSE. C. J. V. Smith* and L. Baranowski-Smith* (SPON: L. Nelson). Univ. of Toledo, Toledo, OH 43606

Monosodium glutamate (MSG) and gold thioglucose (GTG) have both been used to induce obesity in young mice (Brecher and Waxler, Proc. Soc. exp. Biol. Med. 70:498, 1949, and Olney, Science 164:719, 1969). The response appears to be initiated by necrosis of the ventromedial hypothalamic area. Many of the physiological changes resulting from the use of these compounds have yet to be determined. This study questioned whether changes brought about by MSG are via the same physiological pathway as GTG and thus, MSG administration might render the animal insensitive to subsequent GTG treatment. Mice were injected with MSG at 5, 6 and 7 days of age and/or GTG at 21 days of age. Subsequent food consumption, weight gain and body lipid content were determined. Saline injected control mice were also examined. Mean body weights of male mice at 100 days of age were: control, 34.1g; MSG, 33.4g; GTG, 40.5g, and MSG+GTG, 37.9g. Food consumption followed the same pattern. Body lipid contents were: control, 10.7%; MSG, 18.7%; GTG, 22.2%, and MSG+GTG, 30.2%. These data indicate that MSG treatment does not appear to inhibit a subsequent response to GTG.

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MATERNAL DIETARY RESTRICTION: EFFECT ON PLACENTAL BLOOD FLOW AND FETAL GROWTH IN THE RAT. R. A. Ahokas*, G. D. Anderson*, and J. Lipshitz* (SPON: K. W. Scheel). Univ. of Tenn. Ctr. Hlth. Sci., Memphis, TN 38163

Maternal cardiac output (CO) and total uterine (UBF) and placental (PBF) blood flow were measured using radioactive labelled 15 μ microspheres in pregnant rats fed 50% of their normal daily intake of food from day 5 to day 14, 20, or 21 of gestation. Dietary restriction caused a 20% reduction in mean fetal weight by day 21 of gestation, relative to controls from dams fed ad libitum throughout gestation. Total CO was reduced 30% by dietary restriction, but CO per unit body weight was unchanged. Mean blood pressure was not significantly reduced, while heart rate was decreased 15%. There was a 60% reduction in UBF and PBF which resulted from both the decreased CO, and a 30% decrease in the percentage of the CO distributed to the uterus and placentas. No such decrease was observed in the distribution of CO to the kidneys or heart in the malnourished dams. The results suggest that maternal malnutrition induced intrauterine growth retardation may be the result of a redistribution of blood away from the placenta reducing the supply of nutrients available for fetal growth.

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NALOXONE (NAL) SUPPRESSES NORMAL FOOD INTAKE (FI) IN CONTROL (CON) BUT NOT DORSOMEDIAL HYPOTHALAMIC NUCLEI LESIONED (DMN-L) RATS. L.L. Bellinger, L.L. Bernardis and F.E. Williams. Dept. Physiol. Baylor Coll. Dentistry, Dallas, Tx. 75246 and V.A. Medical Center, Buffalo, NY. 14215.

Hypothalamic infusions of endorphins stimulate FI while NAL (Endo Lab) suppresses FI in rats. Rats with DMN-L are hypophagic and hypodipsic with a reduced body weight (BW). In trial 1, 22 rats received bilateral DMN-L while 15 rats were sham operated. BW and lengths (BL) were similar at surgery. Post-surgery (2wks) revealed a ($p<0.001$) suppression in BW,BL and mean FI in the DMN-L rats. On days 1-4 the rats were injected with saline (S) and on day 5 with NAL (0.1mg, 1.0mg or 5.0 mg/kg) 30 min prior to lights out. Food was returned at lights out and recorded hourly for 4 hrs. Compared to S, NAL depressed ($P<0.03$) FI in CON during hr 1(0.1mg/kg) and hrs 1 and 2 (1.0 and 5.0 mg/kg). No FI suppression was seen in DMN-L rats. In trial 2, 25 rats were DMN-L with 25 CON. BW and BL were similar at surgery but differed($p<0.001$) postsurgery (11 days). Injections were given as noted in trial 1 (excluding the 5.0 and adding a 2.0 mg/kg dose) and repeated 13 days later. The FI data were similar to trial 1. Water intake (WI) was also measured. At 0.1 mg/kg WI was depressed ($P<0.03$) in hrs 1-2 in DMN-L but not until hr 3 in CON. WI was suppressed to varying degrees in both DMN-L and CON at the higher doses. It is possible that the hypophagia but not the hypodipsia experienced by DMN-L rats may be due to a lesion disruption of an endorphin feeding (BW regulation) system. NSF PCM 76-84381 BCD funds.

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THE EFFECT OF COLD ON NOREPINEPHRINE TURNOVER IN TISSUES OF SEASONALLY ACCLIMATIZED REDPOLLS (Carduelis flammea). Michael Koban* and Dale D. Feist. Univ. of Illinois, Urbana, IL 61801 and Univ. of Alaska, Fairbanks, AK 99701.

The response of the avian sympathetic nervous system during cold exposure was examined by injecting ^{3}H-norepinephrine and estimating norepinephrine turnover rate (NE-TR) in skeletal muscle, heart, liver, and brain of seasonally acclimatized redpolls (a granivorous passerine) in interior Alaska.. Thermoneutral NE-TR (ng NE/g·h) was greater in winter (January) than in summer (July) for muscle (12 ng, +115%) and heart (65 ng, +62%). This may be correlated to higher resting metabolism of winter redpolls. Acute cold exposure (24 h) necessary to increase metabolism 2 X caused increased NE-TR, compared to thermoneutral NE-TR, in muscle (10 ng, +95% in summer; 18 ng, +57% in winter) and heart (99 ng, +117% in summer; 108 ng, +65% in winter). Endogenous NE concentration declined during cold exposure of summer redpolls by a mean of 22% in muscle, liver, and brain, but not in winter redpolls. Thus, sympathetic nerve activity was stimulated by cold exposure in both seasonal groups, but winter acclimatization may involve an increased capacity to maintain steady state NE levels. A peripheral NE injection (2 mg NE/kg BW) in winter redpolls depressed VO_2 (ml O_2/g·h) by a mean of 31% from resting VO_2 (7.2 ml O_2). This may be due to an effect of NE on thermoregulatory centers in the brain. (Supported in part by USPHS NIH Grants ES-00689 and GM-10402)

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INFLUENCE OF PRECONDITIONING ON THE RAT'S RESPONSE TO ELEVATED TEMPERATURE. A. Gwosdow-Cohen*, E.L. Besch and C.L. Chen. College of Veterinary Medicine, University of Florida, Gainesville, FL 32610.

Male, Sprague Dawley rats were housed individually, in metabolic cages, in a controlled environmental room at control (24.5C) followed by exposure to experimental temperature (32.5C) either directly or in a stepwise mode via 29.0C. The animals were exposed to each temperature for 10 days beginning at 24.5C and returning to 24.5C in the reverse order of initial exposure. Relative humidity of 50 ± 2% and a 12L:12D photoperiod (L=0900 to 2100 hours) were maintained for all experiments. Metabolic rate and evaporative water loss were measured using an openflow system; plasma corticosterone by radioimmunoassay. Food and water were available ad libitum but the amounts consumed were recorded daily. The results indicate a significantly ($P<0.001$) elevated plasma corticosterone and metabolic rate in animals exposed directly to heat (32.5C) from control (24.5C) but not in those animals exposed in an stepwise fashion via 29.0C. In addition, exposure to experimental temperatures resulted in reduced ($P<0.05$) relative food intake and increased ($P<0.05$) water intake. Compared to the control condition of 24.5C, evaporative water loss was significantly ($P<0.05$) elevated when the animals were exposed either directly or in a stepwise fashion to 32.5C. These data suggest that the rat's response to elevated temperatures is influenced by preconditioning. (Supported in part by USDA Cooperative Agreement No. 12-16-5-2221).

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THERMAL DEPENDENCE OF ISOMETRIC CONTRACTILE PROPERTIES OF LIZARD MUSCLES. R.W. Putnam and A.F. Bennett*. Dept of Develop & Cell Biology, Univ. of Calif., Irvine, CA. 92717.

The thermal dependence of the isometric contractile properties were studied at 5° intervals from 10-50C in the iliofibularis and gastrocnemius muscles of lizards with different preferred body temperatures (PBT): Dipsosaurus dorsalis (PBT:40C); Cnemidophorus murinus (40C); Sceloporus occidentalis (35C); and Gerrhonotus multicarinatus (25C). Isometric twitch and tetanic tensions were similar and constant over a broad temperature range (as much as 25C) in all species. Tetanic tension declined by 50% at 45-47.5C in Dipsosaurus, 42.5 in Cnemidophorus, and 40C in Sceloporus and Gerrhonotus. The twitch contraction time to peak tension (CT) increased with decreasing temperature from 10ms to 300ms. At any given temperature, the muscles of Sceloporus and Gerrhonotus had faster CTs than those of the other species. CTs were maximal at the maximum test temperature. The maximum rate of tension development with tetanic stimulation (dPo/dt-used as an indicator of contractile speed and tension) was strongly temperature dependent and was maximum at 40-45C in Dipsosaurus, 40C in Cnemidophorus, and 35C in Sceloporus and Gerrhonotus. The time properties of these muscles are highly temperature dependent and contractile tensions are broadly temperature independent. Except in Gerrhonotus muscle, the combination of twitch speed and tension generating capability is optimal at PBT, although neither parameter alone is maximized at PBT. (Supported by grants NSF PCM81-02331 and NIH KO4AM00351 to AFB and an MDA Postdoctoral Fellowship to RWP)

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THERMAL DEPENDENCE OF ISOTONIC CONTRACTILE PROPERTIES OF SKELETAL MUSCLE AND SPRINT PERFORMANCE IN A LIZARD. Richard L. Marsh* and Albert F. Bennett. Developmental and Cell Biology, University of California, Irvine, CA 92717

The thermal dependence of the force-velocity curves of the iliofibularis (IF) muscle was measured at 5 C intervals from 15 to 45 C in the lizard Dipsosaurus dorsalis (preferred body temperature = 40 C). Maximal running velocity (V_R) and limb cycling frequency (f) were also measured using high speed cinematography. At 40 C the IF muscle has a maximal shortening velocity (V_o) of 20 fiber lengths·sec^{-1} and a maximal power output of 500 W·Kg^{-1}. The peak of the power curve is very broad: at least 80% of the maximum power is maintained between 20% and 70% of the maximum isometric force. Muscle velocity and power decrease between 40 and 25 C in a uniform manner (Q_{10}'s = 1.9 and 2.0 respectively). Between 25 and 20 C maximal tension and velocity decline rapidly causing maximal power output to decline dramatically ($Q_{10} \approx 10$). At 40 C Dipsosaurus has a V_R of 4.7 m·sec^{-1} and an f of 13 sec^{-1}. The behavioral performance of the animal is less temperature sensitive than are the properties of the isolated muscle. Between 40 and 25 C the Q_{10}'s of V_R and f are only 1.3. Below 25 C behavioral performance declines markedly. Other factors must act to mitigate against the thermal dependence of the muscle contractile properties to produce more thermally independent sprint performance over a broad temperature range. (Supported by grants NSF PCM 81-02331 and NIH KO4AM00351 to AFB)

COMPARATIVE PHYSIOLOGY: IONIC REGULATION

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EFFECTS OF HYPOPHYSECTOMY ON CHLORIDE METABOLISM OF JUVENILE BOWFIN. Douglas W. Duff*, Robert C. Hanson and Warren R. Fleming. Univ. of Missouri, Columbia, Mo. 65201

Sodium and chloride fluxes and serum electrolytes were followed after hypophysectomy in young of the year bowfin, Amia calva. Hypophysectomy significantly lowered serum and whole-body chloride below those of sham-operated controls but did not significantly reduce serum or whole-body sodium levels. Significant changes in chloride flux rates were observed, both influx and efflux being reduced in hypophysectomized animals, influx being much more drastically reduced. Prolactin (bovine and ovine) significantly elevated whole-body sodium and chloride above that of hypophysectomized saline-injected controls. However, prolactin significantly lowered serum protein levels below those of saline-injected controls. The results suggest survival failure of hypophysectomized bowfin is due primarily to a loss of the animal's ability to balance chloride uptake with chloride loss. (Supported in part by NSF grants GB2379 and GB38808)

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EFFECTS OF SALINITY ADAPTATION ON ACTIVITIES AND SUBCELLULAR DISTRIBUTION OF Ca^{++}-ATPase IN KIDNEY OF A EURYHALINE TELEOST. Byron A. Doneen*. (Spon: C. Gans). Univ. of Michigan, Ann Arbor, MI 48109

The kidney of euryhaline teleosts becomes specialized for absorption of Ca^{++} when fish are adapted to fresh water (FW), whereas renal Ca^{++} reabsorption is reduced in sea water (SW). In Gillichthys mirabilis, total renal Ca^{++}-ATPase activity (assayed at 2 mM Ca^{++}) was higher in FW- than in SW- and 170% SW-adapted fish. Activities of Na^+-K^+-ATPase and succinate dehydrogenase were also increased in Gillichthys kidney following transfer from SW to FW. Total Ca^{++}-ATPase activity in the FW-adapted kidney could be resolved into high- and low-affinity components. Kinetic features of the high-affinity form were analyzed using Ca^{++}-EGTA buffers to obtain free Ca^{++} concentrations of less than 1 µM. $K_{0.5}$ for Ca^{++} was 0.2 µM for high-affinity Ca^{++}-ATPase. $K_{0.5}$ of the low-affinity form was 0.2 mM Ca^{++}. Kidney basolateral membranes and proximal tubule brush border were prepared using conventional ultracentrifugation and Ca^{++}-precipitation techniques. High-affinity Ca^{++}-ATPase was localized predominantly in basolateral membranes, whereas the low-affinity activity was found in both apical and basolateral fractions. Both high and low-affinity Ca^{++}-ATPase activities were stimulated by FW- adaptation, but only the high-affinity form is likely to be involved in enhanced renal Ca^{++}-transport. (Supported by NSF grant PCM-7922985).

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SALT AND WATER BALANCE IN THE INTACT ADULT YUCATAN MINIATURE BOAR FOLLOWING THE ADMINISTRATION AND REMOVAL OF d-ALDOSTERONE (ALDO) AND DESOXYCORTICOSTERONE-ACETATE (DOCA) IMPLANTS. J.M. Terris and R.C. Simmonds*, Dept. Physiol., Uniformed Services University of the Health Sciences, Bethesda, MD., 20014

Adult Yucatan miniature boars (1-1½ years) were housed in 4'X6' metabolic pens, received tap water ad libitum, and were fed a pre-measured quantity of food supplemented with NaCl. Metabolic measurements were taken daily. After 7-10 days of stable baseline measurements, silicone rubber strips (control, with DOCA, or with aldo) were placed subcutaneously under Surital anesthesia. Sodium (Na) balance significantly increased 24 and 48 hr following DOCA ($p<.05,.01$) and aldo ($p<.005,.02$) implantation. A similar increase in water (H_2O) balance was significant only with aldo ($p<.05$). Decreases in red blood cell count and HCT suggest volume expansion. 72 hrs post-implantation Na and H_2O balances were less than control with DOCA but not significantly. The balances were significantly less than control 4 days following aldo implantation ($p<.05$). There were no significant differences in potassium balance. For several days following implant removal there was a significant natriuresis and potassium retention with little change in H_2O balance. We conclude that these animals experience mineralocorticoid escape within 4 days of steroid administration, that there is a slow depletion of whole body potassium stores which is undetectable in these studies, and that there is little chronic change in extracellular fluid volume. Implants were removed 21 days after implantation.

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MICROVILLAR DESIGN IN THE UPPER MALPIGHIAN TUBULE OF RHODNIUS PROLIXUS MAXIMIZES SOLUTE-WATER COUPLING. Timothy J. Bradley. Univ. of California, Irvine, CA 92717

Insect Malpighian tubules are the site of hemolymph filtration and primary urine formation. In the insect Rhodnius prolixus, ingestion of a large liquid bloodmeal necessitates a rapid diuresis in which one half of the body volume is eliminated as urine in 2-3 hours. The upper Malpighian tubule, the site of urine formation by ion and water transport, has been extensively studied as a model system for hormone stimulation of extremely rapid ion and water transport. I have used transmission and scanning EM to examine the microvilli of this region and have found ultrastructural specializations for rapid transport as well. The microvilli are clustered together in bundles consisting of several hundred microvilli. The membranes of adjacent microvilli are held in close proximity by filamentous material, probably glycoproteins. Rather than actually touching, however, the membranes are held a precise distance ($\approx$ 16 nm) apart along the length of the microvilli ($\approx$ 6µm). This arrangement of clustering the microvilli yet maintaining a narrow space between them maximizes "unstirred" layers and solute-water coupling. The three-dimensional organization of the microvillar border and its significance with regard to current models of isosmotic fluid production will be presented. (Supported by NIH grant GM 27919)

NEURAL CONTROL OF CIRCULATION I

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ALTERED ATRIAL MUSCARINIC RECEPTORS RESPONSES TO SYRIAN MYOPATHIC HAMSTERS. Donald D. Lund, Michael J. Mirro*, Janine A. Davis*, Lucy A. Grina* and Phillip G. Schmid. VA Med. Center CV Center, Dept. of Medicine, Univ. of Iowa, Iowa City, IA

Syrian myopathic hamsters (SMH) with progressive cardiomyopathy have reduced cardiac choline acetyltransferase activity, an index of altered cholinergic innervation. The purpose of this study was to determine the electrophysiological responses to isolated right atria (RA) to acetylcholine (ACh) and biochemical differences in hearts of SMH at two stages of cardiomyopathy and control (C) hamsters of similar ages. The effects of ACh on action potential duration 75% repolarization (APD_{75}) in paced (2000 msec) RA are expressed as % decrease in the APD_{75} compared to age matched controls ($\bar{x}\pm SE$, *$P<.05$).

	10^{-8}M	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M	n
SMH-60 day	6±5	27±9	68±7	80±5	88±2	6
C-60 day	8±4	20±4	72±4	86±3	91±2	6
SMH-360 day	8±4	21±8	43±9	61±7*	66±7*	6
C-360 day	7±5	17±1	52±8	76±4	85±3	6

SMH at 360 days exhibit a reduced physiological response to ACh in conjunction with reductions in muscarinic receptor density measured in quinuclidinyl benzilate binding (SMH=106±13* vs C=155+5 fmol/mg prot) and increases in acetylcholinesterase activity (SMH=1.15±0.07* vs C=0.68±0.10 nm/mg prot/min). These data indicate that a significant reduction in the physiological response to ACh occurs in SMH and may contribute to the pathogenesis of cardiomyopathy. (Supported by HL-24246, HL-14388, HL-26021 and IIIA 80-G-21).

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INTRACELLULAR RECORDINGS FROM THE STELLATE GANGLION IN THE CAT - IN SITU. Zeljko J. Bosnjak and John P. Kampine. Med. Col. of Wisconsin and Wood VA Medical Ctr., Milwaukee, WI 53193.

Intracellular recordings were made, in situ, from neurons of cat stellate ganglion (SG) attached via the stellate cardiac nerve (SCN), to the rest of the animal. Cats were anesthetized with sodium pentobarbitol, followed by tracheal intubation and catheterization of the femoral artery and vein. The upper six ribs from the left side were removed and all nerves to the SG except the SCN were cut. The decentralized ganglion was secured in an organ bath and superfused with modified Kreb's solution equilibrated with 97% 0_2 and 3% CO_2. Ganglion cells had resting membrane potentials of -45 to -80 mV. Spontaneous synaptic input from afferent fibers was observed in 31% of the neurons. When peripheral sympathetic afferent input to the SG was increased (by occluding the descending aorta), some of the neurons exhibited an additional increase in the excitatory post-synaptic potentials and/or action potentials. Most of the synaptic input recorded from the ganglion cells had a close relation with the cardiac cycle and/or respiration. These data and our previous studies, support the contention that sympathetic efferent nerve activity can be modified by peripheral excitatory inputs and that these neural connections may function as pathways for a peripheral reflex at the level of the paravertebral ganglion. Supported by NIH grant HL 16511 and the Medical Research Service of the VA.

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RESPIRATORY SINUS ARRHYTHMIA (RSA) AND ASTHMA. Judith Ann Hirsch and Beverly Bishop. Dept. Physiology: SUNYAB; Buffalo, NY 14214

Respiratory heartrate modulation depends on both central coupling of ventilatory and cardiomotor output and feedback from peripheral structures. We hypothesized that in asthmatics pulmonary receptors might be abnormal, and if so, their distorted feedback to central respiratory neurons might be reflected in the RSA. To test this hypothesis we 1) quantified the relationships of RSA amplitude to breathing frequency (F) and tidal volume (V_T) in physically active adults with a documented history of asthma, and 2) compared these relationships to those of active individuals with no history of cardiopulmonary disease. RSA was measured in 7 asthmatic (A) and 11 control (C) subjects, while the subject maintained an assigned V_T (0.5-3 L) at each of several F's (0-45 cpm). Log RSA, normalized to 1 L V_T, was plotted vs. log F (Proc IUPS 14:140, 1980). In both groups, for F <7cpm. RSA was relatively stable: 8 ± 3 bpm/L in A, 21 ± 4 bpm/L in C ($p<0.01$). At higher F, RSA decreased (20 dB/decade). When RSA was plotted vs. V_T the relationship was linear and slopes were 6 ± 1.4 bpm/L in A and 11 ± 3 bpm/L in C. Even though RSA-F relationships were similar in both groups, suggesting an intact coupling between the vital centers, RSA was significantly decreased for any V_T in asthmatic subjects. These observations suggest that the diminished RSA is a reflection of altered peripheral rather than central mechanisms. (Supported by NIH PO1-HL-14414. JAH is an American Lung Association Training Fellow).

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RESPONSES OF VAGAL AFFERENTS WITH ENDINGS IN THE LUNG TO LUNG INFLATION. M.P. Kaufman*, G.A. Iwamoto*, J.H. Ashton*, and S.S. Cassidy. Univ. of Texas HSC, Dallas, Tx 75235

In dogs, inflating the vascularly isolated left lung reflexly decreases cardiovascular function at a threshold pressure of 10 cmH_2O. Afferent fibers responsible for these reflex effects have not been identified electrophysiologically in this model, although they have been found to travel in the left vagus nerve and are believed to be unmyelinated since a similar reflex is evoked chemically by C fiber agonists. To identify the afferents responsible for these effects, we recorded the impulse activity of afferent vagal fibers with endings in the left lung while slowly inflating the lung to 30-45 cmH_2O and maintaining that inflation pressure for 15 min. The threshold pressures at which firing began were:

	n	$\bar{x}\pm SE$(cmH_2O)	range (cmH_2O)
pulmonary C fibers	11	16.7±2.0	6-30
bronchial C fibers	10	28.0±2.4	17-40
slowly adapting receptors	12	5.8±1.5	2-21
rapidly adapting receptors	9	16.3±4.1	5-45

Furthermore, the firing rates of most of the 21 C fibers were increased over baseline levels for the entire 15 min. The threshold pressures of lung inflation at which pulmonary C fibers start to fire closely paralleled those at which the reflex effects occured. Therefore, these afferent fibers are likely to initiate the reflex cardiovascular responses to lung inflation, although bronchial C fibers may also contribute at inflation pressures of 17-40 cmH_2O.

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STIMULATION OF VAGAL AFFERENT FIBERS FROM THE HEART CAN INHIBIT ACTIVITY OF SPINAL NEURONS PROJECTING TO THE BRAIN STEM. Roger Thies and Robert D. Foreman, Dept. of Physiol. & Biophysics, Univ. of Oklahoma HSC., Oklahoma City, OK 73190

We have studied with extracellular microelectrodes the firing of single neurons in the T_2 & T_3 segments of the left spinal cord in chloralose-anesthetized cats, relaxed with i.v. succinylcholine (60 µg/kg/min) or pancuronium (7 µg/kg/min). Vagal effects on the heart were blocked with methylcholine (1 mg/kg). Spinal neurons could be fired by electrical stimulation across the left stellate ganglion and by squeezing skin and muscle of the left foreleg. Most neurons were antidromically activated by stimulation in the nucleus gigantocellularis. We previously reported that stimulation of either left or right cervical vagus (500 µsec pulses of 34 V. at 50 Hz) often inhibited and sometimes excited these spinal neurons. Stimuli with these parameters applied to the right caudal vagus (RCV, or main cardiac branch) inhibited 8 of 19 neurons tested. Two of these were also inhibited by stimuli to left and right cervical vagi, 2 were inhibited by the right but not the left, 3 were unaffected by either cervical vagus, and one was excited by both right and left vagi. Three of the 11 neurons unaffected by RCV stimulation were inhibited from the left cervical vagus. A few neurons fired in response to coronary artery occlusion, and stimulation of RCV inhibited one of these. Stimulation of RCV produces more effective descending inhibition of spinal neurons than stimulation of cervical vagal trunks. (Supported in part by NIH Grant HL22732 and Tulsa Chapt. of Amer. Heart Assoc.)

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VAGAL AFFERENT INFLUENCES ON CARDIAC SYMPATHETICS IN THE RABBIT H.O. Stinnett and M.R. Magnusson*. UNDSM, Grand Forks, ND 58202

The influence of vagal afferents on the reflex decrease in cardiac sympathetic activity during aortic nerve stimulation in the rabbit has received little attention. In five anesthetized rabbits cervical aortic and sympathetic nerves were cut. Carotid intrasinus pressure was held constant at the same normotensive level in each animal during electrical stimulation (60 Hz, 5 v) of aortic nerves. Reflex HR and mean arterial pressure (MAP) responses were recorded during left (L) or right (R) or bilateral (L+R) nerve stimulation. Procedures were repeated following atropine block (5 mg/kg) of vagal efferents and subsequent vagotomy. Atropine block assessed by loss of HR response to acetylcholine. Prior to nerve stimulation control HR = 296 ± 16 (SEM) b/min and MAP = 107 ± 6 mm Hg prior to and 293 ± 12 and 105 ± 7 after atropine; after vagotomy HR = 294 ± 9 and MAP = 126 ± 11. Results of nerve stimulation included:

Condition		(L)	(R)	(L+R)	
Pre-atropine	ΔHR	-84 ± 5†	-51 ± 4†	-118 ± 9†	Results indi-
Post-atropine		-51 ± 6†	-33 ± 4†	- 64 ± 4†	cate a small
Post-vagotomy		-42 ± 6*	-32 ± 5	- 52 ± 4*	significant in-
Pre-atropine	ΔMAP	-65 ± 7	-52 ± 4	- 74 ± 7	fluence of va-
Post-atropine		-58 ± 5	-49 ± 5	- 70 ± 5	gal afferents
Post-vagotomy		-70 ± 7*	-60 ± 7*	- 81 ± 6*	on cardiac

*p < 0.05, †p < 0.01 from prior value sympathetics is lost following vagotomy; which is prominently exhibited during L only and L+R stimulation. (Supported in part by AHA Dak. Aff. Grant-in-Aid 79-606 and Predoc. Fellowship 79-DA-109)

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EFFECTS OF FENTANYL-DROPERIDOL (INNOVAR) ON HEMODYNAMIC RESPONSES TO ACUTE CORONARY OCCLUSION IN INTACT DOG. S.R. Vallance,* T.S. Skinner,* G.E. Billman, C.L. Fischer,* D.C. Randall, C.F. Knapp,* & J.M. Evans.* Dept. Physiol. & Biophys. & Wenner-Gren Lab, Univ. Kentucky, Lexington, KY 40536.

This experiment compares the effect of an acute coronary occlusion (Occ) upon heart rate (HR), mean arterial pressure (BP) n=5, cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR), n=3, in awake vs sedated dog. Innovar (0.4 mg/ml fentanyl & 20 mg/ml droperidol; .05 ml/kg) has a sedative and analgesic action, but does not produce anesthesia per se. Dogs were instrumented with arterial catheters, left ventricular pressure transducers, flow probes on the ascending aorta and inflatable occluders around the left circumflex coronary artery. The experiments were conducted ca 3 weeks after surgery. Data were analyzed for successive 5 min. control (C) and 5 min. occlusion periods (CO, SV, TPR are percent of C):

	Awake		Innovar	
	C	Occ	C	Occ
HR	84 ± 21	129 ± 35	77 ± 14	106 ± 17
BP	101 ± 18	92 ± 21	90 ± 15	81 ± 17
CO	100	105 ± 18	100	102 ± 5
SV	100	68 ± 9	100	75 ± 8
TPR	100	87 ± 9	100	86 ± 6

Many cardiovascular experiments require sedated subjects, though the advantages of using totally awake subjects are widely recognized. These data show that Innovar does not grossly alter the hemodynamic responses to Occ in dog (HL 19343.)

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EFFECTS OF BEHAVIORALLY CONDITIONED CHANGES IN AUTONOMIC TONE ON A-V TRANSMISSION IN DOG. T.L. Skinner,* S.R. Vallance,* D.C. Randall, K.L. Park,* & C.L. Fischer.* Dept. Physiol. & Biophys., Univ. Kentucky Col. Med., Lexington, KY 40536.

This study examines the effect of behaviorally conditioned changes in autonomic tone on cardiac dromotropism in the unanesthetized dog (n=4). The animals were implanted with atrial pacing leads and left ventricular pressure transducers. They were then conditioned during a 2 week recuperative period. These trials consisted of a 30 sec. control period (C) followed by 1 of 2 differing 30 sec. tones: (1) CS+ which was always followed by 30 sec. of food (F); (2) CS- which was never followed by food (NF). Six of each were given each day. The table below lists the average heart rate (HR) for each period with (β) and without (β) β-blockade (propranolol, .5 mg/kg). Trials were also given in which the heart was paced from 120 to 180/min during the first 15 sec. of each period. The table also shows the mean differences in atrial (i.e., pacing) vs ventricular rate:

	Heart Rates						Mean Differences					
	C	CS+	F	C	CS-	NF	C	CS+	F	C	CS-	NF
β	74	83	107	75	75	74	40.4	28.5	6.6	41.7	47.5	43.5
β	81	79	93	79	80	81	31.0	36.6	8.8	29.9	32.2	36.5

Failure of HR or mean difference to change during CS- serves as an experimental control. The data suggest that conditioned increases in sympathetic tone during CS+ increase A-V transmission, whereas during F, decreased parasympathetic tone appears to contribute to the increased dromotropism. (HL19343)

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MYOCARDIAL RESPONSE TO BEHAVIORALLY vs DRUG INDUCED INCREASES IN BLOOD PRESSURE IN BABOON. D.C. Randall, T.L. Skinner* & K. L. Park*. Dept. Physiol. & Biophys., Univ. Kentucky Col. Med., Lexington, KY 40536.

Elevations in blood pressure (BP) increase the load on the myocardium. This research compares the response of cardiac muscle to phenylephrine (PE) vs behaviorally induced pressor episodes. Ultra-sound crystal pairs were implanted on the anterior surface of the left ventricle at the base of the heart, near mid-heart level and at the apex. End-diastolic muscle length (EDL) and systolic shortening (ΔL) were measured as a percent of control. The baboons were classically conditioned by a 1 min. tone (the conditional stimulus or "CS") followed by apple juice (n=2) or a 0.5 sec. electric shock (n=1). BP increased during the CS from a control of 72 ± 3 (mean ± SD) to 81 ± 3 mm Hg. Heart rate (HR) increased from 108 ± 3 to 119 ± 5/min. The IV bolus of PE increased BP from 69 ± 2 to 86 ± 6 mm Hg (i.e., to about the same levels as during CS). HR decreased from 106 ± 8 to 93 ± 10/min. EDL decreased very modestly (< 2%) during the CS; ΔL was essentially unchanged at mid-heart and apex, but increased at the base (112 ± 2%, n=2). EDL increased modestly (< 5%) following PE; ΔL was again essentially unchanged except at the apex where it was depressed to ca 83 ± 3%. Interpretation of these data is complicated by the different HR response and the small "n", but the results are in harmony with the hypothesis that, unlike the PE trials, increases in sympathetic tone during the CS augment myocardial inotropism. (Supported by NIH grant HL 19343.)

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DIFFERENTIAL PATTERN OF SYMPATHETIC DISCHARGE DURING NASOPHARYNGEAL STIMULATION. D.F.Peterson, J.H. Coote*, M.P.Gilbey*, H.A. Futuro-Neto* & S.Fleetwood-Walker*. Univ. of Birmingham Medical School, B15 2TJ, England.

This study investigates directly the possibility that sympathetic discharge to the heart is decreased while it is increasing to other organs during upper respiratory perfusion with cigarette smoke. Blood pressure (BP), heart rate, ECG and respiratory movements were measured in urethane anesthetized rabbits. Insertion of two cannulae allowed respiration of room air while passing smoke across the upper respiratory nociceptors and out through the nares. Through a retroplural incision, the left stellate ganglion was exposed and a cardiac branch isolated. Similarly, a left renal nerve was isolated. Multiunit nerve recordings were obtained from both nerves. In three control animals, cigarette smoke (50ml) caused apnea, bradycardia (-158 b/min) and increased BP (38mmHg). Activity in the renal nerve increased (241% of control (C)) and activity in the cardiac nerve was reduced (65% C). In these animals after flaxadil and artificial respiration, nerve activity responses were similar (renal, 222%C; cardiac, 69% C). In three other baro-denervated animals neural responses to smoke were similar to those observed with baroreceptors intact (renal, 231% C; cardiac, 56%C). These results indicate that smoke stimulation caused a differential pattern of discharge. The responses observed cannot be accounted for by secondary adjustments through arterial baroreceptors, chemoreceptors or pulmonary receptors.

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BAROREFLEX REGULATION OF BLOOD PRESSURE DURING REST AND EXERCISE IN CONSCIOUS DOGS. S.C. Walgenbach* and D.E. Donald. Mayo Medical School, Rochester, MN 55905

This study examined the effect of progressive removal of arterial and cardiopulmonary baroreflexes on the arterial pressure (ABP) of dogs lying at rest for 1 hour and performing brief (3 min) exercise at 5.5 Km/hr at 21% grade. Dogs were studied intact (I), following aortic denervation (II), following aortic denervation and reversible isolation of carotid sinuses at the "operating point" (III), and following acute vagotomy and carotid isolation (IV). The mean and frequency distribution of ABP in the resting dog were not affected by aortic denervation. Inactivation of both arterial baroreflexes (III) significantly increased the variation in ABP. Additional removal of cardiopulmonary reflexes did not cause further lability of ABP in the quietly resting dog. Moderately severe exercise was attended by a steady increase in ABP in conditions I (18 mmHg) and II (20 mmHg). With both arterial baroreflexes inactivated, ABP fell by 25 mmHg at the onset of exercise but increased by the final minute of running to 30 mmHg above resting ABP. The addition of vagotomy did not change this pattern of response. These data indicate that while demonstration of the role of cardiovascular baroreceptors in the control of ABP by acute sequential interruption of the different baroreceptor systems is evident in a relatively stimulus free environment, it is more strikingly displayed during stress such as exercise.
(Supported by NIH Grant HLO 6143.)

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SYMPATHETIC AND PARASYMPATHETIC CONTRIBUTIONS TO THE BARORECEPTOR REFLEX. R.B. Stephenson* and J.W. Osborn* (SPON: H.V. Sparks, Jr.) Michigan State University, E. Lansing, MI 48824.

We studied effects of autonomic antagonists on baroreceptor reflexes of conscious, resting dogs that had been surgically prepared for reversible vascular isolation of carotid sinuses (Stephenson and Donald, Am. J. Physiol. 238: H809-14, 1980). Complete stimulus-response curves were determined for the effect of carotid sinus pressure on mean arterial blood pressure (BP). Control BP in 5 dogs was 101 ± 2 (SE) mm Hg; the carotid baroreflex could raise BP 21 ± 4 mm Hg above and lower it 49 ± 3 mm Hg below control. Propranolol (1 mg/kg) had no significant effect on control BP or stimulus-response relations. Atropine (0.1 mg/kg) increased control BP to 112 ± 4 mm Hg; the baroreflex could raise BP 10 ± 3 mm Hg above this level but could no longer lower it. Phentolamine (2 mg/kg bolus plus 2 mg/min) lowered control BP 5 ± 4 mm Hg and limited by 21% the ability of the baroreflex to raise BP above control. We conclude that, in the conscious, resting dog, parasympathetic activity directed at the heart is the predominant mechanism by which the carotid baroreflex regulates BP but that sympathetic vasoconstriction contributes to reflex increases in BP; there is minimal sympathetic tone to the heart, and the baroreflex does not depend on cardiac sympathetic mechanisms.
(Supported by Michigan and American Heart Associations and NIH grant HL26628)

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CONTRIBUTION OF THE RIGHT AND LEFT VAGI IN THE TONIC AND REFLEX CONTROL OF THE CARDIOVASCULAR SYSTEM. Vernon S. Bishop and Kirk Barron*. The Univ. of Tx. Hlth. Sci. Ctr. SA, San Antonio, TX 78284.

We determined in the conscious dog the relative contribution of afferents in the right and left vagi to the reflex control of heart rate (HR), arterial pressure (AP) and left ventricular dP/dt max (dP/dt). Dogs with aortic nerves cut were instrumented with catheters in the aorta for the measurement of AP, in the left circumflex coronary artery for the injection of veratridine (ic.V), solid state pressure transducer for the measurement of dP/dt and thermodes for reversible cold block of the right vagus (RVB), left vagus (LVB), or both vagi (BVB). The increases in HR (43±6.7 b/min) and AP (13±1.9mmHg) with RVB were greater (P<0.01) than the increases observed during LVB (9±1.8 b/min and 5±1.2mmHg). HR (66±6.6 b/min) and AP (23±3.0 mmHg) responses to BVB were greater than RVB or LVB (P<0.001). Also, the increases in AP during BVB (22±3.1mmHg) was greater than the sum of the increases due to RVB and LVB (P<0.05). Activation of vagal afferents with ic.V. resulted in decreases in HR (-48±8.3 b/min), AP (-44±5mmHg) and dP/dt (-482±68mmHg/sec). RVB but not LVB attenuated the reflex decrease in HR (-8±3.6 b/min), AP (-22±5.2mmHg, and dP/dt (+108±14lmmHg) due to ic.V. (P<0.05). These data indicate that the principle pathway for vagal afferents from the heart and lung is in the right vagus. Furthermore, the data suggests a facilitory interaction between the R and L vagus with respect to the tonic inhibitory influence on AP. (Supported by NIH Grant #HL12415).

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ARTERIAL PLASMA NOREPINEPHRINE LEVELS IN DIFFERENT EXPERIMENTAL ANIMAL PREPARATIONS. T. Shoji*, R.B. Boatwright* and D.M. Griggs, Jr. Dept. of Physiology, University of Missouri Med School, Columbia, MO 65212

Recent emphasis on autonomic neural control mechanisms requires a better appreciation of the circulating norepinephrine (NE) level in different types of animal preparations. In the present study the arterial plasma NE level (pNE_A) was determined by a sensitive radio-enzymatic method in three preparations as follows: 1) the open chest dog anesthetized with morphine and α-choloralose (OCMC), 2) the open chest dog anesthetized with pentobarbital (OCP), and 3) the conscious resting dog (CR). In the latter preparation blood was obtained from a chronically implanted arterial catheter while the dogs were lying quietly. The pNE_A data obtained in the three groups along with concurrently obtained data on heart rate (H.R.) are presented below.

	CR	OCMC	OCP
pNE_A (pg/ml)	174±21 (S.E.)	137±9	265±24*
H.R. (bpm)	102±5	116±5†	140±5*

* OCP>CR and OCMC P<.01 † OCMC>CR P<.01

Regression analysis of the relationship between pNE_A and H.R. within each group revealed statistically significant positive correlations for CR(r=0.68) and OCMC (r=0.45). The findings indicate that 1) relative to the conscious dog, the pNE_A is elevated in the open chest dog anesthetized with pentobarbital but not with morphine and chloralose, 2) there is a close correlation between pNE_A and heart rate in the conscious resting dog but not in the anesthetized open chest preparations.

NEUROBIOLOGY AND NEURONAL BIOPHYSICS

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OCTAMOLAR CONCENTRATIONS OF ATP INCREASE Ca CURRENTS. A. Yatani* and A. M. Brown. (SPON: D. Baker). University of Texas Medical Branch, Galveston, TX 77550.

Extracellular ATP increases cardiac action potential duration, and cardiac contraction by an action on I_S (Goto et al, 1977) and from its effects on smooth muscle it has also been proposed as a purinergic neurotransmitter (Burnstock, J. Physiol., 1981). We examined the effects on I_{Ca} in Helix nerve cells using the suction pipette method of voltage clamp and internal perfusion. Na currents were suppressed by Tris substitution and K currents by Cs substitution, TEA intra- and extracellularly and 4-AP extracellularly. ATP in doses of 10^{-8} M produced small increases in I_{Ca} after about 10-15 minutes. Peak effects (10-25% increases) were observed at 10^{-6} M and at 10^{-3} M small reductions in I_{Ca} could occur. Kinetics were unaltered, effects were voltage independent, partially or fully reversible and reproducible on responsive neurons. About 30% of the neurons tested showed no response and the responsive cells appeared to be F_1, F_2, D_1, D_2 (Kerkut et al, 1975) although other uncatalogued cells also responded. The non-hydrolysable analog of ATP, AMP-PNP gave larger effects. Potential ATP_o blockers, apamin, and quinidine had no significant effects. The nucleotide agonist sequence was AMP-PNP > ATP > ADP. AMP had no effect or produced a small decrease. ATP_o action was blocked by oligomycin, and enhanced by ATP_i or $[c\text{-}AMP]_i$. We conclude that the increase in I_{Ca} produced by ATP_o is linked to intracellular metabolism. (Supported in part by DHHS. NIH Grants #NS-11453 and #NS-13778.

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INTRACELLULAR CALCIUM AND THE DELAYED POTASSIUM CURRENT. Y. Tsuda*, N. Akaike*, A. Yatani*, G. Isenberg*, H. Higashi* and A. M. Brown. University of Texas Medical Branch, Galveston, TX 77550

The delayed K current, I_{KD}, has an N-shaped I-V curve in the absence of any Ca current (Aldrich et al, J. Physiol., 291, 1979). After confirming these results, we examined the effects of buffering intracellular Ca with EGTA upon I_{KD} using Co substitution for Ca extracellularly to eliminate I_{Ca}. The experiments were done on isolated nerve cell bodies of Helix studied under voltage clamp and internal perfusion using the suction pipette method. Na currents were suppressed by Tris substitution and A current was suppressed by using V_H's of -40 mV and/or 4-AP. $EGTA_i$ reduced peak and steady I_{KD} and greatly attenuated or abolished the N-shape with the effects increasing as the dose went from 1-10 mM. At constant Ca_i of 10^{-8} M and doses of $EGTA_i$ of 1-10 mM, the effects were no longer dose-dependent thus excluding a direct action of $EGTA_i$ upon I_{KD}. The effects of $EGTA_i$ were partially reversible with about 70% recovery after 1.5 hours perfusion with 10 mM $EGTA_i$. The remaining I_{KD} was blocked by TEA, leaving a leakage or non-specific current that became voltage- and time-dependent at potentials greater than +50 mV. We propose that Ca is released intracellularly when the membrane is depolarized. The N-shape results because either the release and/or Ca activation of I_K is/are voltage-dependent or because of differences in the inactivation of I_{KD}. (Supported in part by DHHS. NIH Grants #NS-11453 and #NS-13778)

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THEORETICALLY PREDICTED IONIC CURRENT DENSITIES OF A REPETITIVELY STIMULATED XENOPUS NODE IN WHICH ACTIVE TRANSPORT IS LINKED TO FRANKENHAEUSER-HUXLEY KINETICS. G.M. Schoepfle, J.T. Tarvin* and R.M. Martin*. University of Alabama in Birmingham, Birmingham, Al. 35294.

Analysis of repetitive activity is achieved by iterative solutions of the Frankenhaeuser-Huxley equations to which has been linked an active transport term $I_p = g_p(V - E_p)$ where I_p is pumped current density, g_p is pump conductance and E_p is an emf term which is both sodium and ATP dependent. (The Physiologist, 22:113, 1979; 23:111, 1980; Biophys. J. 33:125a, 1981) For any given g_p there exists a unique $(Na_i)_o$ for which net change in (Na_i) vanishes throughout an interspike interval, thereby determining the correct quasi-steady state profile for any variable. All subsequent profiles are invariant. Leak current densities I_{Na} and I_K are roughly mirror image with respect to current-time profile throughout the post spike interval, with magnitude of I_{Na} predominant over that of I_K. However, P_{Na} exhibits a rapid decline relative to that of P_K over the same post spike interval. The maximum for P_K always appears well ahead of the control post spike undershoot. More nearly related to the time course of post spike hyperpolarization are the curves for I_p and nonspecific leak current density I_l. This is to be expected since both are directly proportional to voltage, whereas I_{Na} and I_K involve voltage dependent permeability factors. The sum of all current densities is, of course, equal to -CdV/dt. NIH support.

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CORRESPONDING INCREASES IN INTRACELLULAR POTASSIUM ION ACTIVITY AND MEMBRANE HYPERPOLARIZATION OF IDENTIFIABLE APLYSIA NEURONS DURING HYPOXIA SUGGESTS AUGMENTATION OF ACTIVE TRANSPORT. P.E. Coyer*(SPON: G.M. Schoepfle) Univ. of Alabama in Birmingham, Birmingham, AL. 35294

During exposure to hypoxic bath conditions, neurons occupying the left rostral quadrant (L_2-L_6) of the Aplysia abdominal ganglion hyperpolarize. Increases in intracellular potassium ion activity (a^iK^+) and concomitant hyperpolarization of the membrane potential were measured simultaneously using double-barrel potassium ion-selective microelectrodes. Neglecting contributions involving P_{Cl}, the control P_{Na}/P_K ratio as given by

$$P_{Na}/P_K = \{(K_i)e^{VF/RT} - (K_o)\} / \{(Na_o) - (Na_i)e^{VF/RT}\}$$

is equal to 0.028 ± 0.003 (S.D.) where $(Na_i) = (Na_o + K_o - K_i)$, the membrane potential $V = -49.1 \pm 2.1$ mV and $a^iK^+ = 123.1 \pm 6.9$ mM. (n=7) Substitution of smaller values for (Na_i) yield negligible changes in P_{Na}/P_K. During hypoxia these values were $V = -54.1 \pm 3.6$ mV, $a^iK^+ = 134.6 \pm 1.5$ mM and $P_{Na}/P_K = 0.029 \pm 0.001$. As indicated by these data, there was a hyperpolarization of the membrane potential and increase in a^iK^+ with little change in the P_{Na}/P_K ratio during hypoxia. These results suggest that hypoxia augments the activity of an electrogenic sodium pump. NIH support.

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EXCITATION BY VASOPRESSIN AND ACETYLCHOLINE OF HIPPOCAMPAL NEURONS IN BRAIN SLICES. A. Camacho* and M.I. Phillips, Dept. of Physiology, Univ. of Florida, Gainesville, Florida 32610.

The hippocampus appears to have a role in memory but the mechanism is unknown. From behavioral studies, acetylcholine and the neuropeptide vasopressin have both been proposed to enhance memory. While various reports indicate that acetylcholine excites cells in the hippocampus, reports demonstrating neural effects of vasopressin in the hippocampus are lacking. The purpose of this study was to test the effects of the arginine vasopressin (AVP) on rat hippocampal CA1 cells and test if it interacts with cholinergic agonist carbachol (CBC). In vitro hippocampal brain slices were used where the test substance could be added directly. Rats were decapitated, the hippocampus removed and slices 450 μ thick transferred to a bath containing a modified Yamamoto's solution kept at 36°C. Spontaneous activity of single cells of CA1 was recorded and tested. Results are summarized in the table below:

Substance	n	% Excitation	% Inhibited	% No Effect
Carbachol	84	92	0	8
Vasopressin	21	86	0	14
CBC + AVP	9	100	0	0

Both carbachol and AVP produced excitation in CA1 neurons but the AVP did not modulate the CBC. Atropine blocked the effects of CBC but not of AVP. (Supported by NIH HL27334A-01)

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INHIBITION OF ANGIOTENSIN II PRESSOR EFFECT BY NALOXONE Laurie J. Hoffmann* and M. Ian Phillips. Dept. Physiology, College Medicine, University of Florida, Gainesville, FL 32610.

Angiotensin II (AII) induces a pressor effect when injected into the brain. The pressor effect consists of vasopressin release and sympathetic activation components. Within the brain, alpha adrenergic receptors appear to be involved in this pressor circuit. The present study investigated the possible inclusion of opiate receptors in the pressor circuit. Unanesthetized male rats with chronically implanted catheters in the femoral artery and vein plus cannulae implanted into the third ventricle were tested with a dose range of angiotensin intraventricularly, and Naloxone intravenously. When angiotensin (100ng in 1 μl) was given alone the expected rise in blood pressure occurred (17.5 ± 1.5 mmHg). When Naloxone (0.8mg/kg) was given alone, no change in blood pressure was observed. When angiotensin was given with Naloxone at the same doses a significant decrease in the pressor response was recorded ($p<0.01$). After Naloxone, angiotensin pressor effect was 8.3mm Hg a reduction of 47.4%. This study confirms that opiate antagonism reduces the central effects of AII which the complications of anesthetics. The site of action within the angiotensin pressor circuitry has not yet been defined.
Supported by NIH:RIHL27334A-01 to M.I.P.

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SEROTONIN DECREASES LATENCY AND THRESHOLD TO FEEDING IN PLEUROBRANCHAEA AND INCREASES BEHAVIORAL STATE LEVEL IN PLEUROBRANCHAEA AND APLYSIA. Reinhard A. Palovcik*, Barbara A. Basberg*, and Jeffrey L. Ram. Dept. of Physiology, Wayne State University, Detroit, MI 48201

Serotonin increases behavioral state level and enhances food arousal in Pleurobranchaea. Intact Pleurobranchaea were injected with serotonin (10^{-7} moles/kg body weight) or sea water and observed in an open field apparatus. Serotonin-injected animals consistently changed from quiescent or still states to alert and moving states ($p<.01$). Appetitive and consummatory feeding responses were elicited with a squid extract solution. For animals injected with serotonin, appetitive feeding responses showed significant ($p<.01$) decreases in both threshold and latency. Consummatory responses exhibited similar decreases in latency and threshold but only for higher food extract concentrations ($p<.025$). Serotonin effects and food extract effects on behavioral state were additive.

Aplysia injected with serotonin (10^{-7} moles/kg) showed increases in behavioral state levels from balled and still to alert and moving ($p<.01$). Serotonin also increased the frequency of non-feeding behaviors such as wider opening of the mantle, increase in siphon diameter, and faster locomotion.

Thus, serotonin modulates behavioral state in Pleurobranchaea and Aplysia. Serotonin-enhanced feeding in Pleurobranchaea may be mediated by changes in behavioral state.
(Supported by NIH Grant NS15041 to J.L.R.)

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CORTICAL MECHANISMS OF TWO-DIMENSIONAL AIMED ARM MOVEMENTS. VII. EFFECTS OF SPATIAL CERTAINTY. John F. Kalaska*, Joe T. Massey*, Roberto Caminiti*and Apostolos P. Georgopoulos. Dept. Physiol., Johns Hopkins Un. Sch. Med., Baltimore, MD 21205.

Trajectories of arm movements are less variable when aimed consecutively rather than intermittently at a given target (J.F. Kalaska et al., Fed.Proc. 39: 601,1980). This suggests that neural processes involved in their generation may be less variable under these conditions of spatial certainty. We investigated this problem by recording the activity of 76 single cells in the motor cortex of two monkeys while the animals performed in spatially certain and uncertain tasks in a two-dimensional step tracking apparatus described previously (ibid.). The activity of each cell was studied under both conditions: in the "certain" condition one of 8 possible targets was presented repeatedly before switching to another target, whereas in the "uncertain" condition the target changed from trial to trial in a pseudorandom sequence. The neuronal response was determined during the reaction and movement times, and the results were evaluated using analysis of variance. It was found that for both the reaction and movement time the variability of the cell response was smaller and its relations to the direction of movement stronger under the spatially certain condition. These results indicate that increased spatial certainty of target location results in more consistent and less equivocal motor commands, as predicted by the behavioral studies mentioned above. (Supported by USPHS Grant 5-RO-EY03167-02 and NS-7226-11).

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SYSTEMATIC ERRORS IN AP STEREOTAXIC COORDINATES IN RAT BRAINS. Joseph Kline* and Kenneth H. Reid. University of Louisville, Louisville, Kentucky 40292.

Errors in AP stereotaxic placements were evaluated for contributions of individual and strain differences in rats. In 14 Long-Evans rats (300 g) the interaural line (IAL) to bregma distance was 4.6 to 6.6 mm (mean 5.27 mm). The actual intracerebral sites of injections made at bregma ranged from 4.8 to 5.8 mm (mean 5.38 mm) anterior to IAL on sections from the atlas of Pellegrino and Cushman (1967). This atlas shows bregma as 5.8 mm anterior to IAL for Long-Evans rats of this weight. Hence, our Long-Evans rats showed a consistently shorter IAL-injection site distance than that predicted using the Pellegrino-Cushman atlas. In addition, there was a substantial individual variation in the IAL-bregma distance. Differences between strains were even more marked. When matched with corresponding sections from the Pellegrino-Cushman atlas, sections of dye-injected brains from 11 Sprague-Dawley-Cox rats yielded a linear relationship ($r = .988$) between the true AP coordinate and the atlas-predicted coordinate. Use of the formula

Atlas AP coord = 1.312 (true AP coord) + 0.284

has permitted us to markedly increase the accuracy of our stereotaxic placements in Sprague-Dawley-Cox rats.

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Kinetic study of ocular dominance

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It has been demonstrated that ocular dominance can be accomplished by a number of physical and surgical manipulations. The mechanism, however, is still unknown. More recently the sensitive period can also be prolonged or shortened by appropriate chemical induction. This study is specially focused on kinetic evaluation of ocular dominance. Taking the normal rate of specialization of neurons as unit, the relative rates of synaptic formation are 1.33-1.42 for monocular exposure, 2.2 for reversal, 1.06 for strabismic operation, and 0.4-0.58 for chemical induction at the age of four weeks. The relative rates of specialization of synapses in reversal are 2.2, 1.0, 0.52 and 0.27 for 28, 35, 42, and 49 days of age respectively, and that for strabismic operation are 1.06, 1.04 and 0.5 for 28, 35 and 49 days of age respectively. The rate for ocular rotation in adult cats is in the range of 0.033 to 0.18. In general, the change in relative rate is inversely proportional to age. No comparative study in chemical induction has been made with this respect.

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CHANGES IN THALAMIC NOCICEPTION BY MORPHINE ADDICTION IN RATS. R. Emmers. Dept. of Physiol., Coll. of P & S, Columbia U., New York, N.Y. 10032

Rats on the addiction schedule of Kerr and Pozuelo (Mayo Clin. Proc. 46:653) were used at intervals for acute electrophysiological experiments. After an i.p. injection of chloralose-urethane, nociceptive neurons were localized in the n. VPL of the thalamus, and responses evoked from individual neurons by single-pulse stimulation of the sciatic nerve were accumulated in a digital computer. The computer registered a burst of spikes followed by a silence of 130-140 msecs, and a single-spike activity at 70-90 msecs, all occurring within a 500-msec scan. The burst of spikes indicates the intensity of a sensation (I spikes); the intervals between the late spikes represent the sensory modality (M spikes). One M-M interval is necessary and sufficient to arouse pain via the nociceptive system (Emmers, R. PAIN. Raven Press, 1981). From day 14 of the schedule, the following changes took place. 1) No M-M intervals were seen until 6 hrs after the last morphine dose. 2) The stimulus threshold for the late spikes dropped rapidly, and at 54 hrs of morphine withdrawal, innocuous stimuli (single taps applied to the foot) produced an M-M interval. 3) Morphine given at a dose sufficient to erase M-M intervals in non-addicted rats facilitated the appearance of additional M-M intervals in addicted rats, indicating that a small dose of morphine may cause a greater discomfort during withdrawal than none at all. (Aided by DA-2916-01 from NIDA).

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DOES THE FOOD DYE ERYTHROSIN B AFFECT TRANSMITTER RELEASE? David F. Wilson, Shawn McMahon*, and James S. Tweddell*. Department of Zoology, Miami University, Oxford, Ohio 45056.

Recent investigations have suggested there is correlation between certain food dyes and behavioral changes in animals and humans. Included in this list is the food dye erythrosin B. In the frog, it has been reported that this food dye can induce a large increase in miniature end-plate potential (MEPP) frequency (Augustine and Levitan, 1980, Science 207:1489-1490) at the neuromuscular junction and hence supports the view that this food dye can alter neuronal activity and could contribute to behavioral changes. The influence of erythrosin B on phrenic nerve activity in the isolated rat diaphragm was examined using intracellular recording techniques. Concentrations of erythrosin B ranging from 10 μM to 100 μM were tested. The mean MEPP frequency was 2.0/sec in control, 2.7/sec in 25 μm erythrosin B, 4.2/sec in 50 μM and 8.2/sec in 100 μM erythrosin B. Hence the influence of this food dye on spontaneous release was minor. The influence of 50 and 100 μM erythrosin B on evoked transmitter release was also examined. End-plate potentials (EPPs) and MEPPs were examined in the cut muscle preparation of the rat diaphragm in the presence and absence of the dye. Erythrosin B did not significantly affect the amplitudes of the EPPs or MEPPs, and it did not alter quantal release. These results do not support the suggestion that erythrosin B has a major effect on neuronal activity.

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CORONARY ARTERY CAPACITANCE. Jinku Lee*, James M. Downey and David E. Chambers* University of South Ala. 36688

We examined capacitance function in the coronary artery. When the left coronary artery was perfused with constant pressure, the onset of diastole was accompanied by a capacitive overshoot in flow with an exponential decay back to a steady-state. Time constants for that decay ranged from 55 ms when tone was present to 105 ms with maximal dilation. Since the transient resulted from a fall in tissue pressure, this represents an estimation of intramural artery capacitance only. Because transients in perfusion pressure, which would also affect epicardial arteries, yielded similar time constants, most of the coronary capacitance resides in the small intramural vessels. Computer models were then built which included 1) only small vessel capacitances (SVC), 2) only vascular waterfalls (VW) and, 3) both SVC and VW. Only Model 3 was capable of reproducing the phasic flow patterns as were actually seen in the dog. Another important difference was that Model 3 predicted that at constant flow perfusion, such as occurs with a large stenosis in the perfusion line, the plot of phasic perfusion pressure against mean perfusion pressure should break below a critical perfusion pressure. Such behavior was observed in the dog hearts. We conclude that 1) most of the coronary capacitance is at the small vessel level and, 2) that only a model which includes both SVC and VW can accurately describe coronary hemodynamics.

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CORONARY CRITICAL CLOSING PRESSURE CORRECTED FOR CORONARY CAPACITANCE EFFECTS. James Downey, Jinku Lee* and David Chambers.* University of South Alabama, Mobile, AL 36688

Measurement of critical closing pressure (CCP) in the coronary artery by the long diastole method may be artifactually high due to coronary artery capacitance. To eliminate capacitance back flow, we perfused the coronary artery of an open chest dog at a constant starting pressure. At selected intervals the AV blocked heart was arrested by discontinuing pacing. After the heart had stopped, the perfusion pressure was abruptly changed to a second pressure. The flow record showed a transient overshoot with a decay back to a steady-state flow within 200 ms. This procedure was repeated using the same starting pressure, and thus the same state of vascular tone, but a different new pressure each time. The flow 200 ms after the transition is assumed to be free of capacitance flow and was thus plotted against the second pressure and a pressure-flow curve was generated for each heart. When the starting pressure was 130 mmHg (high tone) a CCP of 27 $\pm$ 6 mmHg was calculated. When the starting pressure was 50 mmHg (maximal dilation), the CCP fell to 18 $\pm$ 4 mmHg. When CCP was determined by a long diastole in those same hearts, CCP was 39 $\pm$ 11 mmHg with high tone and fell to 23 $\pm$ 4 mmHg with maximal dilation. The results indicate that CCP as determined by a long diastole is artifactually high, but that CCP is still a function of tone.

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TRANSMURAL VARIATIONS IN MYOCARDIAL BLOOD FLOW DURING REACTIVE HYPEREMIA. H. Fred Downey, George J. Crystal, and Fouad A. Bashour. Departments of Physiology and Internal Medicine and Cardiovascular Research Laboratory at Methodist Hospital, University of Texas Health Science Center at Dallas, Texas 75235

Dynamic transmural distributions of myocardial blood flow during reactive hyperemia were studied in 10 anesthetized open-chest dogs. The left anterior descending coronary artery was occluded for 90 sec. Total coronary flow was measured with an electromagnetic flowmeter, and its transmural distribution was determined from regional uptake of 9-10 μm radioactive microspheres injected into the left atrium. Microspheres were injected at: (1) 2 sec pre-release; (2) release; (3) peak hyperemia; and (4) 50% recovery of tone. Endo/Epi ratios (R) of myocardial radioactivity were computed. Results indicate early preferential flow to subepicardium (R_1 = 0.51±0.08; R_2 = 0.78±0.07); transmural uniformity of flow at peak hyperemia (R_3 = 1.02±0.08); late preferential flow to subendocardium during recovery (R_4 = 1.66±0.12). The delay to peak total coronary flow following a brief occlusion appears to be predominantly the result of delayed subendocardial reperfusion. This may also account for the slower recovery tone in subendocardial vessels. (Supported by NHLBI Grant HL-21657 and the Cardiology Fund)

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EFFECTS OF THEOPHYLINE ON ADENOSINE AND CORONARY VASCULAR RESISTANCE DURING INCREASED CARDIAC WORK. J.E. McKenzie, R.P. Steffen, R.B. Price*, and F.J. Haddy. Dept. Physiology, Uniformed Services University, Bethesda, MD 20014

The influence of intracoronary theophyline (Theo) infusion on myocardial adenosine (Ado) content, coronary sinus Ado concentration, Ado output and coronary vascular resistance was studied during isoproterenol infusion. Theo was infused at 19 μmoles/min via a modified Gregg cannula (n=5). In six control dogs, isotonic saline was infused at the same volume rate. Theo block was verified by injecting challenging doses of Ado. In both groups cardiac work was increased by an intracoronary infusion of isoproterenol at 0.764 μg/min. There was no difference in coronary vascular resistance between saline and Theo groups, 0.55±0.07 and 0.45±0.08 mmHg·ml^{-1}·min·100g respectively. Myocardial Ado content increased from 3.4±0.5 to 12.1±4.1 nmoles/g with Theo infusion, which was associated with a twofold increase in coronary sinus Ado concentration from 104.1±9.5 to 228.4±13.3 nmoles/l plasma. There was no change in arterial Ado concentrations; therefore Ado output increased from 121.4±18.8 to 343.4±66.6 nmoles·min^{-1}·100g^{-1} for saline and Theo infusions respectively. The Theo infused group also showed a significant endo/epi ratio(2.8) of myocardial Ado content not seen in the saline group. These data indicate that the failure of Theo to influence coronary blood flow and coronary vascular resistance during isoproterenol infusion may be due to increased Ado concentration, which competes with Theo. (Supported by USUHS Grant #C07635)

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OXYGEN DELIVERY, EXTRACTION, AND CONSUMPTION IN THE REGIONALLY SYMPATHECTOMIZED LEFT VENTRICLE DURING STELLATE STIMULATION. R.B. Boatwright*, T. Shoji*, and D.M. Griggs, Jr. Dept. of Physiology, Univ. of Missouri Med School, Columbia, MO 65212

This study was designed to examine the direct effects of cardiac sympathetic nerve stimulation on myocardial oxygen delivery (MOD), extraction (MOE), and consumption (MVO_2). The posterior region of the canine left ventricle was sympathectomized using a new method of local phenol application. Two weeks later open chest experiments were performed under morphine-chloralose anesthesia. Regional myocardial blood flow was measured with microspheres and oxygen content was measured in arterial and venous blood draining the normally innervated (I) and sympathectomized (Sx) regions. Observations were made in a control state (C) and during stimulation (2-3Hz) of the decentralized left stellate ansae(S). A 3:1 ratio of norepinephrine overflow in I vs. Sx during stimulation was used as a criterion for an acceptable preparation. Mean data obtained in 5 animals are tabulated below.

	MOD (cc/mm/100g)		MOE (A-V/A)		MVO_2 (cc/mm/100g)	
	I	Sx	I	Sx	I	Sx
C	11.9	11.6	.62	.64	7.4	7.5
S	13.0	13.3	.71*	.61	9.3*	8.2
%Δ	12	18	19*	-6	33*	11

* I>Sx (P<0.05) The results reveal an increment in MVO_2 during stellate stimulation that is independent of changes in preload, afterload, and heart rate. This increment in MVO_2 is met by an increase in MOE rather than an increase in MOD.

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MICROSPHERE "LOSS" FROM NONINFARCTED MYOCARDIUM: IMPLICATIONS FOR MEASUREMENT OF CORONARY BLOOD FLOW. N.J.Davenport*, R.E. Goldstein, R. Bolli*, NHLBI and USUHS, Bethesda, Maryland.

Preocclusion microsphere(M) content decreases in ischemic myocardium 24 hours after coronary occlusion(CO). This M loss, a potential source of error in blood flow measurement, has been attributed to dissolution, edema, or infiltration of infarcting tissue. However, we have also observed M loss from ischemic myocardium that is not infarcted. We evaluated persistence of 15 μ M, injected prior to CO, in nonischemic (N) region and risk region (RR) (i.e.,region distal to occluded artery) 4 hours after open-chest left anterior descending(LAD) CO in 11 dogs. Ischemia was documented by low post-CO flows in the RR. Pre-CO M content in RR endocardium (endo) was 21% lower than N endo, indicating M loss; similar evidence of M loss was not seen in RR epicardium (epi) although both RR epi and RR endo had a 4% increase in water content. To determine the distribution of M loss within RR we injected 15μ M prior to closed-chest LAD CO in a second group of 24 dogs. Three days later, RR was divided into infarct and surviving muscle. RR had significant M loss as compared to N epi and endo($p < .01$). M losses were similar in subdivisions of RR (33-45%) and infarct (38%). Thus, in acute ischemia: 1) M loss occurs in ischemic endo by 4 hours after CO; 2) within 3 days M loss occurs uniformly in both infarcted and surviving portions of RR; 3) dissolution, edema, and infiltration of infarcting tissue do not appear solely responsible for M loss.

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ABSENCE OF OVERLAPPING CIRCULATIONS BETWEEN ADJACENT CORONARY ARTERIES. David E. Chambers*, Jinku Lee*, and James M. Downey, University of South Alabama, Mobile, AL 36688

The proposed mechanism for regions of intermediate perfusion between ischemic and normal myocardium is that the circulation of the occluded vessel overlaps that of the patent vessel. To measure this overlap, we separately cannulated and perfused the circumflex (CX) and the left anterior descending (LAD) coronary artery of an anesthetized dog. Radiolabeled microspheres were infused into the CX while fluorescein dye was infused into the LAD. The heart was subsequently removed and sectioned. The perfusion field of the CX was visualized by autoradiography. The developed autoradiograph was then placed over the heart and the field of the LAD was visualized with the aid of a Wood's lamp.The two perfusion fields were then traced on a piece of clear acetate. This procedure was conducted on (1) hearts with both vessels normally perfused and (2) on hearts experiencing LAD occlusions while the microspheres were being injected. The latter was performed to see if coronary occlusion would increase the apparent overlap. In all animals studied, overlap of the two fields never exceeded 1 mm and we conclude that the amount of tissue experiencing overlap flow is negligible in the dog heart.

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CORONARY BLOOD FLOW, REGIONAL MECHANICS AND METABOLISM IN NEWLY COLLATERALIZED PORCINE MYOCARDIUM. J.H. Ngai*, M.A. Matlib*, and R.W. Millard. Dept. Pharmacology & Cell Biophys., Univ. Cincinnati Med. Ctr., Cincinnati, OH 45267

In the pig heart, coronary collateral circulation can be induced during the prolonged imbalance between nutrient supply and tissue demand accompanying chronic progressive coronary artery stenosis. This study examines the relationships among blood flow, cardiac mechanics and mitochondrial function in normal and collateralized myocardial regions. Coronary collateral circulation was induced over 8 weeks in 5 pigs following surgical stenosis of the proximal left anterior descending coronary artery. At the time of study with halothane anesthesia and open chest, myocardial blood flow measured with microspheres was 1.29±0.12 and 1.06±0.12 ml/min/g in epicardium and endocardium of the normal region. In the collateral supplied region, epicardial flow was 0.90±0.17 and endocardial flow was 0.34±0.11 ml/min/g. Regional systolic segment shortening determined by sonomicrometry was 10.5±0.1% in normal regions and 0.7±2.4% of end diastolic length in collateral supplied regions. Despite the marked depression in mechanics, little difference in either function or content of mitochondria isolated from these two regions emerged. The data suggest that the abnormal mechanics in the collateral dependent region are due to blood flow maldistribution, but that energetics as measured in these experiments were not significantly altered.
(Supported in part by NIH grants HL-23558 and -22619 and by Training Grant HL-07382.)

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OCCLUSION OF CARDIAC LYMPH INCREASES TISSUE ACCUMULATION OF ALBUMIN DURING CORONARY ISCHEMIA. **Jerry C. Collins*, Gregory E. Ginn* and Thomas R. Harris. Vanderbilt University, Nashville, TN 37232**

This study was undertaken to measure the effects of lymphatic clearance on the extravascular deposition of albumin during reduced-flow coronary ischemia (RFCI). RFCI was created in anesthetized, open-chest dogs by constriction of a carotid-to-left anterior descending coronary artery (LADCA) shunt. The lymph vessel from the LADCA area was identified by injecting dye into the epicardium, and then was tied shut proximal to the cardiac node. A mixture of the dog's blood containing ^{51}Cr red blood cells and ^{125}I-albumin was then infused over 25 min. In 5 dogs coronary flow was reduced from 44.6±9.9 SEM ml/min to 20.8±4.8. In 5 other dogs flow was allowed to remain at 46.1±7.9 ml/min. Tissue perfused by the cannula was marked by radioactive microspheres. After 2 hr of either RFCI or control, the animal was sacrificed, the heart removed, sectioned and counted. ^{51}Cr was used to calculate extravascular ^{125}I-albumin content. ^{125}I-albumin content in the cannulated segment was normalized to similar activity in the noncannulated segment. Relative ^{125}I-albumin content was significantly increased (2.66±.13 SEM) in RFCI dogs above 2.16±.09 in control. In comparison to similar studies with lymph intact, two-way analysis of variance showed that relative albumin deposition was increased significantly by both RFCI and by lymphatic occlusion. Further, RFCI significantly increased albumin deposition in both groups. We conclude that RFCI increases the blood-tissue exchange of albumin and that lymphatic function can lessen but not eliminate albumin accumulation. (Supported by USPHS. NIH Grant HL-19370)

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CONTRACTILE RESERVE FOLLOWING TWO STAGE CORONARY OCCLUSION. J. X. Thomas, Jr. and J. S. Polakowski*. Department of Physiology, Loyola Univ. Medical Center, Maywood, IL 60153.

Coronary occlusion (CO) preceded by a 15 min period of partial stenosis or "two stage occlusion" (TSO) has been used to limit arrhythmias and early ventricular fibrillation. A previous study from our lab demonstrated that although infarct size was only 50% of that predicted following TSO, the loss in regional function in the ischemic area was not different from that seen in dogs after sudden CO. The purpose of the present study was to determine if contractile reserve of ischemic myocardium is greater following TSO as compared to sudden CO. Pentobarbital anesthetized mongrel dogs were instrumented to continuously measure aortic pressure, left ventricular (LV) pressure, LVdP/dt, segment lengths and wall thicknesses in normal and ischemic myocardium. The LAD was isolated approximately ½ way down its distribution for either type of occlusion. Contractile reserve was assessed by post-extrasystolic potentiation (PESP) using atrial extrastimuli. Regional performance was measured on a beat to beat basis using LV pressure segment length loops. In the normal heart and non-ischemic area, PESP augmented loop areas by 122.33%. One hr after CO, PESP had no effect in the ischemic area. However, 1 hr after TSO, loop areas were augmented with PESP by >100%, although they were significantly less than control. Thus, persistence of active systolic shortening 1 hr after TSO is further evidence that damage from ischemia is less following TSO. (Supported by Chicago Heart Assoc. and E. M. Bane Trust Fund.)

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SUDDEN CARDIAC DEATH AND BARORECEPTOR REFLEXES. G.E. Billman, P.J. Schwartz* & H.L. Stone, Dept. of Physiol. & Biophysics, The Univ. of Okla. HSC, Oklahoma City, OK 73190.

Non-invasive identification of patients at high risk for sudden death (SD) is a critical yet still elusive problem. Fourteen mongrel dogs were chronically instrumented to measure left circumflex coronary flow (LCC), arterial pressure (AP), and ECG. The left anterior descending artery was ligated to produce a myocardial infarction (MI), four dogs died within 72 hrs post-MI. Four weeks after surgery the animals were given bolus injections of nitroprusside (NP, 100 µg/kg) and phenylephrine (PE, 10 µg/kg) to raise or lower systolic AP at least 50 mm Hg. The slope of the R-R interval versus systolic AP relationship was determined by least squares fit linear regression ($r \geq 0.80$). A 2 min occlusion of LCC was initiated at the beginning of the last minute of an exercise stress test (EX) and continued for 1 min after the cessation of E x. Four dogs did not show arrhythmias during the exercise and ischemia test, while the remaining developed ventricular fibrillation. The baroreflex slope was found to be significantly lower (U test, $P < 0.01$) in the animals which developed arrhythmias (4.89±2.0 vs 9.3±1.1, X̄±S.D.). The PE, but not the NP response was also significantly lower ($P < 0.02$). This may indicate a greater vagal component to heart rate control in the SD resistant animals. Control heart rate, AP, and infarct size were not different between the groups. In post-MI patients baroreceptor testing may help to identify sub-groups at high risk for SD. (Supported by NIH grants HL 18798 & HL 07430).

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PLATELET INHIBITION PREVENTS PLATELET-INDUCED MYOCARDIAL ISCHEMIA. C.A. Fisher*, L. Wetstein*, P. Feldman*, J.F. Strauss, A.H. Harken, and V.P. Addonizio. Univ. of Penna., Phila., Penna. 19104

The role of platelets in the induction and propagation of cardiac ischemia remains incompletely defined. We, therefore, evaluated the effects of platelet activation occurring within the coronary circulation and tested the hypothesis that inhibition of platelet function would prevent platelet-induced cardiac ischemia. Normal human platelets were isolated by Sepharose 2B column chromatography; resuspended in Hepes buffer; and added to the perfusate of a Langendorff rabbit heart (platelet counts > 10,000/ul). Without, and with low dose (10 uM) prostaglandin E_1 (PGE_1) a reversible inhibitor of platelet function, immediate and irreversible global cardiac ischemia, as monitored by NADH flourescent photography, ensued (N=4) following platelet activation with thrombin (0.1 to 1 U/ml). Higher doses of PGE_1 (0.1 to 1 mM, N=3) completely prevented this platelet-induced myocardial ischemia. Aspirin, unlike PGE_1, was effective despite its inability to block thrombin-induced platelet aggregation in our in vitro gel-filtered system. We conclude that activation of platelets is sufficient for induction of irreversible cardiac ischemia. The efficacy of aspirin, a cyclooxygenase inhibitor, further suggests that the products of arachidonate metabolism have a fundamental role in the genesis of platelet-mediated myocardial ischemia. (Supported in part by NIH Grants HL 22346 & HL 22315)

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EFFECT OF INHALED LIDOCAINE ON EXERCISE-INDUCED ASTHMA. W.Y. Chen and H. Chai*. National Asthma Center, Denver, CO 80204

To determine whether stimulation of afferent nerve endings in the respiratory mucosa plays an important role in the initiation of exercise-induced asthma (EIA), we used lidocaine to study each of seven asthmatic subjects over two sessions of 10-minute treadmill exercise, with an identical workload in both sessions. Before exercise the subjects inhaled either an aerosol of distilled water or lidocaine hydrochloride (1.5mg/kg), in random order. The median particle size was 7 μm in diameter. In each session, pulmonary functions were measured before aerosol inhalation (baseline), 2-3 minutes after completion of aerosol inhalation (approximately 5 minutes before exercise), and 4-10 minutes after termination of exercise. Our results showed that, with the inhalation of the distilled water aerosol, the mean post-exercise forced expiratory volume in 1 second (FEV-1) and forced expiratory flow during the middle half of the forced vital capacity (FEF 25-75%) were 57% and 43% of the baseline values, respectively. Similarly, after lidocaine inhalation, the mean post-exercise FEV-1 and FEF 25-75% were 54% and 44% of the baseline values, respectively. These data do not support the claim that pre-exercise treatment with lidocaine inhalation reduces severity of EIA. Our results indicate that the neural elements in the respiratory mucosa do not appear to play a major role in the development of EIA.

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EFFECTS OF LOCAL ANESTHETIC ON THE MUSCARINIC RECEPTORS OF AIRWAY SMOOTH MUSCLE. C. Murlas,* J.A. Nadel, and J. Roberts,* CVRI, UCSF, San Francisco, CA 94143 and UCI, Irvine, CA 92668.

To investigate the mechanisms by which local anesthetic may affect the muscarinic receptors of airway smooth muscle, we used in vitro contraction and radioligand binding techniques that we have reported elsewhere. The effects of tetracaine on acetylcholine-induced contraction of trachealis muscle were studied using muscle strips dissected from canine tracheal segments. In the contraction studies, concentrations of tetracaine $\leq 5\times10^{-5}$M produced a parallel shift to the right in the acetylcholine dose-response curve. At higher concentrations, we found a nonparallel shift and a decrease in the maximal response, suggesting noncompetitive antagonism or effects beyond the receptor. These divergent effects were clarified by binding assays for the muscarinic receptors of trachealis muscle using [^{3}H]quinuclidinyl benzilate and particulates made from the muscle. In the absence of tetracaine, the dissociation constant (K_D) was 33±3 pM and the receptor concentration (B_{max}) was 410±34 pM/g protein. At concentrations of tetracaine $>10^{-6}$M, the apparent K_D was increased ($p< 0.01$). At concentrations $\leq 5\times10^{-5}$M, B_{max} was unaffected. However, at concentrations $>5\times10^{-5}$M, B_{max} was reduced ($p< 0.01$). We conclude that at low concentrations, tetracaine acts like a reversible, competitive antagonist of acetylcholine for binding to the muscarinic receptors of airway smooth muscle; and, at higher concentrations, like a noncompetitive or irreversible antagonist. (Supported by NIH Grants HL-07159, HL-24136, and HD-08006)

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EFFECT OF GENERAL ANESTHETICS ON BRONCHOMOTOR RESPONSES. M.J. Holtzman,* B.-E. Skoogh,* H. Hahn,* K. Sasaki,* P. Graf,* and J.A. Nadel. Cardiovascular Research Institute, University of California, San Francisco, CA 94143

We studied the relative sensitivity of components of parasympathetic bronchomotor pathways to depression by general anesthetics. Thirteen dogs were anesthetized initially with chloralose (80-100 mg/kg) and urethane (400-500 mg/kg); bronchomotor responses were assessed by monitoring pressure in a bypassed tracheal segment. We compared reflex bronchoconstriction produced by hypoventilation to bronchoconstriction produced by electrical stimulation of the distal end of a cut vagus nerve. When no additional anesthetic was administered, bronchomotor responses to both types of stimuli increased with time. Small additional doses of anesthetics (thiopental, 1-5 mg/kg; pentobarbital, 1-2 mg/kg; amobarbital, 1-2 mg/kg; or chloralose, 10 mg/kg; each injected at 5-min intervals) decreased the reflex response markedly and reversibly, but the response to motor nerve stimulation was unaffected. Increased doses depressed the responses to both stimuli. Our previous studies showed that barbiturates depress parasympathetic ganglionic synapses (Am. Rev. Respir. Dis. 123:202, 1981); the present studies suggest the central nervous system synapses may be even more sensitive to depression by general anesthetics. (Supported in part by NIH Grants HL-24136, HL-00797, and grants from the American Lung Association of California and Council for Tobacco Research)

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DOSE-DEPENDENT INHIBITION OF COLD AIR-INDUCED BRONCHOCONSTRICTION BY ATROPINE. D. Sheppard,* J. Epstein,* M.J. Holtzman,* J.A. Nadel, and H.A. Boushey. Cardiovascular Research Institute, University of California, San Francisco, CA 94143

We studied whether inhalation of atropine could inhibit cold air-induced bronchoconstriction in a dose-dependent fashion and whether higher doses of atropine would be required than those required to inhibit similar degrees of methacholine-induced bronchoconstriction or to produce a maximal reduction of baseline airway tone. In 7 subjects with asthma we assessed the effects of placebo and of various doses of inhaled atropine (0.13-2.08 mg) on baseline specific airway resistance (SRaw) and on the increase in SRaw produced by 5 min of voluntary eucapnic hyperventilation with subfreezing air. Atropine in doses of 0.13 or 0.26 caused a maximal reduction in baseline SRaw and completely inhibited the increase in SRaw caused by methacholine aerosol (5 breaths, 1.0%) but not the increase in SRaw caused by cold air. Higher doses of atropine inhibited the effect of cold air on SRaw in a dose-dependent fashion. These results suggest that cold air causes bronchoconstriction through vagal pathways and that higher doses of antimuscarinic agents are required to inhibit vagally mediated bronchoconstriction than those required to reduce baseline airway tone or to inhibit the effects of a large dose of an inhaled muscarinic agonist. (Supported in part by NIH Grants HL-24136 and HL-00797, and by the California Air Resources Board, the Council for Tobacco Research, and the Strobel Medical Research Fund of the American Lung Association of San Francisco)

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ASSOCIATION BETWEEN AIRWAY REACTIVITY AND AIRWAY PERMEABILITY TO INHALED ^{3}H-HISTAMINE IN CONSCIOUS SHEEP. W.M. Abraham, L. Yerger*, J.C. Delehunt* and W. Oliver, Jr.* Div. of Pulmonary Disease, Mt. Sinai Medical Center, Miami Beach, FL 33140

The purpose of this investigation was to examine the relationship between airway reactivity (AR) and the permeability of histamine through the airways (AP) in conscious sheep. AR was assessed by measuring the change from baseline in mean pulmonary flow resistance following a controlled 2 min inhalation challenge with 1% histamine, containing 200 uCi/ml of ^{3}H-histamine. The rate of appearance of the ^{3}H-histamine in the plasma during inhalation challenge was used to estimate AP. To perturb the airways, three groups of seven sheep were exposed to either air or O_3 (0.5 or 1.0 ppm) for 2 hrs via an endotracheal tube. AR and AP were determined prior to and 1 day following the exposure. The difference in AR between the pre and post exposure challenge (%Δ AR) was then compared to the change in the rate of uptake of ^{3}H-histamine (%Δ AP) at these respective times. Our results showed that 14 sheep had corresponding increases in %Δ AR and %Δ AP; 4 sheep showed corresponding decreases in %Δ AR and %Δ AP; while only 3 sheep had changes which were divergent. Considering the 21 experiments there was a significant correlation ($r = 0.532$, $p<0.02$) between %Δ AR and %Δ AP. We conclude that changes in AR to inhaled histamine are associated with concordant changes in AP to this agent. These results strongly suggest but do not prove a causal relationship between AR and AP. Supported by NIH Grant HL 07358 and EPRI Contract No. 1373.

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AEROSOL AND PARENTERAL HISTAMINE: EFFECTS ON LUNG MECHANICS IN SHEEP. A.A. Hutchison,* K.L. Brigham, and J.R. Snapper.* Pulmonary Circulation Center, Vanderbilt University School of Medicine, Nashville, TN 37232.

The purpose of this study was to examine the effects of parenteral and aerosol histamine on lung mechanics in sheep. Eleven sheep were chronically prepared with pulmonary arterial (PA) and left atrial (LA) catheters, a tracheostomy, and a silastic envelope in the pleural space. Sheep were studied unanesthetized in a pressure-compensated integrated-flow whole-body plethysmograph, and dynamic lung compliance (C_{dyn}), resistance of the lung (R_L), and FRC were measured. Histamine was infused through PA or LA catheters or given as an aerosol in increasing doses until C_{dyn} decreased by 35%, R_L doubled, or FRC increased by 25%. Parenteral histamine caused a reproducible decrease in C_{dyn}, a variable increase in R_L, and no change in FRC. There were no significant differences between the LA and PA histamine infusions. Aerosol histamine had similar effects to parenteral histamine except some sheep did show an increase in FRC. There was a significant correlation ($r=0.98$, $p < .001$) between the parenteral histamine dose required for a response and the aerosol dose. Among sheep there was a several hundred fold range in responsiveness to either aerosol or parenteral histamine. Repeat studies in 3 animals showed PA histamine infusions to be highly reproducible in a given animal while changes associated with aerosol histamine were slightly less reproducible.

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THE EFFECT OF METHACHOLINE-INDUCED BRONCHOCONSTRICTION ON AIRWAY SITES OF FLOW LIMITATION IN DOGS. Steven N. Mink* (SPON: R.J. King). Univ. Tex. Health Science Center and Southwest Foundation for Res. and Educ., San Antonio, TX 78284.

A retrograde catheter was used to locate flow limiting sites (FLS) during forced vital capacity deflation in 7 opened chest dogs. FLS were located at 42%, 28%, and 12% TLC. Minimal lung volume was determined by helium dilution. FLS were located at baseline (B), after bronchoconstriction by methacholine inhalation (M), and after subsequent bronchodilation with atropine (P). Lateral airway pressure (Ptm') and airway generation number (G#) at these loci, as well as the corresponding values of maximum expiratory flow ($\dot{V}$max) and lung elastic recoil were obtained during each maneuver. The respective (mean ±SD) values of $\dot{V}$max (lps) at the three lung volumes (V_L) were 9.0 ± 1, 6.9 ± 2, and 2.6 ± 2 at B and decreased to 2.7 ± 2†, 1.4 ± 1†, and .26 ± .2† during M. Corresponding values of Ptm' (cm H_2O) which were initially -4.0 ± 2, .4 ± 2, and -2.9 ± 3 became more negative -8.6 ± 6†, -11 ± 2†, and -13.9 ± 7†, during M. During P, $\dot{V}$max and Ptm' returned to baseline. The G# for the respective V_L were initially 2.9 ± 2, 7.6 ± 3, and 4.6 ± 3. During M, FLS locations at 42% and 12% TLC remained unchanged while that at 28% TLC moved downstream into a 4th generation bronchus. These results indicate that during severe bronchoconstriction, despite observed peripheral movement of equal pressure points, the FLS remained proximally located in lobar bronchi. Further, decreasing values of $\dot{V}$max were associated with a more negative Ptm' at the FLS site. (†$p < .05$ from B&P; supported by NIH Award HL 27111)

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THE TIME COURSE OF ANTIGEN INDUCED AIRWAY HYPERREACTIVITY TO HISTAMINE IN ALLERGIC SHEEP: ROLE OF H_2-RECEPTORS. J.C. Delehunt*, L. Yerger* and W.M. Abraham. Division of Pulmonary Disease, Mount Sinai Medical Center, Miami Beach, Fl 33140

The purpose of this study was to: a) document the time course of the increase in airway reactivity to inhaled histamine which follows antigen-induced bronchospasm in conscious sheep and b) determine if an acute depression in H_2-receptor function contributes to this increased reactivity. Five sheep, A. suum sensitive were challenged with 5% histamine(H) aerosol, followed 2 hr later (when mean pulmonary resistance(R_L) had returned to baseline) by an inhalation challenge with A. suum antigen. Subsequent H challenges were performed 2 hr, 1 day and 3 days later. At another time the same protocol was repeated with the exceptions that a) prior to each H challenge, the H_2-antagonist metiamide(3 mg/kg IV) was given (M+H) and b) the initial M+H challenge was performed 1 day prior to the antigen challenge. Mean (± SE) increases in R_L from baseline are presented.

	Prior to	Antigen Challenge + 2 hr	+ 1 day	+ 3 day
H	82 (39)%	212 (47)%	190 (44)%	120 (15)%
H+M	91 (37)%	238 (112)%	187 (56)%	---

Antigen challenge resulted in similar increases in R_L for both the H group (148 SE ± 33%) and the M+H group (191 SE ± 34%). We conclude that in allergic sheep, airway reactivity to H is enhanced up to 1 day following antigen induced bronchoconstriction and that H_2-receptors are functionally depressed prior to antigen challenge and do not explain this enhanced H responsiveness. (Supported by NIH HL 07358 and HL 20989).

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SITES OF AIRWAY RESPONSIVENESS TO HISTAMINE AND METHACHOLINE ADMINISTERED BY AEROSOL OR INTRAVENOUS INJECTION. T. Fuyuki*, H. Inoue*, M.Ishii*, C. Inoue*, N.Matsumoto*, H.Sasaki*, and T. Takishima* (Spon. J. Hildebrandt) Tohoku Univ. School of Med. Sendai, Japan. 980

The effects of histamine (H) and methacholine (M) on central (Rc) and peripheral (Rp) airway resistance were directly measured in anesthetized dogs employing a retrograde catheter for Rc, and a pleural capsule method (J.A.P. 48:982,1980) to detect alveolar pressure for Rp. Rc and Rp were measured at FRC (P_L=5 cm H_2O)by oscillation at 1 Hz. First, a series of increasing doses of H (0.78,3.13,12.5,50, and 200 µg/kg) was injected IV. Rc did not increase until the highest dose was given, whereas Rp showed a steady dose dependent increase, exceeding Rc at 50 µg/kg. Second, H aerosol was inhaled from FRC in a series of three increasing tidal volumes, keeping the total dose of H the same in the three conditions. As after injected H, Rc was little increased, but the increase of Rp was proportional to tidal volume. Third, when M was administered IV, both Rc and Rp showed increases proportional to doses. Finally, inhaled M also caused an increase in both Rc and Rp, although Rp was further augmented as tidal volume was increased. It is therefore suggested that in the dog H mainly increases Rp whether the H is administered systemically or by aerosol, whereas M increases both Rc and Rp. Furthermore, the larger the inhaled tidal volume, the more a pharmacologic aerosol can be deposited in the peripheral airways, and the greater its effect on Rp.

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MAXIMUM EXPIRATORY FLOW-VOLUME (MEFV) CURVES IN THE DIAGNOSIS OF EXERCISE-INDUCED BRONCHOSPASM (EIB). F. Haas and A. Haas (Department of Rehab. Med., N.Y.U. Medical Center, N.Y. 10016).

Diagnosis of EIB is frequently predicated on change in either peak expiratory flow rate (PEFR) or forced expiratory volume at 1 second (FEV_1), parameters that are overly dependent on patient cooperation and effort. In order to assess the most reliably sensitive parameter(s) for detecting EIB we investigated the effects of running on PEFR, FEV_1, forced vital capacity (FVC), the ratio FEV_1/FVC, forced expiratory flow at 25% and 50% VC (FEF_{25}, FEF_{50}), and between 25% and 75% VC(FEF_{25-75}) in 101 subjects. EIB, as assessed by a reproducible post-exercise drop of 5% in one or more of these MEFV parameters, was observed in 60 subjects. Reductions in FEF_{50} and FEF_{25-75} were the most reliably sensitive discriminators of EIB accurately identifying 60% of the group. Despite a general trend for those subjects with more impaired pre-exercise MEFV curves to predict the degree of EIB. Of the 60 subjects, 45 had a history of current or childhood asthma, 10 complained of post-exertional coughing, and 5 denied any respiratory problems or sensations. Three subjects who had complained of post-exertional shortness of breath and coughing had no change in the MEFV parameters on any of 3 separate test occasions. However, these individuals, who represented 5% of the EIB susceptible group, demonstrated marked airflow reduction in the terminal 15% of the MEFV curves. We conclude that, for any given patient, EIB cannot be accurately assessed from a single airflow parameter and that complete MEFV curves should be analyzed.

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AUTONOMIC NERVOUS REGULATION OF CENTRAL, PERIPHERAL AND EXTREMELY PERIPHERAL AIRWAY RESISTANCES AT DIFFERENT LUNG VOLUMES. H. Inoue*, M. Ishii*, T. Fuyuki*, C. Inoue*, N. Matsumoto*, H. Sasaki*, and T. Takishima* (Spon. J. Hildebrandt). Tohoku Univ. School of Medicine, Sendai, Japan 980

We studied the autonomic nervous control of central (Rc), peripheral (Rp), and extremely peripheral (Rep) airway resistance, using a retrograde catheter method together with a pleural capsule method to detect alveolar pressure. Forced oscillation at 1 H_Z was applied to the trachea of anesthetized dogs with the chest widely opened. The relationship of the flow to each resistive pressure difference was obtained to give R. Air flow through the capsule glued onto the multipunctured visceral pleural surface enabled us to estimate Rep, which should reflect mainly the resistance of local bronchioles about 0.5 mm in diameter. Total airway resistance (Rtot) had a minimum (0.85 cm H_2O/L/s) at middle lung volume (V_L) increasing at both high and particularly low V_L. Rep increased curvilinearly as V_L decreased. On the other hand, Rp was unchanged at higher V_L but increased sharply at lower V_L. With the vagus intact, the contribution of Rp to Rtot was 21% at higher V_L (P_L=30 and 10), 39% near FRC(P_L=5) and 63% at low V_L (P_L=2). Vagal stimulation (n=6) increased Rp more markedly than Rc or Rep. Simultaneous stimulation of the stellate ganglia inhibited the increase of Rtot elicited by vagal stimulation by as much as one half; most of the inhibition occurred in Rp. We suggest that Rp is not negligible at any V_L, and that both vagal and sympathetic control of Rp is more extensive than for Rc or Rep.

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DENSITY DEPENDENCE OF MAXIMAL EXPIRATORY FLOW IN DOGS WITH CENTRAL AND PERIPHERAL BRONCHOCONSTRUCTION. R.G. Castile*, O.F. Pedersen*, J.M. Drazen, and R.H. Ingram, Jr. Harvard School of Public Health; and Brigham and Women's Hospital, Boston, MA 02115.

In anaesthetized, vagotomized, intubated, open-chested dogs, we measured lateral and end-hole airway pressures using a pitot-static probe. Volume was obtained as the integral of flow from a dog plethysmograph with frequency response adequate to 10 hz. Equal pressure points (EPP) and choke points (CP) were located before and after 1) partial obstruction of the trachea and 2) intravenous histamine and propranolol. Partial obstruction of the trachea caused flow during the plateau of the maximum expiratory flow-volume curve (MEFVC) to decrease predictably in accordance with the wave-speed equation with the CP remaining in the trachea. The MEFVC plateau was extended to a lower lung volume. At 50% of vital capacity the EPP moved downstream and density dependence remained high. Histamine and propranolol caused the EPP and CP to move towards the periphery and density dependence to decrease. The shape of the MEFVC changed as the plateau was shortened and in some instances abolished. A plateau on the MEFVC could be regenerated by partial obstruction of the trachea. This was accompanied by return of the CP to a more central position and an increase in density dependence. These results support the concept that density dependence is decreased by predominantly peripheral obstruction and increased by central obstruction. (Supported in part by HL14580, HL19170, HL00549, and HL16463)

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SINGLE MOTOR UNIT ACTION POTENTIALS DURING FATIGUE. T.G. Sandercock*, J.W. Albers*, J.A. Faulkner, and P.H. Abbrecht. Departments of Physiology, Neurology, and Physical Medicine and Rehabilitation and the Bioengineering Program, University of Michigan, Ann Arbor, Michigan 48109.

The electromyogram is frequently used to estimate neural activation or localized fatigue in muscle. The purpose of this study was to determine how individual motor unit action potentials (MUAPs) change with fatigue. Single motor units in cat medial gastrocnemius were studied by stimulating isolated ventral roots. Tension was recorded using a force transducer attached to the muscle tendon. MUAPs were recorded using a monopolar needle electrode. The extracellular action potential of a single muscle fiber (FAP) was simultaneously recorded by positioning a microelectrode near an active fiber. The motor unit was fatigued by stimulating at 40Hz for 0.3 sec every sec or continuously at 80 Hz. During stimulation at 40 Hz the MUAPs from all motor unit types showed increased duration and decreased amplitude. The FAP showed a corresponding decrease in amplitude accounting for the observed fall in MUAP amplitude. There was no evidence of blocking (fiber dropout). During stimulation at 80 Hz blocking was observed. Blocking was not seen until the FAP fell to at least 50% of the original value. Changes in MUAP amplitude and shape were variable for different units and showed poor correlation with tension, making this an unreliable measure of fatigue. (Supported by NIH-DE04857)

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FATIGUE IN HUMAN ADDUCTOR POLLICIS. S.A. Esau, Ch. Roussos, R.L. Pardy; McGill University, Montreal,Quebec H3A 1A1 Canada.

The time constant of relaxation(τ) of skeletal muscle prolongs with fatigue. The effect of various fatiguing conditions on τ of human adductor pollicis(HAP) was studied in 4 subjects. With the thumb attached to a strain guage control τ was determined by analysis of tension produced by supramaximal tetanic stimulation of the ulnar nerve at 20Hz. The HAP was fatigued by 1 of 4 protocols: maximum voluntary sustained contractions-ischemic(SCI) or non-ischemic(SCN) or maximum voluntary intermittent contractions(held 3 sec, relaxed 2 sec.)-ischemic(ICI) or non-ischemic(ICN). Stimulation was repeated post fatigue. In all subjects only one test was done per day.

Control τ =42±2(mean±S.D.)msec, without significant inter or intra-subject variation. The τ prolonged under all conditions studied: τ_{SCI}=259±25msec,$p<.005$; τ_{ICI}=133±32 msec, $p<.005$; τ_{SCN}=114±45, $p<.05$; τ_{ICN}=66±5,$p<.005$. Time to fatigue was longer in SCN than SCI ($p<.01$) and ICN than ICI ($p<.01$). τ returned to normal more rapidly post ICN than ICI (2.1±1.6 vs 5.7±1.8, $p<.05$) We have shown that τ of HAP prolongs when fatigue occurs and the degree and duration of this prolongation is influenced by how the fatigue is produced. Supported by: Parker B. Francis Foundation, Royal Edward Laurentian Foundation and Medical Research Council of Canada.

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Fatigability of hypokinetic rat gastrocnemius muscle. R.D. Fell, L.B. Gladden, J. Steffen and X.J. Musacchia, Exercise Physiol. Lab. and Dept. Physiol. and Biophy., Univ. of Louisville, Louisville, KY 40292.

In the hypokinetic rat model (Musacchia, X.J. et. al., JAP, 1980) there is a 20% atrophy of the gastrocnemius within 7 days. This is an investigation of the effects of hypokinesia on fatigability of the gastrocnemius. Male rats (180 g) were suspended with the hind legs non-load bearing. After 7 days rats were anesthetized and the right gastrocnemius exposed, the tendon connected to a myograph transducer to measure isometric tension. The muscle was stimulated indirectly via the sciatic nerve by trains of stimuli (100 msec, 45/min, 50Hz, 0.6 V, 20 min) resulting in a 60% reduction in both hypokinetic and control muscle tension. Fast red fibers (FOG) white fibers (FG) were frozen immediately following 20 min stimulation. Glycogen fell by 35% in FOG fibers in stimulated hypokinetic gastrocnemius compared to resting contralateral muscle. No significant decrease occurred in FOG fibers in control rats. In FG fibers, glycogen decreased (73%) with stimulation in both experimental and control gastrocnemii. Although hypokinetic muscles did not fatigue more rapidly, it appears that fast red fibers derived a greater proportion of their energy from glycogen than did the same fibers from control muscles. Increased dependence on glycolysis agrees with our finding of reduced respiratory capacity in hypokinetic muscles (evidenced by a 12% reduction in citrate synthase activity). (supported by Grad. Council, NIH S07/RR-07153, NASA 2325).

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EFFECT OF HYPOXIA ON DIAPHRAGMATIC PERFORMANCE IN THE DOG. J. Rosso*, S. Sigrist*, and A. De Troyer* (SPON: M. King). Meakins-Christie Labs, Royal Victoria Hosp,McGill Univ.Montreal Canada. H3A 2B4.

Hypoxemia could conceivably lead to diaphragmatic fatigue (JAP 46: 897, 1979). However, its effects on diaphragmatic performance in vivo are still largely unknown. In the present studies, we examined the effects of hypoxia on diaphragmatic performance in 10 adult mongrel dogs. We measured the relationship between the electrical activity of the diaphragm (Edi) and the transdiaphragmatic pressure (Pdi) during spontaneous breathing and during supramaximal stimulation of one phrenic nerve at FRC, at 10, 20, 50, and 100 Hz (force-frequency characteristics) while the dogs were breathing room air or various hypoxic mixtures. Thirty minutes of severe hypoxemia (PaO_2 = 23± 3 mm Hg) did not affect the Edi-Pdi relationship during spontaneous breathing. Similarly severe hypoxemia did not substantially affect the force-frequency characteristics of the diaphragm. During the control period the Pdi generated at 10,20, and 50 Hz was 21 ± 3, 66± 4, and 94 ± 3% of the Pdi generated at 100 Hz (Pdi max), respectively; after 30 min severe hypoxia, Pdi at 10, 20 50, and 100 Hz was 16± 3, 54± 6, 89 ± 8, and 91± 7% of Pdi max, respectively. Prolongation of hypoxia for 3 hours and increasing diaphragmatic work, by means of placing a cast around the rib cage, had no further effect. We conclude that hypoxemia alone has no significant effect on diaphragmatic performance in the dog. (Supported by MRC of Canada).

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O_2 UPTAKE AND LACTIC ACID OUTPUT BY IN SITU MUSCLE DURING PROGRESSIVE ISOTONIC TETANIC CONTRACTIONS. W.N. Stainsby, S.J. Chirtel* and R.W. Barbee*. Dept. of Physiology, College of Medicine, Univ. of Fla., Gainesville, FL 32610

The oxygen uptake ($\dot{V}o_2$) and lactic acid exchange ($\dot{L}$) by the gastrocnemius-plantaris muscle group of the dog were measured during brief submaximal isotonic tetanic contractions. Shortening in the contractions was kept constant while the load was altered by adjusting the stimulation voltage applied to the motor nerve. Incompletely fused tetanic contractions were produced by 200 msec trains of impulses at a frequency of 25/sec. The trains were delivered once a second. Muscle loads were progressively increased at five minute intervals while blood sampling occured during the fourth minute of each load interval. The fifth load was maximal, requiring maximal stimulation voltage to maintain the shortening. $\dot{V}o_2$ during contractions ranged from 8.48 to 170.0 ml/kg min. $\dot{L}$ ranged from -272.6 (uptake) to 687.5 (output) nM/g min. In the average relationships $\dot{V}o_2$ was linearly related to work rate ($\dot{W}$) and $\dot{L}$. Venous Po_2 varied little and at maximal work rates averaged 20.2 ± 1.5 mmHg, suggesting minimal hypoxia and the absence of an anaerobic threshold. It may be inferred that the high oxidative capacity and/or the stimulation parameters precluded the appearance of such a threshold, or that an anaerobic threshold does not exist for isolated skeletal muscle.

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TISSUE PO_2 AND PERFORMANCE OF PAPILLARY MUSCLE. E.W. Kanabus* and W.J. Whalen (SPON: C.W. Smith). St. Vincent Hospital, Cleveland, OH 44115 and Ohio State Univ., Columbus, OH 43210

Progressive reduction of PO_2 has been reported to elicit a graded decline in the tension (T) developed by cardiac muscle in the absence of glycolytic support. It was suggested that this might reflect an adjustment of respiration (VO_2) which could lower O_2 demand during hypoxia (Frezza and Bing, Am. J. Physiol. 231:1620,1976). To evaluate this possibility we measured tissue PO_2 ($Pc O_2$) with microelectrodes in the core of cat papillary muscles (0.9 - 1.4 mm diam.) during driven isometric contractions (6 - 20 min^{-1}, 30° C.). PO_2 of a flowing bath ($Pb O_2$) was lowered from 572 ± 2 Torr (prehypoxia control) until $Pc O_2$ was 0 Torr. In 5 of 6 normal muscles T had not declined when $Pc O_2$ had fallen to 0 - 4 Torr, and actually increased to 102 to 123% of control ($P<0.005$) in 6 of 7 trials in 4 of the muscles. This increase in T was blocked by propanolol and abolished by pretreatment with reserpine. In 10 muscles from reserpinized animals T was 97 ± 4% of prehypoxia control when $Pc O_2$ was 0 - 4 Torr, which occurred at $Pb O_2$'s of 199 ± 28 and 181 ± 50 Torr in muscles contracting at 6 and 12 min^{-1} respectively. The $Pb O_2$-$Pc O_2$ gradient diminished with declining $Pb O_2$, supporting the possibility of reduced VO_2 at PO_2's above that limiting to mitochondrial respiration. We conclude that mechanical performance is maintained until the core is truly anoxic and that catecholamine stores may induce short term enhancement of contractility during brief hypoxic episodes. Support: HL11906, Northeast Ohio Heart Assn., OSU Graduate Sch.

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SITES OF CONTROL OF BLOOD FLOW IN RABBIT TENUISSIMUS MUSCLE. D. Slaaf*, G. Tangelder*, H. Teirlinck* and R. Reneman. Biomedical Centre, Univ. of Limburg, Maastricht, The Netherlands.

In this muscle a simultaneous increase in venous and total muscle tissue pressure - reducing perfusion pressure and transmural pressure - results in arteriolar dilation. The effect was less pronounced in smaller (7-12 μm) than in larger arterioles (15-45 μm) (Reneman et al., MVR 20, 307-318, 1980). In the present study on 6 rabbits, perfusion and transmural pressures were lowered by decreasing arterial pressure (P_a) via aortic occlusion. Four out of 6 muscle preparations showed vasomotion, which was limited to the transverse arterioles (15-35 μm) and the first order side branches. Reducing P_a resulted in disappearance of vasomotion, starting in the larger arterioles. These arterioles dilated to at least the maximal vasomotion diameter. $\bar{P}_a$ at which vasomotion disappeared, ranged from 53-14 mmHg (27 ± 10 mmHg; $\bar{x}$ ± sd; measurements (m): 20). Further decrease in P_a significantly decreased blood flow velocity and caused additional dilation of the initially vasoactive arterioles. The latter was also observed in the 2 preparations without vasomotion. Flow stopped at $\bar{P}_a$ levels between 54 and 14 mmHg (m = 17). This level was 22 ± 7 mmHg (m = 7) in preparations with vasomotion and 30 ± 18 mmHg (m = 10) in those without vasomotion. Higher order arterioles did not show vasomotion or dilation during reduction of P_a, but slightly dilated during reactive hyperemia. These findings indicate that regulation of muscle blood flow mainly occurs in transverse arterioles and their first order side branches.

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THE INFLUENCE OF TEMPORARY ISCHEMIA ON MORPHOLOGY AND CHOLINERGIC INNERVATION OF SKELETAL MUSCLE. Steven S. Segal*, Pedro G. Morales*, and Timothy P. White. Dept. of Physical Education, University of Michigan, Ann Arbor, Michigan 48109.

We tested the hypothesis that temporary ischemia followed by reperfusion would alter the morphology of skeletal muscle and impair its cholinergic innervation. 2 h ischemia (I) was produced in rat soleus (SOL) muscle bilaterally by placing atraumatic clamps on the abdominal aorta and vasculature and ligatures on tendons. Data were compared to data from sham-operated controls (C) and nerve-intact orthotopic SOL transplants (T). All vascular and tendonous attachments were severed in T so restoration of flow was dependent upon de novo revascularization. Groups were studied through 21 days of recovery. At sacrifice the left SOL was assayed for protein content and choline acetyl transferase (CAT) and the right SOL was used for histochemistry. In contrast to regional fiber necrosis in I, virtually complete necrosis occurred in T. Regeneration in both, as evidenced by the appearance of central nuclei, had begun by day 7. SOL mass/body mass and total SOL protein increased above C through day 1 in both I and T. These values fell below C by day 4 in I and by day 7 in T. CAT activities were depressed maximally at day 1 to 25% and 40% of C in I and T respectively, and returned to 65% and 95% by day 21. Reduced necrosis and earlier decline in SOL mass and protein in I compared to T are consistent with differences in the time course of restoration of circulation.

(Supported by Michigan Heart Association)

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EFFECT OF HYPOXIA AND RESISTIVE WORK LOAD ON DIAPHRAM BLOOD VOLUME. N.S. Arora*, D.F. Rochester and B.Y. Croft*. Univ. of Virginia, Charlottesville, Virginia 22908

Blood flow to the diaphragm muscle is increased ten fold when the muscle is contracting against a load. The effect of increased blood flow on intramuscular blood volume and hematocrit (MBV, MHct) was studied in 5 lightly anesthetized dogs subjected to a moderate inspiratory resistive load. Transvenous stimulation of the left phrenic nerve caused the left hemidiaphragm (LHD) to contract vigorously, while simultaneously inhibiting contraction of the right hemidiaphragm (RHD). Hypoxia was induced by inhalation of 16% oxygen. The experimental conditions were imposed for 1 hour, after which samples of LHD and RHD were excised for analysis. Plasma and red blood cell volumes were obtained from intravenously injected ^{125}I labelled albumin and ^{51}Cr tagged RBC. Intramuscular plasma and red cell volumes (MPV, MRBCV) were derived from the activity of ^{125}I and ^{51}Cr in the LHD and RHD samples. MBV was calculated as the sum [MPV+MRBCV] and MHct as the ratio [(MRBCV x 100)/(MPV+MRBCV)]. In RHD, MPV and MBV were .049 ± SD .010 and .088 ± .025 ml/gm wet weight. MHct was 44 ± 7%, the same as body hematocrit. In the paced LHD, MPV was .103 ± .030 ml/gm, MBV .134 ± .026 ml/gm, and MHct 25 ± 7%, all different from RHD values ($P<.05$). The increase in MBV and decrease in MHct in vigorously contracting diaphragm muscle results from increased MPV. This may decrease viscous resistance but increase the diffusion distance for oxygen between RBC and muscle mitochondria. (Supported by Grant #HL-21500-04)

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SARCOMERE SPACING AND MEMBRANE POTENTIAL OF CUT AND INTACT SKELETAL MUSCLE FIBERS. Dennis R. Claflin*, Kevin K. McCully*, and John A. Faulkner. The Bioengineering Program and Dept. of Physiology, University of Michigan, Ann Arbor, Michigan 48109.

Biopsy samples taken from human skeletal muscle for contractile property measurements invariably contain cut fibers. Our hypothesis was that cut muscle fibers function normally except for a damaged, compliant region near the cut end. The resting sarcomere spacing was compared with the sarcomere spacing during a maximum fixed-end tetanic contraction in cut and intact frog sartorius (SRT) muscle and cut mouse gracilis anticus (GRC) muscle. The resting membrane potential of cut and intact fibers from frog SRT muscle and rat diaphragm (DPM) bundles was determined. During a maximum fixed-end tetanic contraction, the sarcomeres of cut fibers were lengthening within 4-5 mm of the cut end for frog SRT and within 5-6 mm of the cut end for mouse GRC. The sarcomeres throughout the remainder of cut fibers of frog SRT or mouse GRC and throughout the length of intact frog SRT shortened during a maximum fixed-end tetanic contraction. We found significant depolarization of the fibers within 9 mm of the cut end of frog SRT and within 6 mm of the cut end of rat DPM. The membrane potentials of intact frog SRT (-86.2 ± 0.5 mV) and rat DPM (-74.4 ± 2.0 mV) did not display regional variation. The depolarization and lengthening of sarcomeres near the cut end of muscle biopsies support our hypothesis that this region is not functioning normally and is adding series compliance to the cut muscle preparation. (Supported by MDA, Inc., and NIH-DE04857)

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CONTRACTILE PROPERTIES OF CUT AND INTACT SKELETAL MUSCLE FIBERS. John A. Faulkner, Dennis R. Claflin*, Kevin K. McCully*, and David A. Jones*. Department of Physiology, University of Michigan, Ann Arbor, Michigan 48109.

Our hypothesis was that isometric and isotonic contractile properties could be measured in vitro on skeletal muscle fibers cut at one or both ends. In in vitro preparations of cut and intact frog and mammalian muscle fibers we measured time to peak tension (TPT), half relaxation time (1/2 RT), maximum rate of tension development (dp/dt), maximum isometric tension of a twitch, and maximum isometric tetanic tension (P_o). Twitch: tetanus ratio (P_t/P_o) and the maximum velocity of shortening at zero load (V_o) were calculated. Compared to intact muscle fibers, the TPT, 1/2 RT, and P_o of cut fibers were not different, but the dp/dt, P_t/P_o, and V_o were lower. The lower dp/dt and P_t/P_o resulted from increased compliance due to damaged sarcomeres near the cut end. No difference in TPT and 1/2 RT, in spite of a slower dp/dt, was due to the rapid decline in the active state. The lower V_o for cut fibers than for intact fibers resulted from an overestimation of the viable fiber length for the preparations of cut fibers. From measurements of sarcomere spacing the sarcomeres 4-6mm from the cut end of fibers lengthen during a fixed-end contraction. After correcting fiber length, the V_o of cut fibers was not different from that of intact fibers. We conclude that valid measurements of contractile properties can be made on cut skeletal muscle fibers. (Supported by MDA, Inc., and NIH-DE04857)

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LENGTH-TENSION PROPERTIES OF THE TWO MUSCLE LAYERS OF THE OPOSSUM DUODENUM. Thomas V. Nowak*, and Sinn Anuras, Dept. of Internal Medicine, University of Iowa, Iowa City, IA 52242.

The longitudinal muscle (LM) and circular muscle (CM) layers of the duodenum differ physiologically and pharmacologically. To further characterize these differences we calculated in vitro length-tension curves for CM and LM strips from opossum duodenum. Muscle strips (2mm x 16mm) cut along the oral-caudal axis were called longitudinal strips; those cut 90° to that axis were circular strips. The strips were mounted in a bath of Krebs solution equilibrated with 95% O_2-5% CO_2 at 37°. Under such basal conditions the strip was subjected to a tension of 0.1g and its length measured (initial length). Each strip was then subjected to tensions of 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 10.0g and its length measured at each level of tension. To determine total and passive forces of the muscle, identical experiments were performed using Krebs solution plus 140mM KCl or calcium-free Krebs solution with 5mM sodium EDTA, respectively. Under basal, active and passive conditions the length-tension properties of LM differed significantly from CM ($p<0.05$). Incubation of LM with either calcium-free or high-potassium Krebs solution caused significant and opposite shifts in the length-tension curve ($p<0.05$). Length-tension properties of CM were affected only by a calcium-free Krebs solution ($p<0.05$). Conclusions: 1) LM of opossum duodenum has different length-tension properties than CM; 2) The two muscle layers differ in sensitivity to extracellular calcium and potassium with respect to length-tension properties.

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EFFECT OF PLASMA ON NOREPINEPHRINE ACCUMULATION IN THE CANINE SAPHENOUS VEIN. William Freas* and Sheila M. Muldoon. Depts. Physiol. and Anesth., USUHS, Bethesda, MD 20014.

The effect of canine plasma on the accumulation and metabolism of ^{3}H-Norepinephrine (NE) in canine saphenous vein was examined. Saphenous vein strips were incubated in ^{3}H-NE (2 x 10^{-7}M) for 30 min in either Krebs Ringer's or Krebs Ringer's solution containing canine plasma in concentrations ranging from 0 to 90%. These plasma solutions resulted in a significant decrease in NE accumulation from 11.2±1.3 to 8.0±1.1 pmoles/mg protein and a significant decrease in the formation of the neuronal metabolite 3,4-dihydroxyphenylglycol from 1.96±0.15 to 1.22±0.08. The O-methylated deaminated metabolites significantly increased to 193% of control values (from 1.94±0.21 to 4.30±0.49 pmoles /mg protein). This metabolite profile is consistent with blockade of neuronal uptake by plasma. Na+ and K+ concentrations were not changed sufficiently to account for this inhibition in ^{3}H accumulation. Canine plasma was boiled (7 min), or dialyzed (8 hrs) and then tested on the saphenous vein. Both treatments resulted in a 50% decrease of inhibitory activity when compared to non-treated plasma controls. Lyophilized plasma following an acetone protein precipitation resulted in a 32.0% decrease of the inhibitory activity as compared to an equivalent volume of unextracted plasma. These results indicate that the inhibition of ^{3}H-NE accumulation by plasma is in part due to a nonprotein component of plasma. Supported by Grants NIH GM25926 and USUHS R07627.

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IDENTIFICATION OF AN α_1-ADRENERGIC SITE IN A SMOOTH MUSCLE CELL LINE. L. E. Cornett* and J. S. Norris* (SPON: P. Rayford), Depts. Physiology-Biophysics & Medicine, Univ. Ark. Medical Sciences, Little Rock, AR 72205.

The DDT_1 smooth muscle cell line was established by explanation from an androgen-estrogen induced leiomyosarcoma occurring in the ductus deferens of a golden hamster. Norepinephrine appeared to increase cell motility in monolayer cultures leading us to examine binding of (^{3}H)-dihydroergocryptine (DHE), a potent α-adrenergic antagonist, to DDT_1 cells. We found that DHE binding to intact cells was of high affinity, saturable, and reversible. The dissociation constants (K_d) for DHE binding to cells in suspension and monolayer cultures were 1.4±0.2 and 1.4±0.3 nM. The number of DHE binding sites, however, was significantly ($P<0.001$) higher in cells grown in suspension (108.1±13.8 fmol/10^6 cells) compared to cells grown as monolayers (46.6±7.0 fmol/10^6 cells). The order of potency of adrenergic agonists in competing for DHE binding to cells grown in suspension was epinephrine (K_i= 0.92 µM)≈norepinephrine (K_i=2.2 µM)>>isoproterenol (K_i=137 µM) and is consistent with an α-adrenergic interaction. Analysis of competition curves with a nonlinear curve fitting computer program using α_1- and α_2-selective antagonists, prazosin (K_i= 0.1 nM) and yohimbine (K_i=90.0 nM), yielded curves consistent with a pure receptor population (>95%) identified as the α_1-subtype. The results indicate the DDT_1 cells will be an ideal *in vitro* model for examining the mechanism of action of α_1-adrenergic receptors. (Supported by NIH AM27450 & AM21458;)

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EVIDENCE FOR A THORACIC AUTONOMIC NEURAL REFLEX BLOCKED BY CHYMOTRYPSIN OR MANGANESE. M. McGill* and J.A. Armour. Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, B3H 4H7.

Ten mongrel dogs weighing 10-25 kg, anesthetized with Innovar and α-chloralose, were intubated, placed on positive pressure respiration and a bilateral thoracotomy was performed. The left sided cardiac nerves, middle cervical ganglion, and vagus were located. Two or three cardiac nerves were placed in an oil bath, desheathed, and laid on bipolar recording electrodes. The thoracic vagus was sectioned above the middle cervical ganglion and the dorsal and ventral ansae subclavia sectioned in order to decentralize the middle cervical ganglion. The thoracic vagus below the origin of the cardiac nerve was stimulated with 5-50 V, 5 msec pulses of varying frequencies. The compound action potentials reflexly generated in small cardiac nerves by these stimulations were not modified by intravenous administration of hexamethonium (5 mg/kg), propranolol (1 mg/kg), Rogitine (1 mg/kg) or atropine (1 mg/kg). Injection of 1 µg of Chymotrypsin into the region of ganglionic cells abolished the reflexly generated compound action potentials for a brief period of time (1-10 sec). Permanent blockade of this reflex was obtained following the injection of 10 mg of Manganese into this same locus. It is postulated that the thoracic autonomic nervous system contains Chymotrypsin sensitive synaptic transmission.

(Supported by the Nova Scotia Heart Foundation.)

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LOCALIZATION OF HORSERADISH PEROXIDASE (HRP) CONTAINING NEURONS IN SYMPATHETIC AND DORSAL ROOT GANGLIA INNERVATING THE MYOCARDIUM IN DOGS. M.A. Moskowitz*, D.D. O'Keefe, M.A. Jacocks*, R.G. Johnson*, G.S. Haas*, G.A. Geffin*, N.T. Zervas*, W.M. Daggett, Massachusetts General Hospital, Boston, MA 02114.

Preliminary studies in 14 dogs were undertaken to determine if middle (MCG), stellate (SG) and dorsal root ganglia (DRG) neurons could be identified after injecting HRP, an axonally transported histochemical marker, into the myocardium. HRP (Sigma Type VI) mixed with pluronics, a liquid polymer, was injected into the myocardial wall along a diagonal branch of the left anterior descending coronary artery. 72 hours later, the dogs were perfused with glutaraldehyde, the ganglia removed and cut frozen into 30µ sections and processed for HRP reaction product using the chromagen tetramethylbenzidine. Significant numbers of neurons containing HRP (in one dog > 500) were demonstrated in SG and MCG. Cells were localized in specific regions of both ganglia indicating a topographic organization of sympathetic ganglia cells which project to the myocardium. Smaller numbers of cells containing HRP were found in DRG at C_5-T_4. In some experiments ischemia at the site of HRP injection induced by coronary artery occlusion seemed to increase the number of labelled sympathetic and somatosensory neurons. To our knowledge, this is the first demonstration of specific connections between a specific region of the myocardium and cell bodies of autonomic and somatosensory ganglia. Information from such experiments may provide a better understanding of pain patterns and sympathetic dysfunction associated with myocardial ischemia. (Supported in part by NIH Grant # HL 12777)

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THE PRESENCE OF A HEXAMETHONIUM DEPENDENT CARDIO-CARDIAC NEURAL REFLEX IN THE CANINE MIDDLE CERVICAL GANGLION. J.A. Armour and M. McGill*. Department of Physiology & Biophysics, Dalhousie University, Halifax, Nova Scotia, B3H 4H7.

Fifteen mongrel dogs weighing 15-23 kg were anesthetized with Innovar and α-chloralose; positive pressure respiration was initiated. A bilateral thoracotomy exposed the left sided cardiac nerves, middle cervical ganglion and stellate ganglion. Two or three left sympathetic cardiac nerves were dissected under oil and placed over bipolar electrodes. The left cervical vagus was cut. Afferent fibers in the left thoracic vagus or a sympathetic cardiac nerve were stimulated with 5 to 50 V, 1-5 msec duration and at varying frequencies. Stimulation of an afferent nerve with a frequency of 1 Hz resulted in generation of compound action potentials in a cardiac nerve after a latency of approximately 20 to 50 msec. At 10 Hz no compound action potentials were generated. Decentralization of the left stellate ganglion or cutting both ansae subclavia did not grossly alter this reflex. I.V. or local injection into the MCG of hexamethonium abolished the reflex. Thus thoracic afferent nerve stimulation in a decentralized middle cervical ganglion preparation can reflexly produce compound action potentials in efferent cardiac nerves via nicotinic cholinergic synapses located in the middle cervical ganglion.

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LIPID PEROXIDATION (LP) IN CORTICAL BRAIN SLICES: INHIBITION BY LiCl. G.B. Kovachich* and O.P. Mishra* (SPON: C.J. Lambertsen). Inst. for Environmental Med., Univ. of Pennsylvania, Philadelphia, Pa., 19104.

Rat brain cortical slices incubated in normal Krebs-Ringer phosphate medium saturated with 100% O_2 form large quantities of malonaldehyde (MA) (Kovachich and Mishra, J. Neurochem., 35:1449, 1980). Production of MA is reduced by about 20% in a medium supplemented with 0.1 or 0.5 mM LiCl ($p<0.05$). Higher or lower conc. of Li had no effect. MA production is accompanied by partial inactivation of NaK-ATPase. 0.1-0.5 mM LiCl protected against this effect of oxygen as well. Non-enzymatic LP of heat treated brain tissue was determined in a medium of 25 mM NaP_i, 25 mM KP_i, 2 mM ascorbate and 0.1 mM EDTA. Production of MA was reduced by 0.05, 0.1 and 0.5 mM LiCl to about 70% of control values ($p<0.025$, 0.05 and 0.02 respectively). Higher or lower conc. of Li had no effect. Conclusions: Li has an inhibitory effect on LP by a non-enzymatic mechanism. The conc. range of Li inhibiting lipid peroxidation coincides with the serum levels of Li optimal for prophylactic treatment of manic depression. The results suggest a mechanism of action for the therapeutic action of Li as a psychotropic agent.

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UPTAKE OF PROLACTIN FROM CEREBROSPINAL FLUID IN RAT BRAIN. S. Landas*, S. Thompson*, R. Lewis*, J. Stamler*, M. Raizada and M.I. Phillips. Depts. of Physiology and Anatomy, Univ. of Iowa, Iowa City, Iowa 52240, and Dept. of Physiology, Univ. of Florida, Gainesville, Florida 32610.

The presence of prolactin in the central nervous system is suggested by several studies. Iontophoresis has shown prolactin-sensitive units. A prolactin-immunoreactive substance has been demonstrated in cerebrospinal fluid (CSF) and in brain. The aim of this study was to observe the regional uptake of prolactin, if present, from the CSF. A fluorescent analogue of ovine prolactin was injected into CSF of adult male rats with and without excess unlabelled prolactin. Rats were decapitated and the brains frozen in liquid N. Ten micron sections were viewed by fluorescence microscopy. Prolactin uptake was visualized in the area postrema, tanacytes of the cerebral aqueduct, and the wall of the anterior cerebral aqueduct near the third ventricle. The uptake process was saturable and well localized. While this fluorescence tracing method may not offer the quantitative data of radioligand binding methods, it is more rapid, efficient and inexpensive for examining localization of peptide binding in whole brain. Specificity of binding, though possible with fluorescence tracing, is better shown by the other methods. The results demonstrate uptake of prolactin from CSF in localized regions of periventricular tissue. The localized prolactin binding sites can be dissected for further analysis by conventional radioligand binding techniques.(Supp. by NIH HL27334A-01)

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POLYPEPTIDE HORMONE STIMULATION OF EXCITATORY INPUT INTO A BUCCAL MASS MUSCLE OF APLYSIA. Jeffrey L. Ram, Dept. of Physiology, Wayne State University, Detroit, MI 48201

Egg laying behavior in Aplysia is caused by a polypeptide hormone (egg-laying hormone, ELH) and is accompanied by inhibition of feeding behavior (Stuart & Strumwasser, J. Neurophys. 43:499), possibly due to direct effects of ELH on the nervous system. ELH activates axons in nerves B4 and CBC of isolated buccal ganglia (ibid.). I now report that the B4 axon has excitatory input to buccal mass muscle I5 (nomenclature as in Kandel, Behavioral Biology of Aplysia).

Extracellular recordings were made from I5 and B4. ELH containing samples were applied to the buccal ganglia and washed off after 10 min. The response in I5 has the following properties: a) Muscle potentials begin increasing in frequency within 5-10 min of sample application. b) Stimultaneous recordings from I5 and B4 show the muscle potential at a constant latency after a nerve spike. c) Both the tonic level and the occurrence of high frequency bursts increase. d) Activity usually returns to baseline within 40 min after washout. e) The response can be obtained repeatedly; there is no refractory period. f) The response increases quantitatively with the amount of ELH.

ELH obtained from successive SP C25 Sephadex ion exchange and Sephadex G50 gel filtration caused a robust response in I5 and also caused egg-laying upon bioassay in Stylocheilus.

Supported by NIH Grant NS15041. Technical assistance by U. Shukla & V. Padgaonkar.

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TWO FAST TRANSIENT CURRENTS IN NON-SPIKING DENDRITES OF CRUSTACEAN MECHANO-RECEPTIVE NEURONS. M. Mirolli, Physiology Section, Medical Sciences Program, Indiana University School of Medicine, Bloomington, IN 47405

The two currents, I_{01} and I_{02}, can be demonstrated when isolated dendrites of the crab coxal receptors are clamped 15 mV or more above their average resting potential (-60 mV). Preliminary estimates for the reversal potential of these currents suggest that both are carried by potassium. However, they differ in the following properties: I_{01} has a rise time (to 95% of maximum) of 3 msec or less, is completely inactivated in dendrites held at -45 mV and its re-activation (by hyperpolarizing voltages) requires at least 10 seconds; I_{02} has a rise time of 10 msec or less, is only 70% inactivated in dendrites held at -45 mV and can be reactivated to its maximum value in 0.5 seconds or less. Both currents are blocked by 4-Amino Pyridine (5 mM added to the saline); Tetra-ethyl-ammonium (0.1 M substituted for sodium) blocks I_{02} completely but only partially I_{01}. The present evidence suggests that I_{01} may account in part for the non-spiking properties of these dendrites, while I_{02} may limit the amplitude of the response to stretch. (Supported by Biomedical Research Grant #22-830-53 of Indiana University School of Medicine)

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GRAVITY PERCEPTION IN GASTROPOD MOLLUSCS. C. Janse. Dept. Biology, Vrije Universiteit, 1007 MC Amsterdam, The Netherlands.

Behavioural experiments on *Lymnaea stagnalis* showed that the gravity perception system in gastropods is highly directional sensitive. A possible explanation is that despite the lack of structural polarization the sense cells in the statocysts of gastropods are directionaly sensitive. In order to investigate this single statocyst sense cells were studied electrophysiologically (*Aplysia limacina*) and anatomically (*A. limacina, L. stagnalis*). The statocyst sense cells appeared to be clearly directional sensitive to positional changes. This property can be explained by the combination of the following properties: the anatomy of the sense cells, the shape of the statocysts, and the dimension of the statolith mass. From these properties it also follows that the direction of maximal sensitivity of the statocyst sense cells to positional changes of the animal will depend on the starting position of the animal.

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A CALCIUM DEPENDENT CODING MECHANISM IN THE PHOTORECEPTORS. Clara Torda. Res.Dpt.N.Y.Center PA.Training,N.Y.(Current addr. P.O.Box 4866,Stanford University,Stanford,Calif.,94305).

Encoding of visual stimuli starts in the photoreceptors. Bioelectric potentials have been recorded from the outer and inner segments of cones and rods of the toad (Bufo Marinus) during various experimental conditions, including altering the intermembrane concentrations of calcium, inhibition of phosphodiesterase (PDE), activity changes of guanylate cyclase, and the reversal of PDE inhibition by calmodulin.The photopigments occur in the sacculi of the outer segment of the rods (and in their equivalents in the cones). During photon capture the rotating photopigment opens calcium channels located in the inner membrane of the outer segment. Version of free calcium into the intermembrane space of the outer segment generates dose-dependent hyperpolarization. The magnitude and changes of hyperpolarization is selfregulated by the ratio of calcium influx(a fast process) and its removal(a slow process) The removal is mainly due to binding on calmodulin and on rediffusion into the sacculi. The speed and efficiency of hyperpolarization depends also on optimal membrane polarization. This membrane polarization is regulated by cyclic GMP related processes. Several regulatory processes were identified. The locally available concentrations of cyclic GMP depends on both a gross regulation of phosphodiesterase activity that depends on the illumination and a fine regulation by complex Ca-dependent mechanisms.The calcium dependent hyperpolarization represents a stimulus coding mechanism. Its accurate, fast and efficient performance depends on regulation of the locally available cGMP.

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THE EFFECT OF PEDALLING RATE ON POWER OUTPUT AND FATIGUE DURING SHORT-TERM, MAXIMAL CYCLE ERGOMETRY. Neil McCartney,* G.J.F. Heigenhauser,* J.R. Sutton,* and N.L. Jones. Dept. of Medicine, McMaster University, Hamilton, Ontario, Canada.

We have investigated the effects of crank velocity on the peak power output, total work, and the decrement in power output during 30 seconds of maximal cycling exercise. An ergometer was used which maintained crank velocity constant (± 3%) at a pre-selected level (13-166 rpm) despite maximal effort of the subject. Measurements of torque, work and power output were recorded for every pedal revolution. Thirteen male subjects performed tests on separate days at 60, 100 and 140 rpm. Maximal peak power was 1548 ± 277.5 watts at 140 rpm, 1467.9 ± 163.2 at 100 rpm, and 1170 ± 135 at 60 rpm. The decline in power output was 59.3% at 140 rpm, 45.2% at 100 rpm and 23.0% at 60 rpm, but the total amount of work performed during 30 secs at the 3 crank velocities was not significantly different. Thus the differences in the rate of fatigue in the 3 conditions were not associated with variations in the total work performed. At faster crank velocities more total work was achieved early in the test, and thereafter the rate and extent of decline in power were significantly greater than at the slower speeds. The results are consistent with the classical relationships between efficiency and frequency of muscle contraction found by A.V. Hill (1922), with maximum efficiency at contractions of 1/sec. (Supported by MRC, Canada).

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EXERCISE BIOENERGETICS FOLLOWING SPRINT TRAINING. George A. Brooks, Kelvin J.A. Davies*, and Lester Packer. Exercise Physiology Laboratory, and Membrane Bioenergetics Group (LBL), University of California, Berkeley, CA 94720

Female Wistar rats (n=10) were sprint trained on a rodent treadmill at 97 $m \cdot min^{-1}$ and 15% grade. Sprint trained rats exhibited a mean $\dot{V}O_2max$ of 70.5±1.9 $ml \cdot kg^{-1} \cdot min^{-1}$, compared with 61.1±0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ for controls (n=10) (15% relative increase, $p<0.01$). Likewise, $\dot{V}CO_2$ at $\dot{V}O_2max$ was significantly higher for sprint trained animals (76.9±1.0 ml $kg^{-1} \cdot min^{-1}$) than controls (70.4±1.1 $ml \cdot kg^{-1} \cdot min^{-1}$) ($p<0.01$). R at $\dot{V}O_2max$ was uneffected. The maximal workload attained at $\dot{V}O_2max$ (aerobic workload capacity) was 25% greater for sprint trained rats ($p<0.01$). Despite these relative improvements, no differences in muscle oxidative capacity, as evidenced by muscle pyruvate-malate oxidase, succinate oxidase, palmitoyl-l-carnitine oxidase, and cytochrome oxidase activities, were observed. The mitochondrial content of muscle assessed by muscle cytochrome c ($+c_1$) and cytochrome a content, was not significantly different between the two groups. Similarly, endurance times at 26.8 $m \cdot min^{-1}$ and 15% grade were not significantly different for the two groups (controls 32.9±1.9 min, sprint trained 35.9±1.5 min). Results indicate that $\dot{V}O_2max$ is not limited by absolute muscle oxidative capacity, but that endurance capacity and muscle oxidative capacity are closely coupled. (Supported by NIH Grant AM19577 and by DOE Contract W-7405-ENG-48).

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EFFECTS OF IRON DEFICIENCY AND BLOOD TRANSFUSION ON THE BIOENERGETICS OF EXERCISE. Kelvin J.A. Davies*, Lester Packer, Casey M. Donovan*, Caino J. Refino*, Peter R. Dallman, and George A. Brooks. Univ. of California, Berkeley, CA 94720, and Univ. of California, San Francisco, CA 94143

Dietary iron deficiency in young rats resulted in anemia (Hgb 4.8 g/dl) and decreased oxidative capacities of muscle (40-90% below controls). Aerobic work capacity and $\dot{V}O_2max$ were decreased by 50%, whereas endurance capacity during sub-max work was 90% reduced. Exchange transfusion of packed red blood cells or plasma, via a carotid artery catheter, was used to adjust hemoglobin concentration to an intermediate level of approximately 9.5 g/dl. Separate control and deficient groups were sham transfused. In the red cell transfused deficient rats, $\dot{V}O_2max$ and aerobic work capacity were largely corrected, to within 15% of control values. In contrast, exchange transfusion did not significantly improve the endurance capacity of iron deficient rats, and thereby resulted in a dissociation between $\dot{V}O_2max$ and endurance capacity. We interpret these results to indicate that defects in $\dot{V}O_2max$ and aerobic work capacity during dietary iron deficiency are primarily caused by impaired oxygen delivery, whereas the loss of endurance capacity is a direct function of the diminished ability of muscle mitochondria to consume oxygen and produce ATP. We propose that muscle oxidative capacity always exceeds $\dot{V}O_2max$ but determines endurance, and that $\dot{V}O_2max$ is not causally related to endurance capacity. (Supported by NIH grant AM 13897, and AM 19577, and by DOE contract No. W-7405-ENG-48).

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INFLUENCE OF TRAINING ON THE SENSITIVITY AND CONTRACTILITY OF HELICAL STRIPS FROM NORMOTENSIVE RATS. J.G. Edwards,* R.D. Matthes,* T.G. Bedford,* and C.M. Tipton. Exercise Science Program, University of Iowa, Iowa City, Iowa 52242

The mechanism(s) responsible for the lower resting systolic blood pressure (SBP) of trained rats are obscure. To determine whether vascular sensitivity to catecholamines or contractility were involved, the in vitro isolated helical arterial strip method, as described by Bohr and colleagues was used. Six month-old male Sprague-Dawley rats assigned to nontrained (NT) and trained (T) (16 weeks) were studied. The T had significantly higher $\dot{V}O_2max$, elevated muscle cytochrome oxidase activity, and lower resting HR. SBPs were 133±5 and 125±5mmHg, respectively, for NT and T groups. Arteries were studied using a cumulative dose response curve for norepinephrine. Values presented are $\bar{X}$ and SE from 7-15 samples.

GROUP	AORTA		RENAL	
	KD_{50} (g/ml)	MAXIMAL TENSION ($kdynes/mm^2$)	KD_{50} (g/ml)	MAXIMAL TENSION ($kdynes/mm^2$)
NT	3.88×10^{-9} ±0.60	4535.0 ±372.5	2.72×10^{-8} ±0.86	4908.1 ±680.5
T	4.62×10^{-9} ±0.54	4303.0 ±535.1	2.15×10^{-8} ±0.39	4292.6 ±435.6

Under the conditions of these experiments, we have concluded that the vasculature may not have been adequately stressed to exhibit a change in these parameters and/or that other mechanisms are responsible for a training effect. (Supported in part by funds from HL-21245-04 and GM-07045-03.)

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EFFECT OF ENDURANCE TRAINING ON HORMONAL AND METABOLIC RESPONSES TO EXERCISE IN THE FASTED STATE. W.W. Winder, M.A. Beattie*, and R.T. Holman*, University of So. Dakota School of Medicine, Vermillion, SD 57069

Endurance exercise training produces major adaptations in hormonal and metabolic responses to exercise. The present study was designed to determine whether or not the differences in hormone responses persist in the fasted condition when liver glycogen is depleted. Rats were run on a motor-driven rodent treadmill 5 days per week for periods up to 2 hr per day for 10 weeks. Trained and non-trained rats were then fasted 24 hr and were run for periods ranging from 0 to 60 min. At the end of 60 min of exercise muscle glycogen was higher in trained rats (2.9±0.3 vs 1.1±0.1 mg/g). Blood glucose was maintained at higher levels in trained rats throughout the course of the exercise (3.2±0.1 vs 2.3±0.1 mM after 60 min). Plasma glucagon increased in both groups during the exercise, but was significantly lower in trained animals after 60 min (372±41 vs 584±59 pg/ml). Plasma epinephrine responses to exercise in the fasted state were also reduced by this endurance training program. It seems clear that the trained animal is able to maintain blood glucose at higher levels and to conserve muscle glycogen during exercise even in the fasted state. The differences between trained and non-trained animals in stress hormone responses to exercise persist in the fasted condition and appear to be a consequence of the increase in muscle capacity to oxidize fatty acids. (Supported by NIH Grant AM 27107 and NIH RCDA AM 00757.)

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REPRODUCIBILITY OF THE CATECHOLAMINE (CA) RESPONSE TO MAXIMAL EXERCISE - Dragana Damjanovic* and Tissa Kappagoda* (SPON: B.J. Sproule) Division of Cardiology, Dept. of Medicine, University of Alberta, Edmonton, Alberta T6G 2G3

This study was undertaken to establish the reproducibility (reprod.) of the CA response, as defined by the concentration of noradrenaline (NA) and adrenaline (A) in venous blood, during submaximal (submax) and maximal (max) exercise in 9 men. The tests were performed on a bicycle ergometer and the loads were increased by 300 kpm/min., every 3 min. The effort was considered max when there was a plateau in the heart rate (HR), the oxygen consumption ($\dot{V}O_2$) and the blood pressure and an inability to continue. Blood was sampled from the antecubital vein: (1)before exercise; (2)at 60% of max; (3)at max; (4) 30 sec. post exercise; and, (5)after recovery. The blood was analysed for A and NA using a radioenzymatic technique. The exercise test was repeated after 10 days. The reprod. of responses was expressed as the mean±SEM of the differences in the two tests.

	HR(bt/min)	$\dot{V}O_2$ml/min	A(pg/ml)	NA(pg/ml)
Submax	6.6±2.0	152±42	109±52	393± 96
Max	4.8±1.6	217±51	377±101	1008±269

This disproportionate variation in [CA] in peripheral blood could not be explained by the random error of the assay. It is concluded that the [CA] in venous blood is not a reproducible phenomenon and that plasma [CA] is unlikely to be responsible for the fine control of the HR response to exercise in normal subjects. It is suggested that the reprod. of the HR response to exercise is mediated by modulation of the vagal tone.

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INFLUENCE OF SYMPATHECTOMY ON THE FUNCTIONAL CAPACITY OF SPONTANEOUSLY HYPERTENSIVE RATS. C. M. Tipton, R. D. Matthes* P. L. Kershner*, and M. S. Sturek*. Exercise Science Program, University of Iowa, Iowa City, Iowa 52242

An increase in the activity of the sympathetic nervous system is considered essential for an elevation in $\dot{V}O_2$ max (Baldwin et al. Med. Sci. Sports Ex. 13:75, 1981) while a decrease in activity is associated with a reduction in the resting systolic blood pressure (SBP) associated with training (T). These relationships were examined in SHR populations. Sympathectomy (SYMX: by ANGF and quanethidine injections) or saline injections (SHAM) were performed in male rats assigned to NT or T groups. At 14 days and thereafter, the SYMX rats (N=31) were significantly lighter than the SHAM (N=35). At 6 weeks of age and before training, SBP values were 142±3 and 99±5 mmHg ($\bar{X}$,SE) for the SHAM and SYMX, respectively. Subsets of the two populations were tested for $\dot{V}O_{2\ max}$ and there were no significant differences noted (SHAM=64±1.0; SYMX=65±2.0 $ml.min^{-1}.kg^{-1}$). However, the SYMX had run durations that were significantly shorter and rectal temperature changes that were markedly higher (3.3±0.2 to 1.6±0.2°C) than the SHAMs. Training of the SYMX group was associated with 12% increase in $\dot{V}O_{2\ max}$ and a lower SBP after 12 weeks of chronic exercise (NT-SYMX=120±5; T-SYMX=108±3 mmHg). These trends suggested that an impairment of the temperature regulating system was a key reason for the reduced run times and that non-SYMX factors can contribute to a lower resting SBP with training. (Supported in part by HL-21245-04 and GM-07045-03).

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EFFECT OF EPINEPHRINE (E) ON HEPATIC (Ra) AND EXTRA HEPATIC GLYCOGENOLYSIS (GLY) DURING EXERCISE. Bela Issekutz, Jr. Dept. of Physiology, Dalhousie University, Halifax, N.S., Canada. B3H 4H7

Well trained dogs with indwelling arterial and venous catheters run on a treadmill (15%, 133 m/min.). A mixture of 3-^{3}H-glucose and ^{14}C-glucose was infused at a constant rate. The former served to measure Ra, the latter to estimate GLY (muscle). Three types of experiments were conducted: A) E was infused (0.5 µg/Kg min) mid-exercise for 75 min.; B) E was infused for 3 hours and exercise started mid-infusion for 75 min.; C) E and exercise began at the same time. In "A" E increased plasma glucose significantly less (+17 mg/dl) than at rest (+60 mg/dl), it failed to increase Ra and transiently decreased the elevated metabolic clearance rate (MCR). GLY was increased as in the resting dog (19 mg/Kg min) yet plasma lactate rose less (20 mg/dl versus 40 mg/dl). In "B" the E-induced hyperglycaemia and hyperlactacidemia were reduced (-65 mg/dl and -20 mg/dl, respectively) by exercise. The increase of Ra was delayed and the rise of GLY was significantly enhanced. In "C" both glucose and lactate showed an early rise followed by a decline. The rise of MCR was delayed and the rise of GLY was significantly greater than in running controls. It is concluded that E-induced hyperglycaemia inhibited the rise of hepatic glucose output. The inhibitory effect of the elevated GLY on MCR was only transient. Supp. by the Medical Research Council of Canada.

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ROLE OF LIVER GLYCOGEN DEPLETION IN DEVELOPMENT OF POST-EXERCISE KETOSIS. M.A. Beattie*and W.W. Winder. Division of Biochemistry, Physiology, and Pharmacology, University of South Dakota School of Medicine, Vermillion, SD 57069.

Depletion of liver glycogen is considered to be essential for allowing a rapid rate of hepatic ketogenesis. The purpose of this experiment was to determine the role of liver glycogen levels in development of post-exercise ketosis. Male rats were either food restricted to partially deplete liver glycogen or were allowed to eat ad lib during the night prior to an exercise test. Rats were then run on a motor driven rodent treadmill for 60 min at 1 km/hr. Liver glycogen and blood ketones were determined in rats killed during the post-exercise period. Blood 3-hydroxybutyrate increased in both the ad lib fed rats and in the food restricted rats. Blood 3-hydroxybutyrate concentration was two-fold higher in the food restricted rats between 30 and 90 min post-exercise than in ad lib fed rats (0.8 ± 0.1 vs 0.4 ± 0.1 mM). Liver glycogen averaged 35 mg/g in ad lib rats and 5 mg/g in food restricted rats during this same period. It is apparent that in the post-exercise period mild ketosis may occur even when livers contain reasonably high concentrations of glycogen, but that development of high blood ketone levels is enhanced by glycogen depletion. (Supported by NIH Grant AM 27107)

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MUSCLE GLYCOGEN LOADING WITH A CARBOHYDRATE DRINK. A. C. Snyder*, D. R. Lamb, T. S. Baur* and G. L. Prah*. Exercise Physiology Laboratory (PEHRS), Purdue University, West Lafayette, IN 47907.

A high carbohydrate (CHO) diet after exercise--glycogen loading (GL)--increases muscle glycogen (G) and is associated with improved running endurance. However, GL pasta diets lead to gastric discomfort. We tested the efficacy of an isotonic, low residue, CHO-rich drink (3.3 kJ/ml) as the major component of a GL diet. Seventeen male runners consumed a 14,651 kJ diet containing 50% CHO for 3 days, had a biopsy from m. vastus lateralis analyzed for G, and ran to exhaustion at 75% $\dot{V}_{O_2max}$. Three weeks later they ate an isocaloric 20% CHO diet for 3 days and ran 24 km to deplete G. Next, for 3 days they consumed a 90% CHO diet emphasizing either rice and pasta (RP,n=8) or the CHO drink (DR,n=9), were biopsied and again ran to exhaustion at 75% $\dot{V}_{O_2max}$. The DR group obtained 82% of CHO from the drink and the remainder from RP. RESULTS: Compared to the 50% CHO condition, RP increased G by 28.3 ± 9.8 mmoles/kg ($\bar{X}$ ± SEM;p=.012) and run time by 7.08 ± 10.00 min (ns); increases for DR were 60.3 ± 14.8 mmoles/kg (p=.002) and 24.50 ± 6.82 min (p=.004). Thirteen of 17 who tried both 90% CHO diets reported less gastric discomfort after DR than after RP. Thus, GL can be accomplished with less discomfort by substituting the drink for some pasta in a GL diet. The apparent advantage of DR over RP in GL (p=.05) may be explained by better assimilation of the liquid diet. (Supported by a grant from Stokely-VanCamp, Inc.)

VASCULAR SMOOTH MUSCLE I

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EFFECT OF OUABAIN UPON MEMBRANE POTENTIAL IN RABBIT CRANIAL VESSELS--EVIDENCE OF ALTERED SODIUM PUMP ACTIVITY. **W.J. Willems and M.J. Marchino*, Medical College of Wisconsin at VAMC, Milwaukee, WI 53193**

Rabbit cerebral vessels exhibit smaller tension responses to norepinephrine and nerve stimulation than do extracranial vessels e.g., ear arteries. The smaller contractility in cerebral vessels may relate to a difference in sodium pump activity or differences in passive membrane properties. Ouabain-dependent intracellular electrical changes can serve as quantitative assessments of resting sodium pump activity. To clarify the role of ouabain-dependent processes in rabbit basilar and ear arteries, we measured in vitro intracellular membrane potential (E_m) under control conditions and during ouabain suffusion. Short segments or rabbit vessels were removed rapidly, mounted in a suffusion chamber, and suffused with oxygenated physiologic saline solution at 37°C. After one hour of equilibration in the suffusion system, vessels were impaled with glass microelectrodes (30-80 Megohms) under micromanipulator control. Ouabain-suffusion partially depolarized smooth muscle membranes in both vessels and produced a significantly greater E_m change in ear artery (33 mV) than in basilar vessels (25 mV). The data suggest that the E_m in basilar vessels is less dependent upon electrogenic ouabain-dependent processes than ear artery in vitro, possibly due to diminished sodium pump activity.
(Funded by research funds from the Veterans Administration).

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INFLUENCE OF LOW EXTRACELLULAR NA^+ AND K^+ CONCENTRATIONS ON RELAXATION OF ARTERY STRIPS BY ADENOSINE. Duane H. Foley. College of Osteopathic Medicine and Department of Zoology, Ohio University, Athens, Ohio 45701.

This study was conducted to determine whether responses of artery strips to adenosine (Ado) would be diminished in bathing solutions deficient in Na^+ or K^+. Helical strips of left coronary and femoral arteries from rabbits were suspended in organ baths in a physiological salt solution (PSS) maintained at 37°C and bubbled with 95% O_2 + 5% CO_2. Isometric contractions were induced with acetylcholine and norepinephrine in coronary and femoral artery strips, respectively. Subsequent addition of 10^{-8} - 10^{-4}M Ado produced concentration-dependent relaxations. Substitution of LiCl for NaCl in the PSS increased mean Ado ED_{50} from 7.5 x 10^{-8} to 3.5 x 10^{-6}M* in coronary, and from 5.8 x 10^{-7} to 8.3 x 10^{-6}M* in femoral artery strips. K^+-free PSS increased Ado ED_{50} from 1.5 x 10^{-7} to 7.2 x 10^{-7}M* in coronary strips, and decreased relaxation of femoral strips by 10^{-4}M Ado from 95% to 53%*. Agonist concentrations were adjusted to produce comparable pre-Ado contractions in normal, LiCl and K^+-free PSS, minimizing the effect of initial tension on Ado response. These results are similar to those of a previous study of effects of ouabain on Ado responses (Physiologist 23:101, 1980), and suggest that inhibition of the sarcolemmal Na-K pump may interfere with relaxation of artery strips by Ado. *(n = 8, P<0.05) Supported by O.U.C.O.M. and O.U. Research Committee.

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THE LYOTROPIC ANIONS (SCN^-, NO_3^-, $CH_3SO_3^-$) DEPRESS THE RELAXING EFFECTS OF ADENOSINE ON SMALL CORONARY VESSELS. Tokumasa Tsukada*, Rafael Rubio, and Robert M. Berne, Dept. of Physiol., Univ. of Virginia, Sch. of Med., Charlottesville, VA 22908

The relaxing effects of adenosine are known to be inversely related to the magnitude of the stimulus used to elicit vasoconstriction. Adenosine may act by depressing Ca^{++} influx. Since the lyotropic anions enhance constrictive stimuli possibly by increasing Ca^{++} influx with the following potency $SCN^- > NO_3^- > CH_3SO_3^-$, it was thought that they would depress the effects of adenosine in the same sequence. In small coronary arteries (0.6-0.5 mm o.d.) of the dog, constricted by 20 mM K^+ in Cl^--physiological salt solution (PSS), adenosine caused relaxation (15% at 10^{-7} - 90% at 10^{-4}M) in a concentration-dependent manner. Total replacement of Cl^- by NO_3^- or $CH_3SO_3^-$ of the PSS resulted in a 10 and 70% relaxation, respectively, in comparison to that caused by adensoine in Cl^--PSS. However, partial replacement of Cl^- for only 20 mM SCN^- totally blocked the response to adenosine. The effects of NO_3^- had higher specificity for adenosine relaxation than did verapamil and nitroglycerin since the relaxing effects of verapamil were only decreased to 70% and the effects of nitroglycerin on large coronary arteries were only decreased to 50% of those in Cl^--PSS. These results indicate that various relaxing agents act at different sites in the chain of events that lead to the increase in Ca^{++} influx that triggers vasoconstriction.
(Supported by NIH Grant HL 19242).

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CALCIUM BLOCK BY LANTHANUM IN DOG ANTERIOR TIBIAL AND ULNAR ARTERIES. D.L. Davis and J.M. Price. University of South Florida, College of Medicine, Department of Physiology, Tampa, FL 33612.

Calcium uptakes were obtained in vessels excised under pentobarbital anesthesia. The adventitia was removed, blood vessels were cut into 4-5 mm rings (10 mg), and equilibrated in HEPES-buffered physiological salt solution (PSS). After loading for 150 min in ^{45}Ca-PSS (5 µCi ^{45}Ca/ml), uptake curves for the entire vessel ring plateaued at 1600 µM/kg wet tissue weight. Uptake curves employing the Lanthanum method at 4°C yielded equilibrium values of 190 µM Ca/kg tissue (a value similar to that reported for other blood vessels in other laboratories). Uptake curves from anterior tibial arteries could not be distinguished from those of ulnar arteries. The entire Ca uptake curves, including the final equilibrium values, were dose-dependently decreased by La. These concentrations of La (10-50mM) also inhibited the increases in Ca-uptake curves induced by norepinephrine (NE). The blocking effect of La on resting Ca uptake contrasts with that reported previously from this laboratory (Fed. Proc. 40:442, 1981). Our earlier data showed that resting Ca uptake curves were unaffected by concentrations of verapamil (10^{-5}M) which markedly depressed contractile responses to NE. These data confirm earlier reports that La and verapamil block Ca influx via different mechanisms. (Supported in part by the American Heart Association, Florida Affiliate, Palm Beach Chapter).

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COMPARISON OF VERAPAMIL, DILTIAZEM, AND NIFEDIPINE FOR INHIBITION OF NOREPINEPHRINE CONSTRICTION IN ISOLATED SEGMENTS OF RABBIT FEMORAL ARTERY. S.F. Flaim, S.C. Swigart*, and B.S. DeLong*. Cardiology, Penn State Univ College of Med, Hershey, Pennsylvania 17033

In a previous in vitro study, the rabbit femoral artery (RFA) was shown to be similar in some respects to some coronary arteries. We, therefore, studied the effects of the "calcium channel blockers" verapamil (VP), diltiazem (DZ), and nifedipine (NF) at 3 concentrations (10^{-7}, 10^{-6}, 10^{-5}M) on the norepinephrine (NE, 10^{-8} through $5x10^{-5}$M) concentration-response relationship. The RFA was divided into 4 regions: iliac (IL), proximal (PF), middle (MF), and distal (DF) femoral segments. The data are Kd (NE concentration x 10^{-7}M needed to elicit half maximum tension response); *=p<.05 compared to Kd at 10^{-7} 10^{-6} 10^{-5}M lower drug concentrations, †=p<.05 compared to parallel Kd obtained using different drugs. These data support the following conclusions: 1) at 10^{-5} M, VP>DZ>NF for inhibiting the NE tension response in RFA; 2) in general, the sensitivity of RFA segments to calcium channel blockers is DF>MF>PF> IL excepting VP which appears to be equipotent in this vessel. Conclusion #1 is supported by studies on conscious rats using microspheres where similar effects on muscle flow occurred.

VP IL	15.1	13.9	39.2*†
VP PF	13.2	10.0	36.5*†
VP MF	18.8	18.2	41.1*†
VP DF	24.2	22.2	41.1
DZ IL	6.1	12.3	14.0
DZ PF	6.3	16.0	18.3
DZ MF	5.2	11.8	23.7
DZ DF	6.6	22.6	34.4*
NF IL	6.4	7.1	7.9
NF PF	6.4	7.0	10.9
NF MF	5.5	6.6	12.0
NF DF	5.8	7.0	15.1*

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RELAXANT EFFECTS OF MONENSIN ON THE ISOLATED CANINE CORONARY ARTERY. Harry L. Anderson III*, Raymond J. Winquist and David F. Bohr. Department of Physiology, University of Michigan Medical School, Ann Arbor, MI 48109.

Monensin, a monocarboxylic sodium ionophore, causes coronary vasodilatation at doses lower than those needed to produce increased myocardial contractility and increased aortic blood pressure in the anesthetized dog (J. Cardiovasc. Pharm. 1:123-38, 1979). In order to further elucidate this relaxant effect on the coronary vasculature, we examined the direct action of monensin on the left anterior descending coronary artery of mongrel dogs in vitro. Helical strips were attached to isometric force transducers and suspended in aerated physiological saline solution (PSS) in tissue baths. When cumulatively added, monensin produced dose-dependent inhibition of an ED_{80} 5-hydroxytryptamine (5HT, 3 X 10^{-7} M) contraction. Studied in another way, monensin (10^{-6} M, n=11) caused a reversible 77±4% (mean±SEM) inhibition of an ED_{50} 5HT (10^{-7} M) response. The inhibition was not attenuated by indomethacin (5 µg/ml, n=2), aminophylline (10^{-5} M, n=2) or propranolol (5 X 10^{-7} M, n=1). However, ouabain (10^{-5} M, n=3) and K^+-free PSS (n=3) significantly reversed the inhibition by monensin ($p<0.05$). These results suggest that monensin causes relaxation by increasing intracellular sodium concentration which stimulates the Na^+/K^+ ATPase. This is an electrogenic pump which causes membrane hyperpolarization and hence a decrease in excitability.
(Supported by NIH Grants HL 18575 and HL 06080)

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EFFECT OF DIET ON THE ISOPROTERENOL-INDUCED RELAXATION OF RAT AORTA. Jeremiah T. Herlihy and Byung P. Yu. Dept. of Physiology, Univ. of Texas Health Science Center, San Antonio, Texas 78284.

Vascular strips were obtained from aortas of 6 and 12 month old Fisher 344 rats subjected to several nutritional regimens. Control animals (A) were fed ad lib; food restricted animals (R) were fed 60% of the intake of A; protein restricted animals (P) were fed an isocaloric diet but with only 60% of the protein of A. Cross-over animals were fed either ad lib until 6 months old and then food restricted (AR) or were kept on a food restricted diet until 6 months of age and then allowed to eat ad lib (RA). The maximal isoproterenol (10^{-6}M) induced relaxation of strips pre-constricted with 30 mM K^+ is expressed on the following table as % of maximum relaxation.

Group	A	R	AR	RA	P
6 month	19±2	13±1	——	——	19±1
12 month	18±2	13±1	11±1	21±2	20±2

Food restriction (R vs A) significantly reduced relaxation, whereas protein restriction (P vs A) had no effect. Food restriction begun at 6 months (AR) results in a decline, while ad lib feeding begun at the same time (RA) causes an enhancement of the relaxation. These results indicate that 1) food restriction can alter vascular smooth muscle function even when initiated in adulthood and 2) protein restriction is not the underlying cause for the action of food restriction.
(Supported by Grant #AG01188 from the NIH.)

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PRESSURE DEPENDENCE OF THE AORTIC CHARACTERISTIC IMPEDANCE STUDIED DURING REFLEX ADJUSTMENTS AND AFTER ALPHA BLOCKADE. Dana N. Stone* and J-P.L. Dujardin, Department of Physiology, O.S.U., Columbus, Ohio 43210.

Earlier experiments have demonstrated reflex changes in the canine aortic input impedance spectrum and in characteristic impedance (Z_c) elicited by alterations in circulating blood volume. These findings applied only to steady state conditions at different mean arterial pressures. The current experiments were performed to study the passive pressure dependence of Z_c under control conditions, after hemorrhage (-15% of the estimated blood volume), after volume expansion (+15%), and after alpha blockade. Z_c was calculated from measured pressure and diameter using $Z_c = (4/\pi) \times [(\rho/2D^3) \times (\Delta p/\Delta D)]^{1/2}$. The diameter D was determined by means of a sonomicrometer. All determinations were made during diastole. Z_c was determined for each condition, in a wide pressure range caused by slow oscillations(period = 5 s) in aortic pressure and diameter induced with an external piston pump. Z_c was found to exhibit a minimum when plotted as a function of pressure under all conditions. When compared to control curves, hemorrhage increased Z_c over a wide pressure range and increased the pressure at minimum Z_c. Alpha blockade lowered Z_c and shifted the curves to lower pressure at minimum Z_c. These results suggest that sympathetic control of the aortic smooth muscle can profoundly affect the physical characteristics which determine pulsatile hemodynamics of the proximal aorta.
(Supported by PHS grant HL-23239 and by a grant from the COHC.)

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UTERINE ARTERIAL SENSITIVITY TO ANGIOTENSIN II AND NOREPINEPHRINE IN PREGNANT AND NONPREGNANT RABBITS. D.Moisey* and T.Tulenko. Depts. of Physio.-Biochem. & Obstet.-Gynecl. The Medical College of Penna.,Phila.,PA 19129

Uterine arteries from near term (0.92) pregnant and nonpregnant rabbits were examined for their sensitivity to norephinephrine (NE), angiotensin II (AII) and potassium chloride (KCl). Helical strips were prepared and suspended isometrically in Krebs-Henseleit solution under optimal preload conditions and cumulative dose response experiments were performed. Arteries from pregnant and nonpregnant rabbits responded with similar dose-dependent increases in tension when stimulated with NE and KCl. However, the response of uterine arteries to AII differed significantly ($p<0.01$) between the two groups. Arteries from the pregnant group exhibited a 2.3 fold ($p<0.005$) greater sensitivity (ED_{50}) to the vasoconstricting effect of AII than arteries from the nonpregnant group. This increased sensitivity observed in the pregnant group was not due to activation of adrenegic mechanisms since pretreatment of arteries with cocaine (10^{-5}M) or phenoxybenzamine (10^{-6}M)did not alter the AII response. However, pretreatment of uterine arteries from pregnant rabbits with either meclofenamate (10^{-5}M) or indomethacin (10^{-5}M) for 12 min depressed the AII response. These findings suggest that the increased AII sensitivity may result, at least in part, from stimulation of synthesis of vasoconstricting prostaglandin(s). (Supported in part by NIH Grants HL07443, HL24512 & RR05418)

MEMBRANE TRANSPORT

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THE ORIGIN OF ACTIVE Na CHANNELS: PROCAINE AND TETRODOTOXIN REDUCTION OF COOPERATIVE EFFECTS IN PASSIVE Na CHANNELS. Alfred Strickholm. Physiology Section/Medical Sciences Program, Bloomington, IN 47405

Theories on the origin of active sodium channels include: 1) passive Na permeability represents the random appearance of active sodium channels, 2) active Na channels result from a modification of passive Na channels, and 3) passive and active Na channels are separate entities. To examine these theories, passive Na conductances $g_{Na} = T_{Na}G_m$ were determined in crayfish giant axons from measurements of membrane conductance (G_m), and the dependency (T_{Na}) of membrane potential on external Na where $T_{Na} = \Delta V_m/\Delta E_{Na}$ (Strickholm and Clark, Biophys. J. 19:29). g_{Na} was measured from pH 4 to 10 in normal saline (K_o = 5.4mM) and when K depolarized (K_o = 40mM). The results indicated that imidazole and phosphatidic acid have considerable control over passive Na conductance. In the K depolarized axon, cooperative changes occurred when pH was altered over the imidazole pK region. This cooperativity had a Hill coefficient n of 4 which could result from four interacting groups on protein. Tetrodotoxin had minimal effect on the absolute resting conductance but reduced the cooperative Hill coefficient n from 4 to near 2. Procaine similarly reduced the Hill coefficient n. The results are interpreted as favoring the interpretation that active sodium channels result from modified passive sodium channels. (Supported by a grant-in-aid from the American Heart Association, Indiana Affiliate, Inc.)

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COMPARISON OF ACTIVATION AND DEACTIVATION KINETICS OF THE TIME-DEPENDENT OUTWARD CURRENT IN CAT VENTRICULAR MUSCLE. Craig W. Clarkson* and Robert E. Ten Eick. Pharmacology Dept., Northwestern Univ. Medical Sch., Chicago, IL 60611

It is currently believed that the time course of the time-dependent outward current (I_K) in cat ventricular muscle can be described by a Hodgkin-Huxley, two state model. Using cat papillary muscles and trabeculae, this hypothesis was examined using a single sucrose gap voltage clamp technique. Membrane currents evoked by voltage clamp pulses were analyzed by fitting them to an equation of the form:

$$y = Ae^{-t/\tau_1} + Be^{-t/\tau_2} + Ce^{-t/\tau_3} + D$$

Comparison of the time constant for I_K activation obtained from 9s depolarizing pulses with the time constant for I_K deactivation following 2s conditioning pulses to +10mV suggests that the kinetics of I_K activation and deactivation are different at several levels of membrane potential, even when the currents said to be produced by accumulation or depletion of K^+ in the interstitium have been accounted for. The voltage dependence of I_K time constants was such that the ratio of activation/deactivation time constants was >1 at -40 and -30mV, but <1 at -10mV. This finding is inconsistent with a single gate, two state Hodgkin-Huxley model which predicts that activation and deactivation occur with identical time constants at a given membrane potential. Therefore a new model defining the kinetics governing I_K needs to be developed. (Supported, in part, by NIH grants H1207026-01 and training grant G M 07263).

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TOWARD A BROADER UNDERSTANDING OF THE MECHANISM OF ALDOSTERONE ACTION: THE BARNACLE MUSCLE FIBER AS A PREPARATION. E. Edward Bittar and Jude Nwoga*, Department of Physiology, University of Wisconsin, Madison, Wisconsin 53706.

A principal feature of experiments with barnacle fibers preexposed in vivo overnight to 10^{-6}M or 10^{-10}M-aldosterone is that injection of $GTPNa_2$ or (Gpp(NH)p into the cannulated, ouabain-poisoned fiber not only leads to a marked stimulatory response of the Na efflux that is greater than that seen in unexposed, ouabain-poisoned fibers but also to a response that is *sustained*. This develops in the absence of a fall in Em. Both the magnitude of the response and its sustained nature are unaffected by prior exposure to actinomycin D, cycloheximide, colchicine and cytochalasin. However, the magnitude of the response is drastically reduced by injecting protein kinase inhibitor or R_{II} subunits, and completely abolished by injecting Mg^{2+} before or after GTP(and Gpp(NH)p). The response is similarly reduced by external application of verapamil, injection of EGTA, or omission of Ca_e. Further, the data show that a marked reduction in the response occurs as a result of applying trifluoperazine or imipramine (50 μM) before or after injecting GTP (or Gpp(NH)p). It therefore seems likely that calmodulin plays a prominent role in mediating the response to guanine nucleotides and that calmodulin-sensitive adenylate cyclase is the posttranslational site of aldosterone action. Whether aldosterone also acts by increasing cytosolic ATP (Edelman) and whether ATP and GTP limit the reassociation of regulatory with catalytic subunits (Rangel-Aldao and Rosen), is not yet known.

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THE IDENTIFICATION OF ETHANOLAMINE PLASMALOGEN AS A UNIQUE LIPID IN ERYTHROCYTE PLASMALEMMAE FROM DYSTROPHIC CHICKENS. Mark Kester*, C.A. Privitera Department of Biological Sciences, SUNY, Buffalo, New York 14260

Erythrocyte plasmalemmae prepared by osmotic lysis, differential centrifugation and homogenization were obtained from age and sex matched normal (Line 412) and dystrophic (line 413) chickens. Membrane purity was assessed through marker enzymes. Phospholipids were separated by two dimensional thin layer chromatography (T.L.C.). Correlated with the onset of overt dystrophic symptoms (day 30 EX OVO) is the emergence of a measurable and distinct polar lipid, seen only on dystrophic T.L.C. plates. This lipid comprises 3 to 7% of the phosphlipid content from dystrophic erythrocyte membrane over time. However, this polar lipid is observed as early as day 7 EX OVO, as a nondistinct shoulder on the phosphatidylethanolamine (PE) T.L.C. spot. This unique lipid has been identified as ethanolamine plasmalogen. The plasmalogen differs from PE in that the alpha fatty acid is bonded via an ether linkage to the glycerol moiety of the polar lipid, rather than an ester linkage as in P.E. The identification of this plasmalogen has been confirmed through several techniques including T.L.C., gas liquid chromatography, ^{14}C labelling and biochemical assays. The data on this unique polar lipid will be correlated with other data from this laboratory on normal and dystrophic erythrocyte osmotic fragility, erythrocyte turnover time, ion permeability, phospholipid content and fatty acyl profile.

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TAURINE EFFLUX FROM INTERNALLY DIALYZED MYXICOLA GIANT AXON. Lyle W. Horn* (SPON: L. Goldman). Univ. Maryland Sch. Med. Baltimore, MD 21201.

Assay of axoplasm collected from axons dialyzed internally for up to 4 hrs shows that the amino acid composition can be controlled effectively. The membrane potential of dialyzed axons remains stable, and no significant axon volume change occurs, for up to 6 hrs of dialysis with solutions of different amino acid composition. When 3H-taurine is introduced the tracer efflux rises to a steady state within 20 min and remains stable for hrs. 3H-taurine can be removed from the axon by dialysis for 30-40 min with tracer-free solution. Measurement of efflux at several internal taurine concentrations, and a constant internal Na concentration of 100 mM, indicates that $K_{\frac{1}{2}}$ could be as high as 50 mM and V_{max} as high as 3-4 pmoles/cm^2sec. Results are consistent with injected axon experiments. Trans inhibition of efflux by Na can be demonstrated. The effect requires that internal Na be greater than 50 mM, as concluded from injected axon work. A 39 mV depolarization of the axon causes about a 1.5 fold efflux increase, a response expected if the taurine system is electrogenic. Internal dialysis should be a useful method for the quantitative study of Na-coupled amino acid efflux mechanisms. (Supported by NIH Grant NS-14569.)

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SIMULATION OF KING-ALTMAN AND HILL KINETIC MODELS OF CARRIER AND PORE TRANSPORT ON SPICE2 AND NET2 USING NETWORK THERMODYNAMICS. D.C. Mikulecky and B. Bunow*, Med. Col. Va., Richmond, Va. 23298 and NIH, Bethesda, Md. 20205.

Network thermodynamic methods can be used to extend the graphical analysis of kinetic schemes such as the King-Altman method or the Hill method (Free Energy Transduction in Biology Academic Press, 1977) to study transient behavior as well as steady states. Also for some pore models (for example: 4 site, multiple occupancy) the number of partial diagrams needed to derive the state populations and fluxes is in the thousands. These models can be directly simulated in transient and/or steady states using network thermodynamic methods (Bunow and Mikulecky, Proceedings of the VI School on the Biophysics of Membrane Transport, Jastrembia Gora, Poland May 4-13, 1981 [in press]). Examples will include a four site pore model and for a carrier model, the effect of trans concentration effects, use of tracers, and counter transport effects. A simple subcircuit is made for each node (state) in a graph and another for the branches (state transition kinetics) to keep programming as simple as possible. In this manner, the graphical representation directly generates the kinetics of the model as in the King-Altman and Hill methods, but in this case it is not necessary to write any equations at all to obtain the solution by simulation. This makes the method highly accessible to the experimentalist without requiring special mathematical modelling skills.

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EFFECTS OF ANIONS ON VOLUME-DEPENDENT CATION MOVEMENTS IN DOG RED BLOOD CELLS (RBC). John C. Parker. University of North Carolina at Chapel Hill, Chapel Hill, N.C. 27514.

Davson (J Physiol 101:265) reported that anion substitutions had opposing effects on the permeabilities to Na and K (PNa and PK) of dog RBC. When cells were suspended in K media with different anions PNa decreased in the sequence $Cl-NO_3-SCN$, whereas in the same sequence PK increased. These data are reinterpreted in terms of anion-cation cotransport and Ca-gated K movements. Dog RBC have a cotransport system for KCl that becomes manifest when the cells are swollen; a NaCl cotransport pathway is seen in shrunken cells. Both pathways are inhibited by replacing Cl with NO_3 or SCN. The apparent increase in PK in NO_3 and SCN solutions noted by Davson is due to the opening of Ca-dependent K channels. Davson suspended RBC in Na-poor, K-rich media with small amounts of Ca. Ca entry into dog RBC is stimulated by low-Na media (J Gen Physiol 71:1). Under these conditions Ca enters the cells and opens up Ca-dependent channels through which the movements of K are limited by the conductance (g) of the accompanying anion. Since gNO_3 and gSCN are greater than gCl, K movements in this circumstance are stimulated by replacing Cl with the other anions. Thus, dog RBC have KCl and NaCl cotransport pathways responsive to cell volume, plus a Ca-gated K channel which can be activated by introducing Ca into the cells via the Ca-Na exchange route. Furthermore, it appears that Ca influx is faster in NO_3 and SCN.
(Supported by USPHS grant AM11356)

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VANADATE REVERSES THE DIRECTION OF THE HCO_3/CO_2-DEPENDENT PD AND I_{SC} IN TURTLE BLADDER. G. Ehrenspeck. Ohio Univ. Col. of Osteopathic Med. & Dept. Zool. & Microbiol., Athens, OH 45701.

Vanadate(VAN) inhibits sodium-independent Cl and HCO_3 absorption in the turtle bladder (Biochim.Biophys.Acta 601:427, 1980). The effect of VAN on the net acidification rate, measured as the I_{SC} in ouabain-treated bladders (1.5 cm^2 area) bathed by HCO_3/CO_2-rich, Cl-free Na media at pH 7.6 and 22-25C, was further analyzed. The control PD and I_{SC} (means ± S.E.) were -25.0 ± 3.3 mV and -14.1 ± 2.5 μA (N=14), serosal fluid (S) negative to mucosal fluid(M). After 1 mM VAN in S or both S & M, the I_{SC} (&PD) in 7 bladders decreased toward zero (-2.4 ± 1.2 μA) and in 7 others, after reaching zero, reversed in polarity, attaining a sustained value of +3.5 ± 1.0 μA) in 60-90 min ($P(I_{SC}=0)<0.001$ by t-test). VAN failed to reverse the remaining I_{SC} when the HCO_3 of the medium was replaced by SO_4 or bladders were pretreated for 60 min with 1 mM acetazolamide in S. When the I_{SC} was decreased to near zero by 0.2 mM SITS in S, VAN elicited an I_{SC} of +7.3 ± 1.4 μA(N=5) in 5-10 min and the earlier observed oscillations in I_{SC} & PD(ibid.). The reversed (+)I_{SC}, attributed to HCO_3 secretion (Fed.Proc. 40:709, 1981), was stimulated by isobutylmethylxanthine and subsequently inhibited by acetazolamide. It is concluded that VAN decreases the net rate of mucosal acidification by accelerating a HCO_3 secretion process, although a concurrent inhibition of the acidification pump is also possible. (Supported by grants from Ohio Univ. Baker Fund and Col. of Osteopathic Medicine.)

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EVIDENCE FOR A PASSIVE, ELECTROGENIC Na-Cl SYMPORT IN IN VITRO FROG STOMACH. T. C. Chu*, G. Carrasquer, W. S. Rehm and M. Schwartz. Depts. of Medicine and Physics, Univ. of Louisville, Louisville, KY 40292.

Previous studies in Cl media (Biophys J 21a:169, 1978) have shown that step decreases of Na (choline (Ch) for Na) in nutrient fluid (NF) decreased positivity of NF (opposite to that for a simple Na conductive pathway but right for a Ch conductive pathway). Lack of linearity of ΔPD vs. log [Ch] ruled out Ch conductive pathway. For Na, ΔPD vs. log [Na] is almost linear from 6 to 102 mM with ΔPD = -6 mV per tenfold decrease in [Na]. In present work, we found the anomalous PD response for Na resulted also for 1) K-free bathing fluids and 2) 10^{-3} M ouabain in NF. These results could be attributed to a passive, electrogenic Na-Cl symport. Theoretical considerations, for m Cl's and n Na's transported per cycle with m > n, predict an anomalous ΔPD for Na and a normal ΔPD for Cl. Step changes of Cl in NF in Na and also in Ch solutions gave normal PD responses (i.e. decreases in positivity of NF with decreases in [Cl]), indicating that the symport accounted in part for total Cl conductance. Sulfate solutions were expected to eliminate the anomalous response. With 4 mM K in both solutions, anomalous effects resulted sometimes for both increases and decreases in [Na] but more often only for increases in [Na]. With zero K on both sides or with ouabain present in NF, no anomalous response in PD was observed in SO_4 solutions. A modified model including the Na-K antiport will be considered. (NIH and NSF support)

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VOLTAGE-INDUCED PASSIVE MOVEMENT OF Na AND WATER IN TOAD BLADDER: A MODEL FOR PASSIVE WATER TRANSPORT. J.S. Chen and M. Walser, USUHS, Bethesda, MD 20014 and Johns Hopkins University Medical School, Baltimore, MD 21205

We have previously obtained a theoretical model which states that the equilibrium unidirectional passive ion flux in the absence of a chemical gradient or when net flux = 0 can be represented by the logarithmic mean of bidirectional passive ion fluxes in the presence of a chemical gradient. In an attempt to find a model suitable for analyzing passive water transport, in the present study we measured steady state mucosa-to-serosa (M-S) and serosa-to-mucosa (S-M) passive fluxes of Na and water in the isolated toad bladder after ouabain 1.89 x 10^{-3} M) at 100 mV and subsequently at 170 mV (serosa + relative to mucosa). The data showed that Na transport number was increased from 0.33 ± 0.02 (12) at 100 mV to 0.42 ± 0.03 at 170 mV, suggesting that there was a change in membrane permeability induced by the voltage gradient at 170 mV. We also found that net water flux was not present at 100 mV, while a voltage-induced net M-S water flux was observed at 170 mV. Using the bidirectional water fluxes observed at 170 mV we calculated the equilibrium unidirectional water flux from the logarithmic mean flux equation. It was shown that the calculated data was almost identical to the unidirectional water flux observed at 100 mV under which net water flux = 0. Thus, it appears that the logarithmic mean flux model is also suitable for analyzing steady state passive water transport across epithelial tissues.

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CONTROL OF INSTABILITY OF TRANSEPITHELIAL POTENTIAL DIFFERENCE OF CULTURED A6 EPITHELIA. P. POPOWICZ*, A. PRESTON*, J. HANDLER , AND R. STEELE* NHLBI, BETHESDA, MD 20205.

Cells of the line A6, derived from kidney of Xenopus laevis, form an epithelium in culture with a high transepithelial electrical resistance (>3000 ohm-cm^2) when grown on collagen coated nucleopore filters. Replacing the medium on both sides of the epithelium as in "feeding" the cells every two days results in a transient increase in potential difference of the order of 100% in two hours (baseline ∿ 20mV). The instability is a problem in evaluating steady state transport properties under sterile conditions and in testing the effect of hormones and drugs. It may be the result of insufficient nutrient or waste exchange at the epithelium. The instability can be reduced (<30% of basal potential difference) if the epithelium is maintained on an orbital shaker, by feeding every two hours, or by growing the epithelium on more permeable supports such as collagen membranes or millipore filters.

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ELECTROPHYSIOLOGIC STUDIES OF CHLORIDE SECRETION IN CANINE TRACHEAL EPITHELIUM. Stephen Shorofsky,* Michael Field and Harry Fozzard, University of Chicago, Chicago, IL 60637.

Conventional microelectrodes were used to investigate the mechanisms of Cl secretion by canine tracheal epithelium. All tissues were treated with indomethacin to decrease baseline secretion. After obtaining baseline measurements, secretion was stimulated with epinephrine (EPI) and subsequent steady-state measurements were obtained. EPI caused Vsm to hyperpolarize (19 → 28mV), Rsm to decrease (616 → 456Ωcm^2), Vcm to depolarize (-39 → -32mV) and Ra/Rb to decrease (1.7 → 0.8). Vcs did not change significantly (m=mucosa, s=submucosa, c=cell and a and b=cell's apical and basolateral membranes). Assuming that Rms=(Ra+Rb)Rs/(Ra+Rb+Rs) where s=shunt pathway, these results indicate that EPI (1) decreased Ra and (2) also changed Rb, Rs or both. Effects on Vcm of changes in [Na]m, [K]m and [Cl]m were determined. Under baseline conditions, a change of [Na]m from 20 to 144mM or [K]m from 5 to 50mM depolarized Vcm by about 5mV. Altering [Cl]m from 146 to 49mM depolarized Vcm by 9mV. Following EPI, the same Δ[Cl]m caused a 18mV depolarization of Vcm. In a single experiment, EPI reduced by more than 50% the effect on Vcm of the change in [Na]m. These changes in Vcm suggest that EPI causes an increase in the Cl selectivity of the apical membrane. Taken together these results support the notion that EPI stimulates tracheal Cl secretion by increasing the Cl permeability of the apical membrane.

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Possible involvement of tyrosyl-residues in renal sodium-D-glucose cotransport

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In order to characterize the amino acids essential for sodium-D-glucose cotransport, calf renal brush border membrane vesicles were chemically modified by incubation with 0.2 mM NBD (7-chloro-4-nitrobenzo-2-oxa-1,3-diazol), 0.3 mM TNM (Tetranitromethane) and by iodination. These maneuvers inhibit sodium gradient driven D-glucose transport into the vesicles by 70%, 65% and 25%, respectively. NBD and TNM inhibit D-glucose uptake also under tracer exchange conditions; they do, however, not alter the glucose independent sodium uptake by the vesicles. The inhibition of D-glucose transport is not reversed by treatment of the membranes with dithiotreitol suggesting that tyrosyl-residues and not SH-groups have been modified. About 250 pmole iodine are incorporated per mg of membrane protein.
These result provide evidence that modification of tyrosyl-residues inhibits the sodium-D-glucose cotransport system. It might be speculated that - as in sodium channels - a tyrosyl residue is involved in the binding of sodium to the sodium-D-glucose cotransport system.
(This work is supported by Start-Fund of Albert-Einstein College of Medicine of Yeshiva University, BRSG # 613-4564)

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EFFECT OF HEMOGLOBIN CONCENTRATION ON BUFFERING OF LACTIC AND CARBONIC ACIDS IN HUMAN BLODD IN VITRO. Kenneth C. Wessling* and Hugh G. Welch. University of Tennessee, Knoxville, TN 37916.

This study assessed in vitro effects of changing hemoglobin concentration, carbon dioxide tension, and lactic acid concentration on normal human blood pH and bicarbonate concentration. Hemoglobin concentration was varied among separated plasma, normal blood, and high hematocrit blood samples with 0, 2.1, and 2.4 mM mean hemoglobin concentrations, respectively. The carbon dioxide tension was held constant at either 40 or 20 mm Hg while the oxygen tension was always 95 mm Hg. Lactic acid concentration was maintained within a low range of 1.0 to 2.7 mM and within a high range of 10.7 to 11.7 mM. The pH and bicarbonate responses to a constant lactic acid load among the three hemoglobin levels indicated that bicarbonate was the major buffer of lactic acid. Estimates were made of the relative contributions of plasma bicarbonate, plasma proteins, erythrocyte bicarbonate, and erthrocyte proteins to the total lactic acid buffering. There was no increase in lactic acid buffering when hemoglobin concentration was increased by 12.7%. There was also an indication that lactate participated in the chloride shift when lactic acid was added to blood. (Supported in part by American Heart Association, East Tennessee Chapter and by NIH grant 5507RR07088-11.)

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A STUDY OF THE OSMOLALITIES IN BODY FLUIDS MEASURED BY AN AUTOMATED STAT/ROUTINE ANALYZER AND A MICRO-FREEZING POINT OSMOMETER. William C. Foster and Robert A. Donato*. Lab. of Clin. Chem., Jeanes Hospital, Philadelphia, PA 19111.

Disturbances in fluid balance of the body may be reflected by changes in osmolality. Measurement of the serum osmolality was accomplished with an automated stat/routine analyzer (Beckman Astra-8). Osmolality in this instrument was derived by computation, using the equation of H. F. Weisberg.[1] Results were compared with those obtained from an automated high sensitivity micro-osmometer[2] using only 50 ul of sample, whereas in the first named instrument 220 ul were necessary. Osmolalities of urine and other body fluids except serum and plasma, could not be measured with this instrument because of extreme differences in constituent levels of ionized and non-ionized electrolytes, and non-ionizable constituents, as glucose and urea. The micro-osmometer was set with precise salt standards of 100 and 500 mOsm. A range of 277 to 291 with a mean of 284 mOsm, compared to values of 259 to 286, and mean of 272 mOsm on the automated stat/routine analyzer. The expected higher values on the former instrument were confirmed.

1. ASCP - Commission on Continuing Education, pp. 25-28 (1971)
2. Precision - Micro-Osmette.

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IN VITRO PROPERTIES OF THE MEALWORM RECTAL COMPLEX: THE MOST POWERFUL WATER REABSORBING SYSTEM YET ANALYSED. John Machin. Univ. of Toronto, Toronto, Ont. M5S 1A1

The excretory system of beetle larvae adapted for feeding on dry grain products consists of a sheath of ion transporting tubules surrounding and osmotically coupled to the rectum. Water is apparently reabsorbed by means of standing osmotic gradients in the tubules which routinely reach 6.7 Osmols. kg^{-1} at their posterior ends. The rectal complex operates either in a counter-current mode to dehydrate the feces or, with the anus open, to absorb water vapor. Water reabsorption continues to minimum water activities of 0.88. Isolated rectal complex preparations under mineral oil, provided they are supplied with appropriate ions, display essentially the same transport characteristics as the intact animal. Water transport depends on typical insect potassium pumps conveying ions to the tubules from the blood or rectal lumen either separately or simultaneously. Water is transported only from the rectal lumen to the tubules. The *in vitro* preparation readily extracts water from 3M sucrose solutions. The extremely high osmotic pressures generated by the rectal complex is seen to be partly due to comparatively low water permeabilities and flow rates which are characteristic of the majority of insect excretory systems.
(Supported by Natural Sciences and Engineering Research Council Canada, operating grant A1717).

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EFFECT OF HYPERCAPNEA AND INSPIRATORY FLOW-RESISTIVE LOAD (R_I) ON P100 AND WORK OF BREATHING IN PRETERM INFANTS. Shahnaz Duara*, Soraya Abbasi*, William W. Fox*, Thomas H. Shaffer. Children's Hospital of Philadelphia, and Temple University, Department of Physiology, Philadelphia, PA. 19104

To evaluate the depressed carbon dioxide (CO_2) response curve seen with inspiratory resistive load in premature infants as previously reported (Duara et al., Peds. Res. 1981), occlusion pressures by P100 and work of breathing (WOB) were studied in preterm infants during progressive hypercapnea, with and without loading. The infants, 31.5±.91 weeks by gestation (mean ±SEM), at study were 38.1±.63 weeks conceptional age and 1.94± .08 kgm. in weight. Resistive load (R_I)=100 cm H_2O/L/sec at a flow-rate of 1 L/min. All infants were studied during quiet sleep, breathing room air. Minute ventilation ($\dot{V}_E$) and P100's, unloaded and loaded, were compared during progressive hypercapnea (n=5). Hypercapnea produced a linear increase in $\dot{V}_E$ and P100 in all patients. With loading, the slope of $\dot{V}_E$ ($\Delta\dot{V}_E/\Delta PACO_2$=16.87±3.6 ml/min/torr$CO_2$) decreased significantly ($p<.02$) but there was no significant change in the P100 slope ($\Delta P100/\Delta PACO_2$=.28±.22 cm H_2O/torrCO_2). WOB (n=9) was studied during progressive hypercapnea, unloaded and loaded, and showed no significant alteration in the slope ($\Delta WOB/\Delta PACO_2$) following load application. These data suggest that preterm infants do not augment either P100-or WOB-hypercapnea responses with a flow-resistive load. (Supported in part NIH Grant #HL-22483)

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RESPIRATORY WORK RESPONSE TO RESISTIVE LOADING IN PREMATURE NEONATES. Soraya Abbasi*, Shahnaz Duara*, William W. Fox*, Thomas H. Shaffer. Children's Hospital of Philadelphia and Temple University, Dept. of Physiology. Phila., PA. 19104

To evaluate the effect of inspiratory resistive loading on work of breathing, 9 premature infants were studied. Mean ±SEM birthweight 1503±135 grams, gestational age 32.5±0.7 weeks, study age 30.4±8.4 days, study weight 1700±98 grams. Control data including dynamic compliance (C_L), tidal volume (TV), minute ventilation (MV), respiratory frequency (f), alveolar carbon dioxide ($PACO_2$) and inspiratory work of breathing ($\dot{W}_I$) were obtained prior to application of 100 cm H_2O/L/sec (R_1) and 150 cm H_2O/L/sec (R_2) at 1 L/min flow rate. Infants were breathing room air throughout the study. Studies were repeated immediately, 5 and 10 minutes following application of R_1 and R_2. Mean ± SEM control values were: C_L = 3.49±1.48, TV=13.5± 1.5 ml, MV=745.9±55 ml/min, f=57±4.3 breaths/min, $PACO_2$=34.5± 3.3 mmHg, $\dot{W}_I$=.04±.005 kg.m/min. There was a significant decrease immediately, at 5 and 10 minutes for TV=7±1.3 ml ($p<0.05$), MV=355±54 ml/min ($p<0.05$), $\dot{W}_I$ = .02±.004 k.gm/min ($p<.01$). There were no significant changes in frequency and $PACO_2$ immediately, at 5 or 10 minutes. There was no significant difference between all parameters obtained for R_1 and R_2. These data indicate that there is an immediate and continuing decrease in ventilation and work of breathing with R_1 and R_2. This lack of compensation to added inspiratory resistive load over time by premature infants may be important in some infants with obstructive apnea. (Supported by NIH Grant #HL-22483).

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ELECTROPHYSIOLOGICAL CHARACTERISTICS OF PREMATURE LAMB CARDIAC PURKINJE FIBERS. Steven R. Houser. Department of Physiology, Temple University School of Medicine, Phila., Pa. 19140.

Little information exists concerning the basic electrophysiological properties of cardiac Purkinje fibers from preterm animals. The goal of the current investigation was to determine basic electrophysiological parameters in preterm (106 days gestation) lambs using standard microelectrode techniques. In addition, all preparations were exposed to ouabain ($5x10^{-8}M$). Pregnant sheep were given spinal anesthesia and the lambs delivered by cesarean section. Hearts were removed from both mother and baby and Purkinje fibers (PF) removed and placed in an oxygenated tissue bath. Preparations were stimulated at rates from 30-150/min and were allowed to equilibrate for one hour. The results of the study showed that at normal K^+ concentrations (5.4mM) there were major alterations in the shape of the action potential recorded from PF of premature lambs. In particular the following were most significant. 1) A decrease in plateau height. 2) A decrease in action potential duration (APD). In addition Ouabain had significantly different effects on PF's from the premature lambs. Specifically, upon addition of Ouabain the APD decreased in adults whereas in premature the APD lengthened. Both depolarized over time as toxicity developed. There was no apparent difference in the time to develop toxic arrhythmias. These results suggest these cells have fewer ion channels in the membrane. (Supported by NIH #'s HL 22843-04, HL 22673)

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CARDIAC OUTPUT (CO) AND ITS DISTRIBUTION IN THE PREGNANT GUINEA PIG (GP) WITH LOW LEVELS OF CARBOXYHEMOGLOBIN (COHb). Joachim Wolf-Priessnitz*, A. Roger Hohimer and James Metcalfe. Oregon Health Sciences University, Portland, OP 97201

Arterial catheters were implanted in 10 near-term pregnant GPs 4-6 days before radionuclide-labeled microspheres (15 µm) were injected into the left ventricle to determine CO and its distribution (gestation 59-66 days; term 68 days). GPs were studied before (C) and 1-2 hrs after (E) exchange transfusion (5-16 ml) with donor blood containing 100% COHb. Control (C) maternal COHb concentrations were <1%; experimental (E) 2.3-5.2% with fetal 3.8-11.6%. No significant hemodynamic differences were observed between C and E groups ($\bar{x}$ ± SD):

	CO ($ml \cdot min^{-1}$)	CO ($ml \cdot min^{-1} \cdot kg^{-1}$)	MABP (torr)	HR (bpm)
C	296±28 (n=8)	282±24 (n=8)	56±6 (n=9)	295±32 (n=8)
E	323±63 (n=7)	309±48 (n=7)	55±6 (n=9)	279±27 (n=9)

The % distribution of CO also remained constant (n=8, $\bar{x}$ ± SD):

	Uterus & Contents	Kidneys	Heart	Brain	Lungs	GI Tract	Carcass
C	12.2±4.2	9.0±1.7	2.3±.5	1.8±.5	9.2±2.1	11.9±1.8	53.5±5.9
E	11.2±4.8	8.8±2.1	2.3±.5	1.8±.5	8.9±2.7	12.4±1.3	54.9±5.1

The results show that no major maternal hemodynamic changes or redistribution of CO occurs in response to acute exposure to low COHb levels in the near-term GP. (Supported by USPHS Training Grant HD07084 and Research Grants HL25731 & HD10034)

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TRACHEAL MECHANICS IN PRETERM LAMBS AFTER LIQUID VENTILATION: V.K. Bhutani* and T.H. Shaffer; Department of Physiology, Temple University School of Medicine, Phila. Pa. 19140.

Liquid Ventilation(LV) with fluorocarbon (FC-80) has been demonstrated as a viable mode of ventilatory support of preterm lambs. The effect of L.V. and its high inflating pressures (68.8 ± 3.8 SE cmH_2O) were evaluated on the mechanical behavior of the trachea of 7 preterm lambs of 134 ± 1.5 SE days gestation (90% term gestation) after liquid ventilation (57.6 ± 13.0 SE mins.). The extrathoracic trachea was dissected and the non-ventilated segments (Group I) were compared to the ventilated segments (Group II). Mean ± SE values of diameter (D), volume (V) per 1 cm segmental length, and pressure-volume (P-V) curves (by plethysmography) were obtained in both groups. Tracheal specific compliance (C_S) was computed from the deflation limb of the P-V curves at 0 to 10 cmH_2O pressure.

	D(mm)	V(ul)	C_S (cmH_2O^{-1})
Group I	5.9 ± 0.24	204.2 ± 11.3	0.0274 ± 0.0011
Group II	6.7 ± 0.21*	331.8 ± 10.1*	0.0192 ± 0.0012*

These results demonstrate significant[*$p<0.05$]changes with 13.6% increase in D; 25.6% increase in V; and 29.9% decrease in C_S. The magnitude of these alterations are comparable to those observed following gas ventilation of term animals (Bhutani et al Ped. Res 15: 829-832, 1981). Data suggest that mechanical and dimensional deformation of the trachea are similar in both gas and L.V. [Supp. by PHS HL 22843].

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CARDIOPULMONARY FUNCTION IN VERY PRETERM LAMBS DURING LIQUID VENTILATION. T.H. Shaffer, N. Tran*, E.M. Sivieri*, and V.K. Bhutani*. Department of Physiology, Temple University, School of Medicine, Phila., Pa. 19140.

Cardiopulmonary function was evaluated in 5 preterm lambs (106 ± 0.7SE days gestation, 1.66 ± 0.12SE Kg. Birth Wt.) during fluorocarbon (FC-80) ventilation. Lambs were delivered by caesarean section following spinal anesthesia. Indwelling arterial, venous and tracheal cannulae were placed before clamping the cord. Lambs were then mechanically ventilated with oxygenated (P_IO_2 = 658 mmHg, P_ICO_2< 5 mmHg) fluorocarbon for a duration of 110 ± 26 SE min. During liquid ventilation it was possible to achieve the following mean ± SE data for cardiopulmonary function: PaO_2 = 242.5 ± 49.4 mmHg; $PaCO_2$ = 30.8 ± 1.0; pH = 7.29 ± 0.02; Base deficit = 10.9 ± 0.9 meq. HCO_3^-; A-a O_2 = 415.5 ± 50.0 mmHg; mean arterial pressure = 58 ± 14.7 mmHg; central venous pressure = 7.9 ± 1.1 mmHg; and heart rate = 156 ± 20 b/min. Transpulmonary pressure, liquid flow and tidal volume tracings in 3 lambs enabled determination of lung compliance, C_L = 0.58 ± 0.12SE ml/cmH_2O/kg. These results demonstrate that it is possible to maintain adequate gas exchange and stable cardiac function in very preterm lambs using fluorocarbon ventilation. Lung compliance of the 106 day old fluorocarbon-filled lung is similar to the more mature 138-143 day old air-filled lung in preterm lambs. (Shaffer et al, Respiration Physiol., 1976).

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BODY COMPOSITION AND WATER METABOLISM IN TWO SUBSPECIES OF THE COTTON RAT, Sigmadon hispidus. Elizabeth Miescher* and Henry Prange, Med. Sci. Prog., Indiana Univ., Bloomington, IN 47405

The subspecies of cotton rat indigenous to Kansas (KSh) produce larger litters than those indigenous to Tennessee (Sh). We examined the effect of litter size on body composition and water turnover. KSh rats were larger than Sh rats but the proportion of fat (as measured from tritiated water dilution estimates of total body water) was less; however, the absolute amount of fat was not different for the 2 subspecies. Although KSh rats produced larger litters the wt of the individual pups was not different and the total litter wt as a proportion of the maternal wt were similar. The decline in fat of the mothers during lactation measured in absolute terms was the same for the 2 subspecies, but the total wt gain of the KSh litters was greater than that of the Sh subspecies. The water turnover as a function of body mass of Sh rats was greater than that of KSh rats. However, during lactation the differences between the subspecies disappeared. When compared with non-reproductive females, lactation was associated with a reduction in body water turnover. Our results suggest that 1) the larger litter size of KSh rats is a function of maternal body mass, 2) the food intake of the KSh rats during lactation is proportionally greater than that of the Sh rats, 3) the greater water turnover of Sh rats is possibly a function of greater surface area, 4) the reduction in water turnover during lactation is greater for the Sh rats and may reflect a greater renal concentrating mechanism.

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EFFECTS OF DISULFIRAM ADMINISTRATION ON REPRODUCTIVE ACTIVITY IN FEMALE RATS. A. A. Krum and P. L. Rayford, Dept. of Physiology-Biophysics, Univ. Ark. Med. Sci., Little Rock, AR 72205.

There is a paucity of data concerning disulfiram ingestion by female animals and it is further recommended that pregnant women refrain from its use. Daily disulfiram administration to adult female rats was investigated for its influence upon the estrous cycle, reproductive capability as to the number of young born and their birth weight, and growth of the pups during lactation. Rats were divided into 3 groups. Group I received corn oil (vehicle). Groups II and III received 30 and 60 mg disulfiram in corn oil, respectively. All treatment was via oral intubation into the stomach. Vaginal smears were taken daily. Smears from the drug treated animals exhibited a preponderance of cornified cells and cycles were prolonged. The number of full term pregnancies observed was 8 of 8 in controls; 7 of 8 at 30 mg; and 5 of 8 at 60 mg. Birth weights of all groups were similar and no gross abnormalities were noted. The number of young delivered was significantly less in rats treated with 60 mg of disulfiram (7.2) when compared to controls (11.4). Growth of all the young was linear during lactation, however, slopes of regression lines of treated rats were reduced ($P<0.01$) compared to controls. We conclude that in rats disulfiram has a deleterious effect on the reproductive cycle, reproductive capability and growth of newborn.

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METABOLIC AND CARDIOPULMONARY RESPONSES OF GERIATRIC WHEELCHAIR DEPENDENT AND AMBULATORY PATIENTS DURING LOCOMOTION. C.A. Simsen-Harold*, R.M. Glaser, J.S. Petrofsky, D.E. Stanley*, S.E. Kahn*, A.G. Suryaprasad*. Wright State Univ. Sch. of Med., Dayton, OH 45435 and VA Medical Center, Dayton, OH 45428

The purpose of this study was to determine the magnitudes of metabolic and cardiopulmonary responses of geriatric wheelchair dependent (WD) and ambulatory patients during locomotion at their comfortable velocities. For this, 8 WD ($\bar{x}$ = 62 yr) and 10 ambulatory ($\bar{x}$ = 58 yr) residents of the VA Medical Center were instructed to propel their wheelchairs or walk on a level, tiled surface at their preferred velocities. During two subsequent 5 min tests, subjects were paced at their chosen velocities and oxygen uptake ($\dot{V}O_2$), pulmonary ventilation ($\dot{V}E$) and heart rate (HR) were determined during the final min of each test. Mean results were as follows: velocity = 2.0, 3.1 $km \cdot hr^{-1}$; $\dot{V}O_2$ = 0.535, 0.814 $l \cdot min^{-1}$; $\dot{V}E$ = 19.4, 26.2 $l \cdot min^{-1}$; and HR = 95, 92 bpm during wheelchair locomotion and walking, respectively. Although $\dot{V}E$ and $\dot{V}O_2$ were less for WD individuals, the HR values were similar suggesting comparable relative stress for these forms of locomotion. Considering the physical work capacity (PWC) for wheelchair locomotion (arm work) is lower than that for walking (leg work), it appears that both groups performed at similar % of their PWC. The 37% lower velocity for wheelchair locomotion as opposed to walking could reduce rehabilitative capabilities. (Supported in part by Rehabilitative Engineering R&D Service of the VA and the VA Rehabilitation Engineering Center)

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PHYSIOLOGICAL RESPONSES OF GERIATRIC PATIENTS TO CONVENTIONAL AND ARM-CRANK WHEELCHAIR PROPULSION. D.E. Stanley*, R.M. Glaser, J.S. Petrofsky, C.A. Simsen-Harold*, S.E. Kahn*, and A.G. Suryaprasad*. Wright State Univ. Sch. of Med., Dayton, OH 45435 and VA Medical Center, Dayton, OH 45428

Stresses involved in propelling the handrims of conventional manual wheelchairs could hinder rehabilitative efforts for geriatric patients. The purpose of this study was to determine the benefits of an arm-crank wheelchair propulsion system with respect to locomotive ability of these individuals. For this, oxygen uptake ($\dot{V}O_2$), pulmonary ventilation ($\dot{V}E$), and heart rate (HR) responses of 5 geriatric VA Medical Center patients ($\bar{X}$ age = 59) were determined during wheelchair locomotion using conventional handrim propulsion and an arm-crank propulsion system. The patients operated both wheelchairs at their own "chosen" velocities as determined by an electronic speedometer. After 3 trials, $\bar{X}$ chosen velocity was found to be 2.2 and 2.8 $km \cdot h^{-1}$; whereas $\dot{V}O_2$ was 0.564 and 0.562 $l \cdot min^{-1}$, $\dot{V}E$ was 19.9 and 19.1 $l \cdot min^{-1}$, and HR was 96 and 93 bpm for the conventional and arm crank wheelchairs, respectively. The equality of $\dot{V}O_2$ for operating these wheelchairs at the chosen velocities suggests that this selection was based upon metabolic demands. The 27% higher velocity for the arm crank wheelchair and the lower $\dot{V}E$ and HR values indicate that this form of locomotion is more efficient and may improve the rehabilitation of geriatric wheelchair-dependent patients. (Supported in part by Rehabilitative Engineering R&D Service of the VA, and the VA Rehabilitation Engineering Center)

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SELECTIVE ADVANTAGE OF GOMPERTZIAN AND OTHER HYPOTHETICAL POPULATIONS DISPLAYING SENESCENCE. H. R. Hirsch. Dept. of Physiology and Biophysics, U. of Kentucky, Lexington, KY 40536

Rates of natural increase, r, of several hypothetical populations are calculated by numerical solution of an integral characteristic equation. The r value is used as a measure of selective advantage. A population is characterized by its longevity function (probability of survival of an individual vs. age) and by its maternity rate. Senescence is represented by an increase in death rate with age and is reflected in the degree of rectangularity of the corresponding longevity function. The evolutionary consequences of senescence are separated from the effects of simple extension of longevity by normalizing the mean of the longevity function. Senescence is shown to have selective advantage (a) whether the longevity function is determined by the Gompertz law or by a power law and (b) whether the maternity rate is constant or follows a quasi-human function of age. When the parameters of the longevity function are selected to approximate human data, the shape of the function departs considerably from the rectangular form which depicts maximal senescence, but the calculated r value closely approaches the limit associated with this form. Other results indicate that reproduction early in the life of an organism is strongly favored over reproduction late in life but is limited by the requirements of its program of development.

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AGE-RELATED PLASMA ENZYME AND HORMONE RESPONSES TO RESTRAINT. Barnett A. Rattner, Sandra D. Michael*, and Paul D. Altland. NIH, Bethesda, MD 20205 and SUNY, Binghamton, NY 13901.

Immobilization is a routine laboratory procedure that has been extensively utilized as a model for stress in adult rodents, yet the physiological consequences of restraint at different ages have not been thoroughly investigated. To ascertain age-related responses, immature (28-35 day), young adult (50-60 and 140-170 day), and middle aged adult (395-425 day) Sprague-Dawley rats were housed without food and water (controls) or lightly restrained without undue compression in perforated tubes (n=10/treatment/age) for 4 h. Body weight (BW) and T_{re} were determined, and then rats were bled by cardiac puncture. Factorial ANOVA (control or restraint by age) indicated that there was a treatment by age interaction ($P<0.01$) for plasma activities of alanine and aspartate aminotransferase, and creatine kinase, which were elevated ($P<0.05$) in only immature and middle aged rats. Restraint reduced ($P<0.005$) unit BW (g/100g), T_{re}, and plasma luteinizing hormone concentration, and increased ($P<0.003$) the activities of fructose-diphosphate aldolase, lactate dehydrogenase, and corticosterone concentration; these responses were of a similar magnitude in all age categories. On the basis of these changes in plasma enzyme activities, young adult rats (50-60 and 140-170 day) appear to be slightly more tolerant to restraint than immature and middle aged rats. This is in contrast to marked age-related differences in tolerance observed with other stressors (e.g., hypoxia, temperature extremes).

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GENE EXPRESSION IN AGING RAT LIVER: INVESTIGATION OF CHANGES IN THE EXPRESSION OF THE GENE FOR α_{2u} GLOBULIN WITH A CLONED cDNA PROBE. Bandana Chatterjee*, T. Surend Nath*, and Arun K. Roy. Dept. Bio. Sciences, Oakland Univ., Rochester, MI 48063.

Hepatic synthesis of α_{2u} globulin is under the primary inductive influence of the androgen while several growth and developmental hormones such as thyroxine, glucocorticoids, growth hormone and insulin synergistically influence the androgen action. Both prepubertal (<40 days) and senescent (>24 mo) male rats do not synthesize α_{2u} globulin. In order to explore the molecular mechanisms of the age and hormone dependent synthesis of α_{2u} globulin we have cloned the double stranded cDNA for α_{2u} mRNA in the plasmid vector pBR 322. Examination of the hepatic mRNA from rats of various ages with cloned cDNA hybridization and also by in vitro translation revealed that age-dependent synthesis of α_{2u} globulin closely parallels both the levels of translatable α_{2u} mRNA and sequences complementary to the cloned cDNA. Analysis of the androgen receptor activity of the hepatic tissue showed that androgen insensitivity of the prepubertal and senescent male rats is due to an absence of the cytosol androgen receptor. From these results it can be concluded that age-dependent changes in androgen receptor activity may regulate the transcription of α_{2u} gene. (Supported by NIH grant AM-14744-10 and RCDA K04 AM00141)

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CELLULAR METABOLITE DISTRIBUTION IN THYROTOXIC PERFUSED RAT LIVER EXPOSED TO ETHANOL. Sant P. Singh and Ann K. Snyder,* VA Medical Center and Chicago Medical School, North Chicago, IL 60064

Both ethanol (ETOH) and thyroid hormones can influence hepatic glucose output in fasted state. In the present study, normal and thyrotoxic rat livers were exposed to ETOH during perfusion and the levels of intermediary metabolites were measured to determine the location of the combined effects of ETOH + thyroxine (T_4) on gluconeogenesis from alanine. Rats, 150-200g, were rendered thyrotoxic by ip injection of ℓ-T_4 (250 µg/100g B.W.) daily X 7. After 24h fast, livers from T_4 treated and control (diluent treated) rats were perfused for 120 min with recirculating KHB-albumin medium enriched continuously with alanine. After 60 min perfusion, ETOH was added (final concentration 20 mM). In parallel experiments, ethanol was omitted. At the end of perfusion, liver was freeze-clamped for determination of gluconeogenic intermediate levels. Thyrotoxic liver, without ETOH, displayed higher concentrations of oxalacetate, malate, p-enolpyruvate (PEP) and 3-P-glycerate (3PGA) but lower concentration of pyruvate (P) than normal liver. ETOH obscured this crossover point by enhanced formation of triose phosphate from 3PGA. Concentration of fructose diphosphate was increased, but levels of fructose-6-phosphate and glucose-6-phosphate were comparable to corresponding values in euthyroid liver. (Supported by the Veterans Administration.)

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Major Change of Intermediary Metabolism by Behavioral Rest States. R. Jevning and A.F. Wilson*, University of California, Irvine, CA 92717.

Present understanding of intermediary metabolism is mostly based upon study of "basal", or else of activated, physiologic states. We describe profound acute and chronic departure from "normal" metabolism during the "transcendental meditation technique" (TM), a state of decreased activation elicited regularly by numerous individuals. Study is complete in 10 long-term TM subjects, and in 13 individuals studied prior to learning TM, of relative forearm pulsatile blood flow change and arteriovenous difference of O_2, CO_2, and blood lactate content change at 15 minute intervals during, and for 30 minutes after, 45 minutes of practice (TM for the TM group, and ordinary, unstylized rest for the other group). Respiratory quotients were calculated using the Fick principle: R=CO_2 elimination rate ÷ O_2 consumption rate = ($CvCO_2$-$CaCO_2$) x blood flow ÷ (Ca_{O_2}-Cv_{O_2}) x blood flow, that is, AV difference of CO_2 divided by AV difference of O_2. Significant declines of oxygen extraction occurred in both TM and rest subjects during practice (32% and 25%, respectively), as reflected in narrowed AV difference. Striking decline of CO_2 generation occurred during TM (95%) and during rest (25%). CO_2 generation in TM subjects was markedly lower than the rest group throughout the study. Mean (± S.E.) initial R values were .25 ± .02 and .75 ± .03 for TM and rest groups, respectively. These data imply major departure from "normal" metabolism due to rest state elicitation. (Partial support: NIMH 29791)

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CHRYSAORA TOXIN AND SITE SPECIFICITY IN MITOCHONDRIAL RESPIRATION. John Wolk* and James Watrous. Saint Joseph's University, Philadelphia, PA 19131

Chrysaora nematocyst toxin, a proteinaceous substance isolated from tentacles of the Chesapeake Bay sea nettle, affects a variety of membrane associated phenomena, especially those involving cation movement. Chrysaora toxin has been shown to affect O_2 consumption in rat liver mitochondria, but its exact mode of action has not been elucidated. This study employed appropriate combinations of substrates and inhibitors to functionally isolate segments of the electron transport chain in intact rat liver mitochondria. Chrysaora toxin (50ug/mg mitochondrial protein) stimulated O_2 consumption rates both in the presence and absence of ADP. This stimulation was accompanied by a reduction of the acceptor control ratio. The P/O ratios were also diminished, but to a lesser extent. The observed increases in respiration occurred regardless of substrate used (glutamate/malate; β-hydroxy butyrate; succinate/rotenone). These data suggest that the mode of action of Chrysaora toxin more closely resembles an uncoupler rather than a respiratory chain inhibitor. Supported in part by NSF grant SPI-7926889.

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WITHDRAWN

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METABOLISM MEASUREMENT IN AN OPEN CIRCUIT SYSTEM - MATERIAL BALANCE ANALYSIS. Trudy Abrams* and Paul Webb. Webb Associates, Yellow Springs, Ohio 45387.

We have used the principles of mass balance to construct a mathematical model of our open circuit Metabolic Rate System which identifies requisite parameters and possible sources of error in the system. The model has been incorporated into a computer program which accepts as its input ambient conditions of temperature, humidity, and pressure; total air flow per minute; and projected physiological conditions of $\dot{V}_{O_2}$, RQ, and ventilatory ratio. The aim is to determine a Δ $\%O_2$ while any one of the inputs varies, and to construct a plot with the varying input as the independent variable and the Δ $\%O_2$ as the dependent variable. The program accomplishes this by doing a repetitive material balance on the components of each of four gas flow streams: room air pulled through a face mask; room air inhaled; exhaled air; and the main air stream containing respiratory products diluted by room air. The model bridges the gap between what the analyzers actually measure - changes in partial pressures of gases - and what we really want to measure, V_{O2} and V_{CO2}. It also shows the effect of each variable involved in bridging the gap, which is the basis for improving measurements and calibrating the system.

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INCREASED LEVELS OF ENERGY EXCHANGE IN WOMEN AFTER OVULATION. Paul Webb. Webb Associates, Yellow Springs, Ohio 45387.

We measure energy exchange by continuous direct calorimetry and continuous indirect calorimetry (metabolism) for 36 to 46 hours. Our direct calorimeter is a heavily insulated suit with a cooling network of water-filled tubing next to the skin. Metabolism is measured with an open circuit system employing a ventilated full face mask. Conditions for this study were standardized in a "quiet day" of sedentary activity, including reading, watching TV, and conversation, with regular meals and 8 hours of sleep in bed at night. We measured energy exchange in 10 women in their 20's, 40's, and 50's, either weekly for 4-6 weeks or 4 to 8 times sporadically. Eight women were menstruating, one was a castrate, one postmenopausal. Time of ovulation was determined from the succeeding onset of menses, plus urinary pregnanediol and early morning temperature data in some subjects. Both heat loss and metabolism were higher following ovulation, by up to 15% of the preovulatory levels. Also, body temperature (rectal site) ran higher postovulation. The two non-ovulating women showed no change in energy or temperature levels. One menstruating young woman taking a birth control pill showed no change in levels.

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DIETARY INDUCED HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS IN BROOK TROUT (Salvelinus fontinalis). A.P. Farrell* and B.I. Munt* SPON:(W.R. Driedzic). Mount Allison University, Sackville, N. B., Canada. EOA 3C0.

Hypercholesterolemia was induced in 2 year old fresh water trout by supplementing their normal hatchery diet with 0.05 g /day cholesterol. Control fish (n = 3) on a normal hatchery diet had an average serum cholesterol level of 165 ± 45 mg. dL^{-1} over the 14 week experimental period, compared to 383 ± 45 mg.dL^{-1} in the cholesterol supplemented fish (n = 3). The fish were sacrificed at the end of 14 weeks and the coronary arteries were histologically examined for atheromatous lesion formation. A low percentage (7.7 ± 2.5%) of the arterial sections examined (n = 200) in the control fish contained an early form of a lesion, while the remainder appeared normal. In contrast, of the 200 arterial sections examined from the cholesterol fed fish almost half of them (48.5 ± 4.6%) had lesion sites. In addition, severe lesion activity, i.e. ulceration or very extensive medial thickening, was seen in 3.0 ± 1.2%. These results are consistent with hypercholesterolemia promoting atherosclerosis in coronary arteries of fresh water trout. Since the time course of these pathological changes was relatively short (14 weeks) and the dietary changes were simple, the trout should be considered as a good experimental animal for future atherosclerosis research.

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EFFECT OF FASTING, FATTY ACIDS AND WORK ON CARNITINE TRANSPORT IN ISOLATED PERFUSED RAT HEARTS. Thomas C. Vary and James R. Neely. Department of Physiology, Penn State University, Hershey, PA 17033

The maintenance of intracellular myocardial carnitine may depend upon uptake from the blood. At physiological serum carnitine concentrations, 85% of the total carnitine uptake appears to occur via a carrier-mediated transport system. However, factors which regulate this uptake process have not been elucidated. Uptake was studied in rat hearts perfused with Krebs-Henseleit buffer supplemented with 40 μM ^{14}C-L-carnitine and either 11 mM glucose or 1.2 mM palmitate. Fasting resulted in a 2.5 fold increase in tissue level of long chain acyl carnitine, but did not alter the rate of carnitine transport. Hence, large variations in intracellular carnitine and free carnitine had no effect on uptake of extracellular carnitine. At low work, addition of 1.2 mM palmitate increased carnitine transport by 50%. With 11 mM glucose as substrate, increasing the perfusion pressure to 140 mm Hg did not increase carnitine transport. However, high work+1.2 mM palmitate stimulated transport 70% over the glucose perfused hearts. Thus, the rate of carnitine transport was enhanced by fatty acids in the perfusate at both work levels. Futhermore, when fatty acid uptake was stimulated by high work, carnitine uptake was further stimulated. These results suggest that carnitine transport may be coupled to fatty acid utilization. (Supported by grant #HL-13028).

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HISTAMINE METABOLISM AND ITS POTENTIAL REGULATION IN BOVINE AORTIC ENDOTHELIAL CELLS. Alicia Orlidge* and Theodore M. Hollis. Penn State Univ., University Park, Pa. 16802.

Endothelial cell (EC) histamine metabolism was examined in vitro for purposes of characterizing histamine synthesis, catabolism, and substances influencing these events. The rationale is based on previous in vivo work implicating EC histamine synthesis in early phases of atherogenesis and in experimental diabetes. A linear relationship exists between extracellular histidine concentration and EC histidine decarboxylase (HD) activity. ^{3}H-histidine uptake is saturable by 60 min; the K_m is 4.0 μM, with a Vmax of 400pM/10^6 cells/15 min. Insulin (1 U/ml,0.1 U/ml) increases histidine uptake while reducing both HD and histamine methyltransferase (HMT) activity. α-hydrazinohistidine (αHH) depresses histidine uptake while significantly inhibiting both HD and HMT activities; glucose (300 mg/dl) reduces HD activity but has little effect on histidine uptake and HMT activity. Incubating αHH with all the above results in further decreases in HD and HMT activities and substrate uptake. EC histamine is associated with altered large vessel permeability to circulating macromolecules during atherogenesis. Accordingly, the ability of both insulin and αHH to independently reverse all measured alterations in histamine metabolism seen in both atherogenesis and experimental diabetes suggests that artery wall histamine metabolism represents an important component of the atherogenicity of diabetes. (Supported by the American Health Assistance Foundation).

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INFLUENCE OF INSULIN ON AORTIC ENDOTHELIAL (EC) AND SMOOTH MUSCLE CELL (SMC) HISTAMINE METABOLISM IN EXPERIMENTAL DIABETES. Jeffrey C. Yost* and Theodore M. Hollis. Pennsylvania State University, University Park, Pa. 16802.

Previously we have shown that both EC and SMC histamine synthesis, mediated by histidine decarboxylase (HD), is increased under a variety of atherogenic stresses including diabetes mellitus. Studies have also shown that this effect is completely reversible with exogenous insulin administration. The present study has been undertaken to determine if aortic histamine synthesis, mediated via HD, is modulated by insulin, i.e., is dose dependent, under conditions of streptozotocin diabetes. Animals were held for 21 days, followed by insulin administration (either 0, 2, 4, or 6 U/24 hr) for 6 additional days. With respect to control, both EC and SMC HD activities were significantly elevated in aortas from untreated diabetic animals. High doses of insulin reduced HD activity to near control values; intermediate insulin doses were associated with intermediate alterations in HD-dependent histamine synthesis. Results suggest that histamine metabolism within the aortic wall may be insulin-dependent under conditions of experimental diabetes. Based on a potential role of histamine as a modulator of aortic transmural macromolecule uptake, these results suggest that insulin may be important in modulating atherosclerosis severity in diabetes through its potential to regulate aortic histamine metabolism. (Supported by USPHS. NIH Grant HL #20460)

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EFFECTS OF CELLULAR VIABILITY ON INSULIN BINDING AND DEGRADATION IN CULTURED HUMAN FIBROBLASTS. R.L. Clark*, D.M. Mott*, and B.V. Howard* (SPON: R.J. Hansen). Phoenix Clinical Research Section, NIAMDD, NIH, Phoenix, AZ 85016.

During studies of insulin binding (IB) and degradation (ID) marked differences in IB and ID were found between cells harvested by treatment of the monolayer with .05% EDTA (EH) vs .05% trypsin plus .02% EDTA (TH) though a positive correlation ($p<.05$) was found between cell-mediated insulin degradation and the obesity of the donor. EH cells as compared to TH cells exhibited an increase in the concentration of unlabeled insulin (3.37 vs 28.6 ng/ml; $p<.001$) necessary to displace ½ of the bound 125-I-insulin, an increase in the high affinity K_D (6.16 vs 24.3 x 10^{-10}M, $p<.001$), greater nonspecific binding, an increase in R_0 (2.52 vs 1.14 x 10^5 sites/cell; $p<0.001$), and greater insulin degrading activity (626 vs 120 fmoles/10^6 cells/4h; $p<.02$). Treatment of EH cells with trypsin or TH cells with EDTA had no effect on insulin degrading activity. EH cells were less viable, and reduced viability was positively correlated with ID ($p<.002$), nonspecific binding ($p<.0002$) and K_D ($p<.002$). Positive correlations of nonspecific binding with K_D ($p<.003$) and with insulin degrading activity ($p<.001$) were also found. These data suggest that insulin degradation has marked effects on insulin binding characteristics. In addition the possible relationship between insulin degrading activity and donor obesity must be conducted under more carefully controlled conditions.

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EFFECT OF PROTEIN SYNTHESIS INHIBITION ON REVERSAL OF TRYPSIN-ENHANCED SUGAR TRANSPORT IN MUSCLE. S.M. Garthwaite* and J.O. Holloszy. Washington University School of Medicine, Department of Preventive Medicine, St. Louis, Missouri 63110

Trypsin enhances the rate of sugar penetration into muscle. This effect may be mediated either by an effect on the insulin receptor or by a direct effect on the membrane and/or the sugar carrier. Incubation of isolated frog sartorius muscle in trypsin (2 µg/ml) resulted in a significant increase in permeability of the muscle to 3-O-methylglucose (3MG). Trypsin did not increase muscle permeability to the mannitol which was used as an extracellular space marker. After washing and incubation in medium containing glucose and trypsin inhibitor, trypsinized muscles regained the control rate of 3MG transport. The addition of the protein synthesis inhibitor cycloheximide, 0.5 mM, to the recovery medium did not block the return of transport to the baseline level. We previously reported a similar finding in insulinized muscles, whereas we found that when sugar transport rates are elevated by stimulation of muscle contraction, inhibition of protein synthesis prevents recovery. We conclude that the increases of sugar transport brought about by trypsin and by stimulation of muscle contraction are mediated by different mechanisms.

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FAILURE OF SOMATOSTATIN TO MODIFY THE EFFECT OF GLUCAGON ON CARBOHYDRATE METABOLISM IN THE CONSCIOUS DOG. KE Steiner*, WW Lacy, PE Williams* and AD Cherrington. Depts. of Physiol. and Medicine, Vanderbilt Univ., Nashville, TN 37232

Somatostatin (S) is widely used to inhibit insulin (I) and glucagon (G) release in studies of metabolic regulation in vivo. To determine whether the peptide can directly modify the metabolic effects of glucagon in overnight fasted conscious dogs G was increased in the presence (+S) and absence (-S) of somatostatin. Either S (0.8 µg/kg-min) or a two stage pancreatectomy was used to inhibit the endocrine pancreas and at the same time replacement infusions of I (290 µU/kg-min) and G (0.65 ng/kg-min) were given. Following a 40 min control period the plasma glucagon level was raised 4 fold in the presence of a fixed basal insulin. Plasma I in both groups were similar (12±2 (+S) and 9±1 (-S) µU/ml). G rose from 64±11 to 225±19 and 92±11 to 219±20 pg/ml in the +S and -S groups respectively. Tracer determined (^{3}H-3-glucose) glucose production rose by 5.28±1.02 (+S) and 4.25±1.12 (-S) mg/kg-min at 15 min and fell similarly over 3h in both groups. Plasma glucose rose similarly in both groups peaking at 195±15 (+S) and 174±8 (-S) mg/dl. Plasma alanine fell similarly over 3h (133±35 (+S) and 138±42 (-S) µmol/mL). Conversion of ^{14}C alanine to ^{14} glucose rose progressively over 3h in both groups eventually being elevated by 210±58 (+S) and 148±48 (-S) percent. We conclude that in the dog S does not alter glucagon's effect on carbohydrate metabolism. (Supported by NIH grant AM 18243-06)

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N$^{\tau}$-METHYLHISTIDINE EXCRETION AND MUSCLE PROTEIN TURNOVER IN BEEF CATTLE STEERS IN VIVO. R. Gopinath* and W.D. Kitts* (Spon: C.F. Cramer) Univ. of B.C., Vancouver, Canada V6T 2A2

The urinary excretion of N$^{\tau}$-Methylhistidine (N$^{\tau}$-MH) was studied quantitatively in 8 beef steers to measure muscle protein degradation (MPD) at different stages of growth. The steers used in this study were part of an experiment wherein the effects of estrogenic anabolic compounds were investigated. The amount of MPD and fractional rate of muscle protein breakdown (FBR) were calculated from 24h urinary N$^{\tau}$-MH excretion. The amount of muscle protein synthesized (MPS) was estimated as the difference between MPD and the amount of muscle protein gained per day. Regardless of the treatment given the mean N$^{\tau}$-MH excretion on 28, 42, 56 and 63 days of the study was 1551.4 ± 111, 1847.7 ± 147, 2347.3 ± 200 and 2055.9 ± 102 µmol/day, respectively. Both MPD and FBR were found to increase in proportion with body weight of the steers up to day 56 of the study. Mean MPD, MPS and FBR values were 567.4 ± 25 g/day, 645 ± 28 g/day and 1.79 ± 0.07%/day, respectively, over the entire experimental period. Daily N$^{\tau}$-MH excretion and MPD values were higher in steers implanted with anabolic compounds than in unimplanted controls. There was also a high positive correlation (r = .9842) between muscle protein synthesis and degradation. Considering the high growth response and MPD it is concluded that in rapidly growing beef steers implanted with estrogenic anabolic compounds, the increase in body weight is a reflection of rapid muscle protein turnover. (Supported by NSERC A0132).

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QUANTITATION OF DANSYLATED AMINO ACIDS FROM BRAIN AND SERUM USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC). V.T. Wiedmeier, S.P. Porterfield and C.E. Hendrich. Dept. of Physiology, Medical College of Georgia, Augusta, GA 30912.

The development and refinement of HPLC has led to considerable interest in using this technique for the separation of amino acids since it is less costly and faster than the amino acid analyzer. We have developed a technique which entails precolumn derivitization of these compounds with dansyl chloride (5-dimethylaminonapthalene-1-sulfonyl chloride), separation on a C-18 reverse phase column using gradient elution and quantitation of peaks with a flourometer and integrating recorder. Protein free extracts of either brain or serum (0.1 ml) were buffered with sodium bicarbonate and the pH adjusted to 8.5. Dansyl chloride in acetone (6 mg/ml) was added (0.1 ml) and the samples incubated overnight. Water (0.8 ml) was then added and an aliquot chromatographed along with an internal standard. The mobile phase consisted of 95% 9 mm acetate buffer (pH 4.15)-5% tetrahydrofuran in pump "A" and 90% acetonitrile-10% tetrahydrofuran in pump "B". The gradient (2 stages) was developed over 60 min. and the time from beginning the gradient to completion of regeneration of the column was 70 min. The relative retention times are: TAU<ASN<GLN<SER<ASP<HYPRO<GLU<THR<GLY<ALA<ARG<γ ABA<MET<PRO<VAL<PHE<TRP<LEU<ILE<LYS<TYR<HIS. This method offers a rapid and economical means of measuring the above amino acids in biological tissues and fluids. Supported by NIH Grant #R01 HD11411 and Eagles Max Baer Heart Fund.

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COLLAGEN TYPE SIMILARITIES IN DUPUYTREN'S DISEASE AND HEALING TENDONS. Henry Brown, H.Paul Ehrlich*, Kurt C. Lange* and Paul M. Newberne*. Harvard Univ. and MIT, Boston MA 02215

One etiology of Dupuytren's Disease has been trauma, to wit, Dupuytren's 1833 description of the disease in the coachman from trauma from the reins or the wine merchant from lifting wine casks. If true, collagen types of diseased palmar fascia would be expected to have similarities to collagen types from other trauma, as for example healing tendons. To test this hypothesis, collagen patterns from Dupuytren's Disease were compared with those of healing rodent gastrocnemius tendon, our laboratory model for studying healing tendon. Palmar fascia from seven patients with Dupuytren's Disease was solubilized by peptic digestion, fractionated with 1.0 and 2.2M sodium chloride and collagen types were determined quantitatively by densitometry of stained bands from sodium dodecylsulfate polyacrylamide gel electrophoresis. Types I, III and V or AB collagens as well as type I trimer were isolated, the latter three types being in greater concentrations that controls. Similar fractionation of collagen from healing rodent gastrocnemius tendon indicated a similar pattern 10 and 20 days after suture repair. The pattern has characteristics of hypertrophic scar as well. From these studies, it is concluded that the collagen pattern in Dupuytren's Disease, by comparing it to healing tendon is consistent with trauma as an etiology. (Supported in part by a Grant from the American Society for Surgery of the Hand.)

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DIFFERENTIAL ACTIONS OF BRANCHED-CHAIN AMINO ACIDS ON PROTEOLYSIS BY MUSCLE FROM BURNED RATS. R.E.Shangraw and J.Turinsky. Dept. Physiol., Albany Medical College, Albany, NY 12208

A 3-second scald on one hind limb stimulates protein turnover in muscle underlying the wound without affecting the contralateral unburned limb muscle of rats. Since it has been asserted that branched-chain amino acids act to reduce net proteolysis in muscle, soleus muscles from rats burned on one hind limb and from uninjured controls were incubated in KRB with or without 2 mM leucine, isoleucine or valine. In the absence of branched-chain amino acids, muscles from the burned limb released 103% more alanine and 131% more tyrosine than controls ($p<0.001$). Muscles from the unburned limb of burned rats, however, did not differ from controls. All three branched-chain amino acids independently stimulated alanine release in controls about 45% ($p<0.001$) but did not alter the release by either muscle of burned animals. Control muscle release of tyrosine, an index of net proteolysis, was not changed by inclusion of any branched-chain amino acid. Leucine and valine also had no effect on muscles from burned animals. In contrast, isoleucine stimulated tyrosine release by burned and unburned limb muscles 19% and 28% ($p<0.04$), resp. These results show that muscles from injured animals respond to branched-chain amino acids differently than those from controls. In addition, they demonstrate that the influence of isoleucine is quite distinct from that of either leucine or valine in that it appears to exacerbate the already accelerated net proteolysis in injured muscle. (Supported by USPHS Grant GM-22825)

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NITROGEN (N) AND ZINC (Zn) BALANCES OF TRAUMA AND CONTROL RATS ON TOTAL PARENTERAL NUTRITION (TPN). Augusta Askari,* Ronald H. Birkhahn, Calvin L. Long,* J. Daniel Kramer*, Medical College of Ohio, Toledo 43699

It is reported that skeletal trauma increases urinary N and Zn losses. TPN alone provides for a more positive N balance; however, it causes a greater loss of urinary Zn. This research was undertaken to evaluate the effects of both skeletal trauma and TPN upon whole-body N and Zn metabolic balances. Male Sprague-Dawley rats weighing 170 ± 2.5 g were anesthetized with 10 mg ketamine-HCl/100g body weight, fitted with a back button, and cannulated for intravenous feeding. Of these, 16 rats were designated as controls and 17 rats, while still under anesthesia, were additionally traumatized by having both femurs broken through digital manipulation. All animals were then given the same volume of unsupplemented TPN daily over 7 days. The mean ± SEM balances on day after injury were 45.4 ± 12.6 mg N and -6.7 ± 1.2 ug Zn for controls; 21.4 ± 14.2 mg N and -9.8 ± 1.3 ug Zn for trauma rats. The means over the 7 day study were 136.5 + 15.8 mg N and -3.8 ± 0.7 ug Zn for controls; 107.0 ± 16.6 mg N and -10.2 ± 1.1 ug Zn for trauma rats. Mean weight gains by day 7 were 4.1 g for controls and 0.9 g for trauma rats. While both groups of rats did grow, about 22% less N and about 11% less Zn were retained by the trauma rats. Thus, trauma elicits greater N and Zn losses than are necessitated by TPN alone. (Supported by USPHS. NIH Grant No GM23065.)

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ZINC (Zn) AND NITROGEN (N) BALANCES OF RATS ON ROUTINE OR EXPERIMENTAL INTRAVENOUS (iv) NUTRITION OR STARVATION. Ronald H. Birkhahn, Augusta Askari,* Calvin L. Long,* David Fitkin,* J. Daniel Kramer,* Medical College of Ohio, Toledo, 43699

Studies in man on diverse clinical diets show changes in Zn and N balances. It is desirable to quantify analogous changes in a rat model for further research in trace element balance and kinetic studies following trauma. N (but not Zn) balances of rats on iv intakes have been reported. To explore whole-body Zn-N metabolism, 82 male Sprague-Dawley rats weighing 337.1±8.8g were anesthetized, fitted with back button, cannulated for iv feeding. Rats were in 6 groups: group 1 starved, group 2 got total parenteral nutrition (TPN), groups 3-6 had iv hypocaloric diets. Intake and output were monitored for 24 hr periods over 7.5 days/rat. Ranges of Zn and N in intake were 0-24.6 ug Zn/day, 0-372 mg N/day; output had 7-18 ug Zn/day, 180-405 mg N/day. Zn was in intake by contamination. N was analyzed by Microkjeldahl; Zn, by atomic absorption. Daily mean±SEM ug Zn and mg N balances were, respectively, -11.1±2.2 and +93.7±18.1 for TPN, +14.2±1.2 and -207.8±8.3 for 5% amino acids, +4.2±1.0 and -247.9±19.2 for 5% glucose, -11.2±2.0 and -186.5±12.6 for 5% monobutyrin, +78.4±2.8 and -178.5±10.6 for 5% monoacetoacetin, -6.7±0.7 and -198.4±20.3 for starvation. TPN gave the most positive N balance, but also large negative Zn balances. Further studies will determine how much Zn supplementation and in what ratio to N will give optimal balances for both Zn and N. (Supported by USPHS. NIH GM 26872, GM 23065.)

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EXTRARENAL BUFFERING DURING DIABETIC KETOACIDOSIS.

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Each experimental rat was given a single intraperitoneal injection of 100 or 150 mg Streptozotocin per kilogram body weight and sacrificed one,two,three or four days thereafter. Control rats were the same age as the experimental animals. Both groups were allowed free access to rat chow and water. Following the onset of ketonuria, plasma pH, Pco_2 and $[HCO_3^-]$ fell progressively with time. Plasma sodium concentration remained at control levels when plasma $[HCO_3^-]$ > 10mEq/l, but fell sharply at lower plasma $[HCO_3^-]$. Plasma potassium concentration was stable at control levels during ketoacidosis. Skeletal carbon dioxide, sodium and potassium concentrations declined from control levels; the skeletal content of these electrolytes was directly related to the plasma total carbon dioxide content during diabetic ketoacidosis. The bicarbonate stores of bone were the primary source of the carbon dioxide released from bone. Skeletal muscle intracellular pH fell progressively along with plasma pH; whereas no intracellular acidosis occured in the heart until plasma $[HCO_3^-]$ was less than 10 mEq/liter. Thus, it is apparent that both bone and skeletal muscle act as extrarenal buffers during diabetic ketoacidosis. (Supported by a Young Investigator Award from the National Heart, Lung and Blood Institute HL-19601).

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PHOSPHOLIPASE A_2 IN ALBUMIN INDUCES THE ACROSOME REACTION IN VITRO OF GUINEA PIG SPERM. Crystal L. Singleton* and Gary J. Killian* (SPON: R.T. Heath). Kent State Univ., Kent, OH 44242

Bovine serum albumin (BSA) is a common component of media used to capacitate sperm and induce the acrosome reaction (AR) in vitro. The present study was undertaken to determine if phospholipase A_2 in BSA affects the induction of the AR in vitro. Cauda epididymal sperm, obtained by backflushing, were incubated in an AR-inducing medium containing 0.1% BSA. After 6 hr, 54% of the sperm underwent the AR and 52% were motile. In medium lacking BSA, only 19% of the sperm underwent the AR and 53% were motile. When phospholipase A_2 was added to medium lacking BSA, at levels similar to that detected in BSA, 53% of the sperm underwent the AR and 36% were motile. Inhibition of phospholipase A activity with p-bromophenacyl bromide in medium with BSA significantly reduced sperm AR to 34% with 48% motility. However, the dimethyl sulfoxide solvent for the inhibitor had no effect on sperm AR or motility. Further studies with ^{14}C-phosphatidylcholine confirmed work of others that sperm phospholipase activity increases with incubation time and AR. Corresponding to a 4-6 fold increase in sperm AR from 2 hr to 6 hr incubation, ^{14}C-phosphatidylcholine degradation per hr to ^{14}C-glycerolphosphorylcholine and ^{14}C-phosphorylcholine was 2-5 fold greater for the last 2 hr of the 6 hr incubation than that degraded for the first 2 hr. These findings suggest that phospholipase A associated with BSA may contribute to the induction of the AR in vitro by mimicking sperm phospholipase. (Supported by NIH grant HD 13422)

NEONATAL CIRCULATION

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FEMORAL BLOOD FLOW AUTOREGULATION IN DEVELOPING SWINE. Nancy M. Buckley, Paul Brazeau* and Isaac D. Frasier*. Albert Einstein College of Medicine, New York, NY 10461.

Pressure-flow relationships (P/F) in the femoral circulation were determined in 20 swine aged 2-4 days and 1, 2 and 4 weeks, under pentobarbital anesthesia. Aortic and inferior vena caval pressures and femoral arterial flow were recorded. Blood gas composition, pH and Hct were monitored. The P/F was first determined while perfusion P was decreased (for 2 min at each P) by abdominal aortic occlusion. Next the left lumbar nerve was isolated and the left femoral artery was cannulated for in situ perfusion of the hindlimb with blood withdrawn from a carotid artery by pump. The P/F was then determined by changing pump F (for 2 min at each F) while recording perfusion P. Records were analyzed for transient (3 sec) and steady state (2 min) changes. In swine as young as 2 days of age, readjustments in femoral resistance (R) were stabilized within 2 min after changing P or F. Normalized graphs of steady state data showed a "plateau" in the P/F even in these youngest animals. At each age, denervation by lumbar nerve section always lowered femoral R. Infusion of vasoactive substances (norepinephrine, 0.2 μg/kg/min; acetylcholine, 16 μg/kg/min) did not prevent the autoregulatory response to changing F. We conclude that femoral blood flow autoregulation is active in swine within the first few days after birth. (Supported by USPHS, NIH grant 21865.)

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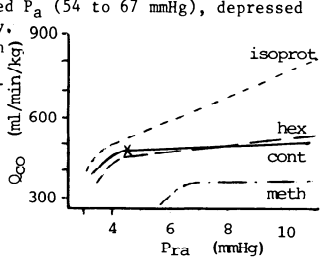
CHANGES IN FETAL CARDIAC FUNCTION FOLLOWING HEXAMETHONIUM, METHOXAMINE OR ISOPROTERENOL. R. D. Gilbert, Loma Linda School of Medicine, Lima Linda, CA 92354.

To better understand fetal cardiac function, I measured cardiac output and vascular pressures following baroreceptor blockade (hexamethonium), β receptor stimulation (isoproterenol) and increases in arterial pressure (methoxamine) in 17 chronically catheterized lambs. Cardiac output (Q_{co}) was related to right atrial pressure (P_{ra}), varied by changes in blood volume. The average control Q_{co} and P_{ra} (X) place the fetal heart on the plateau of the normal cardiac function curve (cont). Hexamethonium (hex) did not change the shape or position of the normal cardiac function curve, though arterial pressure (P_a) increased from 42 to 55 mmHg at high P_{ra}. Methoxamine (meth), which increased P_a (54 to 67 mmHg), depressed cardiac function significantly. Isoproterenol (isoprot), which stimulated the heart but kept P_a within a normal range (45 - 57 mmHg), increased cardiac function. Therefore, baroreceptors do not depress cardiac function during volume loading, but increases in P_a do. Cardiac function will increase if the heart is stimulated, as with isoproterenol, but P_a does not rise.



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PRESERVATION OF CEREBRAL AUTOREGULATION IN THE UNANESTHETIZED HYPEROXIC AND HYPOXIC NEWBORN DOG
D.J. Camp, U.R. Kotagal, L.I. Kleinman, U. Cincinnati College of Medicine, Department of Pediatrics

In an attempt to study regulation of cerebral blood flow in the neonatal animal, cerebral blood flow (CBF) was measured in 6 hyperoxic (HE) and 6 hypoxic (HO) awake newborn puppies using radioactive microspheres. In the HE group PaO_2 was maintained above 250 torr with 100% O_2 and in the HO group PaO_2 was maintained at 35.8 torr ± 3.0 SEM by continuous administration of 12% O_2. $PaCO_2$ was constant during each period for all animals. Following control measurements (period I), puppies were made hypotensive (period II) by withdrawing 15-25 ml/kg of blood in the HE group and 20-60 ml/kg in the HO group. In the HE group during period II, BP fell 20.5% ± 2.8* and cardiac output (CO) decreased 20.9% ± 5.7* while CBF flow was unchanged (31.37 ± 3.76 and 32.69 ± 5.90 ml/100g/min in periods I and II respectively). When HO animals were made hypotensive, BP fell 30.1% ± 3.2* and CO decreased by 55.3% ± 6.9* while CBF flow was unchanged (49.37 ± 3.23 and 48.74 ± 4.19 ml/100g/min in period I and II respectively). The fraction of cardiac output to the cerebrum increased from 2.8% ± 0.4 to 3.8% ± 0.8* in the HE animals and from 2.8% ± 0.5 to 6.1% ± 0.7* in the HO group during hypotension. Thus, in the presence of decreased mean blood pressure and cardiac output in both HE and HO neonatal puppies, CBF is maintained demonstrating the presence of cerebral autoregulation.

* $p < 0.05$

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RAPID ALKALI INFUSION IN HYPOXIC NEWBORN DOGS
U.R. Kotagal*, U. of Cincinnati College of Medicine (Spon. L.I. Kleinman)

Rapid infusions of alkali are used in hypoxic newborn infants primarily as a plasma buffer and are implicated in intracranial hemorrhage. $NaHCO_3$ may also work by improving cardiac output (CO) and oxygen delivery to the tissues. The cardiovascular effects of rapid $NaHCO_3$ infusion (2meq/kg diluted 1:1 in D_5W over 3-5') were studied in 9 awake hypoxic newborn dogs using radioactive microspheres; 4 control hypoxic animals received 4ml/kg of D_5W over 3-5'. Puppies in both groups were made hypoxic by decreasing the F_iO_2 to .12 beginning 30 min prior to baseline measurement and continuing 15 min post $NaHCO_3$ or D_5W infusion. Control animals demonstrated no significant change in any of the parameters measured.

	pH	PCO_2	PO_2	HCO_3	BP	CO
Hypoxic	7.42	26.9	32.0	17.42	63	277
2' post $NaHCO_3$	7.49*	24.3	33.8	22.3*	58	331*
15' post $NaHCO_3$	7.44	28.4	36.8	19.2	56	345*

*$p<0.05$ Compared to baseline hypoxia

CO ml/kg/min, HCO_3 meq/L

There was no change in cerebral blood flow following $NaHCO_3$ infusion. The major effect of $NaHCO_3$ in hypoxic newborn animals may be enhanced cardiac output.

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STROKE VOLUME WITH POSITIVE PRESSURE VENTILATION IN PREMATURE INFANTS USING SYSTOLIC TIME INTERVALS
M.D. Reller*, U.R. Kotagal*, R.A. Meyer*, S. Kaplan*, University of Cincinnati College of Medicine (Spon. L.I. Kleinman)

Twenty premature infants were investigated utilizing systolic time intervals (STI) obtained by echocardiography. Cardiac cycles occurring during expiration were compared to cycles that occurred during peak inspiration. In six infants breathing spontaneously, the mean left ventricular pre-ejection period (LPEP) increased by 6.8% from 59.9 msec to 64.0 msec ($p<.01$) while the mean left ventricular ejection time (LVET) decreased by 3.1% from 180.1 msec to 174.6 msec ($p<.01$). In 14 other infants requiring positive pressure ventilation for respiratory distress, the mean LPEP decreased by 3.3% from 60.2 msec to 58.2 msec ($p<.01$) while the mean LVET increased by 2.8% from 160.8 msec to 165.3 msec ($p<.01$) at peak positive pressure inspiration. The increase in LPEP and decrease in LVET in the infants breathing spontaneously, represents a decrease in left ventricular stroke volume at peak inspiration. The decrease in LPEP and increase in LVET in the infants on mechanical ventilation is consistent with enhanced left ventricular stroke output during peak positive pressure inspiration.

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HISTAMINE AND ITS RECEPTORS IN THE VASCULATURE OF THE FETUS, PLACENTA AND ADULT.
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The actions of histamine and its binding to histamine receptors were analyzed in adult aorta, fetal aorta and fetal umbilical arteries of the rabbit. Helical strips of these arteries were prepared and suspended in 10 ml of aerated physiological salt solution. Histamine produced dose-dependent increases in developed tension in all arteries studied. However, the fetal aorta was 3.3 times more sensitive to the histamine contractions than the umbilical artery and 17.3 times more sensitive than the adult aorta ($p < .01$). Pretreatment of the arteries with the H_1 receptor antagonist pyrilamine shifted the dose response curve to histamine to the right in a competitive fashion in all arteries. Similar pretreatment with the H_2 receptor antagonist metiamide was without effect. Antagonist binding constants (pA_2) for pyrilamine, as determined using Shield plots, produced binding constants of 8.16 in the fetal aorta, 8.35 in the adult aorta and 7.51 ($p < .01$) for the fetal umbilical artery. In conclusion, (a) The relative order of sensitivity observed to histamine was: fetal aorta > fetal umbilical artery > adult aorta and (b) both the fetal aorta and adult aorta possess classical H_1 type histamine receptors while those of the extrafetal placental arteries appear to possess a "new" sub-type H_1 histamine receptor. Supported in part by NIH grants No. HL-24512 and RR-05418.

GASTROINTESTINAL PHYSIOLOGY

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CYTOPROTECTIVE 16,16 DIMETHYL PROSTAGLANDIN E_2 STIMULATES H^+ TRANSPORT IN RAT GASTRIC MUCOSA.
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In a previous report (Fed. Proc. 40:511, 1981), we showed that a cytoprotective concentration of 16,16 dimethyl prostaglandin E_2 (1.6×10^{-8}M $dmPGE_2$) stimulates oxygen consumption of isolated rat parietal cells. Since the principal function of these cells is acid secretion, we further examined the effect of this cytoprotective concentration of $dmPGE_2$ on H^+ transport in the isolated rat gastric mucosa. Mucosae in flux chambers were short-circuited, buffered and the pH-stat set at pH 7.40 to eliminate the chemical gradient for H^+ back-diffusion. H^+ transport was determined from the titer of base required to maintain the pH at 7.40 in the mucosal solution during acid secretion. Compared with the average of pre- and postcontrol rates, H^+ transport was significantly increased by 51±14% after 15-30 minutes exposure to cytoprotective $dmPGE_2$ on the submucosal side. The stimulatory effect of cytoprotective $dmPGE_2$ was also reflected in the acid-mediated accumulation of the labeled weak base, ^{14}C-aminopyrine. The accumulation ratio of labeled aminopyrine in the mucosa to that in the medium increased significantly above unity to 1.52±0.15 during incubation with cytoprotective $dmPGE_2$. In conclusion, the actions of cytoprotective $dmPGE_2$ to stimulate H^+ transport and aminopyrine accumulation by isolated rat gastric mucosa support the hypothesis that prostaglandins mediate secretory responses not only in the intestine but also in the stomach.

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DIPEPTIDE TRANSPORT IN NORMAL (NV) AND PAPAIN-TREATED (PTV) BRUSH BORDER MEMBRANE VESICLES FROM MOUSE INTESTINE.
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The transport of glycyl-phenylalanine (Gly-Phe) and glycyl-leucine (Gly-Leu) was studied using NV and PTV in order to compare peptide transport in the presence and absence of hydrolytic events associated with the membrane. The 70% removal of oligopeptidase activities in PTV allows the study of peptide transport in the complete absence of free amino acids up to 1 min of incubation for Gly-Phe and 5 min for Gly-Leu. Both peptides were taken up into an osmotically active intravesicular space with insignificant binding to the membrane. A comparison between the time course curves of Gly-Phe uptake by NV and PTV showed that the overshoots seen in the presence of a Na^+- or K^+-gradient with NV were no longer evident with PTV. Such a comparison for Gly-Leu showed the absence of overshoot phenomena and similar uptake curves with Na^+- or K^+-gradient. For both peptides, linear relationships between initial rates of uptake and peptide concentrations were observed. Also, uptakes were inhibited to various extents by other di and tripeptides, but inhibitions never exceeded 43% and 33% for Gly-Phe and Gly-Leu respectively. These results demonstrate that intact peptide transport occurred down a concentration gradient by a non-Na^+-dependent process involving both passive and facilitated diffusion mechanisms.

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IN VIVO MEASUREMENT OF PASSIVE PERMEABILITY OF THE RAT DUODENUM. G.M. Johnson,* R.S.K. Chung. Department of Surgery, Veterans Administrative Medical Center & University of Iowa Hospitals & Clinics, Iowa City, Iowa 52242

In order to measure changes in passive permeability, we perfused the rat duodenum with a mixture of low molecular weight (M.W.) polymers of PEG (150-502 daltons) in vivo. The duodenum was cannulated under anesthesia and perfusion in situ was set up with a recirculating circuit, incorporating a pH stat for maintaining pH. PEG composition before and after perfusion was determined by quantitative gas-liquid chromotography for polymeric components, and results were expressed as percentage ± SE of polymeric components absorbed: (n = 8)

M.W.	194	238	282	326	370	414
pH 6.0	13.8±2.1	9.5±2.5	10.0±3.4	6.2±3.2	5.2±3.6	4.6±3.7
pH 1.7	19.2±4.8	14.2±4.0	11.9±3.8	9.7±4.4	8.8±4.2	9.8±5.5

By increasing the rate of perfusion, maximum absorption was attained at each pH. Using data of maximal absorption, effective pore diameter was calculated. This was 12Å at pH 6 and 15.3Å at pH 1.7. We conclude that this is a simple method independent of variables such as surface area, thickness of unstirred layers inherent in other methods.

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NEONATAL PRETREATMENT WITH CHOLESTYRAMINE (CT) RESULTS IN PERSISTENT ENHANCEMENT OF RATE-LIMITING ENZYME OF BILE ACID BIOSYNTHESIS. *A.S. Hassan, L.S. Gallon* and M.T.R. Subbiah* Univ. of Cincinnati Medical Center, Cincinnati, Ohio, 45267.*

Guinea pigs treated with CT during neonatal life have been shown to have increased fecal excretion of bile acids (mg/100 gm body wt.) even 4 weeks after the animals had been removed from the treatment diet and fed stock diet (Cont. 7.86 ± 0.45 vs CT-treated, 14.02 ± 1.87). It was hypothesized that pretreatment with CT early in life resulted in persistent enhancement of the activity of cholesterol 7α-hydroxylase, the rate-limiting enzyme of bile acid biosynthesis. We have examined that hypothesis. Two-days old guinea pigs were fed stock diet or stock diet supplemented with 2.5% Questran (1.11% CT Resin) for 8 weeks, following which all the animals were fed stock diet for 4 weeks. At the end of 4 weeks on stock diet, animals from both groups were killed and their livers assayed for cholesterol 7α-hydroxylase activity. The results are shown below:

Group (N)	*Cholesterol 7α-hydroxylase activity ($pmoles \cdot mg^{-1} \cdot 20\ min^{-1}$) (Mean ± S.E.M.)*
Control (4)	*9.34 ± 0.57*
Questran-pretreated (4)	*21.27 ± 1.70**

**Significantly different from control, $p < 0.01$.*

The results confirm the above hypothesis and explain why CT pretreated animals are better able to handle a cholesterol challenge (Li et al. Atherosclerosis, 32:93, 1979). (Supported by Grant #HL24263 from NHLBI)

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SODIUM DEPENDENT TAUROCHOLATE UPTAKE BY RAT LIVER SINUSOIDAL MEMBRANE VESICLES. M.Inoue*, T.Tran*, R.Kinne and I.M.Arias* Albert Einstein College of Medicine, Bronx, New York 10461

In order to elucidate the first step in the chain of events comprising vectorial transport of bile acids by the liver cell, sinusoidal membrane vesicles (SMV) were isolated from rat liver by differential centrifugation and sucrose Ficoll density gradient centrifugation. The membranes were enriched 26 fold in $Na^+ K^+$ ATPase activity, no enrichment was observed for marker enzymes of the canalicular membranes, endoplasmic reticulum, mitochondria and lysosomes. Taurocholate (TC) uptake into these membranes was studied by rapid filtration technique.

Initial uptake of TC by SMV was stimulated 2.1 fold by 100mM Na NO_3 gradient compared to a KNO_3 gradient. The sodium-dependent uptake was inhibited by reduction of the temperature from 25° to 0°C and reduced by decrease of intravesicular space. Sodium-dependent transport showed saturation kinetics with respect to TC (apparent K_m - 56μM, Vmax-0.65n Mole/mg x 15 sec. at 100mM sodium) and sodium (apparent K_m 48mM at 50μM TC). Cholic acid selectively inhibits sodium dependent transport.

The results indicate that a stereospecific, high affinity TC transport system is present in sinusoidal membranes. Its sodium dependence suggests that it is a sodium-cotransport system that participates in the sodium dependent transcellular transport of bile acids in the liver.

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DEVELOPMENT OF AN APPARATUS FOR THE PRACTICAL CLINICAL DETERMINATION OF ANORECTAL MOTILITY. Edward B. Borden*, Scott J. Boley. Montefiore Hospital and Medical Center, New York,N.Y.

The reflex responses of the internal and external anal sphincters to rectal distension have been widely studied in humans. Anal canal pressure measurement, by means of latex balloons or perfused catheters, with simultaneous distension of the rectum by air filled balloon, has found widespread use as a screening test for Hirschsprung's disease in constipated children. Some investigators have also studied external sphincter response to rectal distension by means of needle electromyography. We have combined the use of anal canal pressure measurement, external sphincter surface electromyography, and rectal distension by air filled balloon to provide a multivariable anorectal motility profile. The apparatus, in the form of an easily constructed probe, provides reliable data for the investigation of disorders of fecal continence in adults and children. By using surface, rather than needle electromyography, the technique is made non-invasive and more acceptable to the patient. Pressure measurement by miniature semiconductor strain gage transducer in the anal canal yields accurate, high fidelity pressure recordings. Early results, from the study of over 60 patients ranging in age from newborn to 81 years, show that this is a useful technique for detecting underlying causes of constipation and incontinence.

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EFFECTS OF PREGNANT MARE SERUM GONADOTROPIN (PMSG) ON INDUCTION OF PRECOCIOUS PUBERTY IN THE FEMALE GUINEA PIG.
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An injection of PMSG as early as 21 days of age in the female rat results in precocious vaginal opening and ovulation 3 days later. In order to determine minimum age at which PMSG induces precocious puberty in the female guinea pig, two injections (s.c.) of PMSG (80IU) on consecutive days were given to animals at age 10, 25 or 35 days. Saline was injected in control animals at equivalent ages. As an immediate effect of PMSG treatments the first vaginal opening for 10, 25 and 35 day groups occurred at 16.6 ± 0.2 (n=15, $p<0.001$), 34.5 ± 1.7 (n=13, $p<0.001$) and 44.5 ± 1.2 days (n=15, $p<0.001$), respectively, and were significantly earlier than controls (58.0 ± 3.1, n=33). Premature ovulation, however, did not occur in animals of any age group immediately following the PMSG treatments nor the first vaginal opening. The age at the first ovulation was advanced in all 3 age groups: 49.9 ± 2.4 days ($p<0.001$), 49.3 ± 0.9 ($p<0.001$), 56.1 ± 2.7 days ($p<0.01$) respectively, when compared to experimental controls (67.3 ± 3.0 days). Thus, 1) PMSG treatments in the immature female guinea pig, age between 10 and 35 days, induces an acceleration of true puberty, but 2) the advancement is not earlier than around day 50, despite age differences at the time of treatment. This result further indicates that the maturation of the hypothalamo-pituitary-ovarian axis in the female guinea pig differs from that in the rat. (Supported by grant HD11355).

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THE EFFECTS OF CASTRATION ON THE HYPOTHALAMIC-PITUITARY AXIS OF MONOSODIUM GLUTAMATE TREATED RATS.
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Adult mice and rats that received monosodium glutamate (MSG) as neonates exhibit obesity, stunted growth, hypothyroidism and have fewer cell bodies in certain brain nuclei than saline treated controls. The hypothalamic-pituitary-gonadal axis of the MSG treated rat differs anatomically and functionally from the saline control. We have studied the effects of castration on adult male rats that were treated with 4 mg/g MSG or isomolar NaCl at age 2,4,6,8 and 10 days. The pituitary LH and FSH concentrations of MSG rats were significantly ($p \leq 0.01$) higher soon after castration (days 4 and 8), but were equal to control castrates by 40 days postcastration. Serum LH and FSH concentrations were elevated following castration in both saline and MSG treated rats. However, the rise in serum gonadotropins was significantly ($p \leq 0.01$) lower in MSG treated rats. Both MSG and saline treated rats secreted LH in a pulsatile fashion as early as 24 hours postcastration. Forty days following castration, the mean plasma LH concentration in saline treated animals was 357 ng/ml (samples were collected every 15 min for 6 hrs) and the pulse amplitude ranged from 250 to 748 ng/ml. The MSG treated rats had a significantly ($p \leq 0.01$) lower mean plasma LH concentration(246 ng/ml) and the pulse amplitude ranged from 50 to 360 ng/ml. These results indicate that following castration, MSG lesioned rats secrete LH in pulses. However, LH secretory dynamics appear to be impaired in these rats. Supported by NIH Grants HD14586 and AM26252 and the Vincent Research Fund.

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DIURNAL INFLUENCE OF PROGESTERONE ON LH RELEASE IN OVARIECTOMIZED RHESUS MONKEYS.
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In the female rat effects of both estrogen (E) and progesterone (P) on gonadotropin release are influenced by the time of day of injections. By contrast, in the rhesus monkey an E-induced LH surge appears not to be affected by the time of day of injections. Since we have shown that a P injection following E readily induces an LH release (Endoc. Abstr. #217, 1979), the diurnal influence on P-induced LH release was investigated. Nine long-term ovariectomized monkeys were housed under lights on 0600-1800h and received small E capsule implants 2 wks prior to each of the following 3 experiments. Exp. I: 10 µg estradiol benzoate (EB) was given at 0830 with P (2.5 mg) 30 h later (1430). Exp. II: A 12 h shift of both steroid injections - EB at 2030 and P 30 h later at 0230. Exp. III: Only P was advanced 6 h - EB at 0830 and P 24 h later at 0830. In all 3 experiments LH surges with similar latencies after P, durations and amplitudes were induced.

Experiment	Latency (h)	Duration (h)	Amplitude
I	6.7 ± 0.5	22.0 ± 1.5	80.9 ± 20.6
II	7.7 ± 0.5	22.7 ± 2.1	73.7 ± 25.7
III	6.2 ± 1.8	27.3 ± 3.0	119.3 ± 43.2

Thus, unlike the rat, the facilitatory effects of P on an LH surge in the rhesus monkey appear to be independent of the light phase but of consistent latency from the time after P injections. (Supported by NIH grants HD15433 and RR00167).

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NEUROENDOCRINE MEDIATION OF PERICOPULATORY ENDOCRINE RESPONSES IN MALE RATS.
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Male rats discharge LH and PRL after they are exposed to external cues which predict sexual encounters. The time domain associated with pericopulatory changes in circulating LH levels is reminiscent of the transitory increase in blood LH which follows a single intravenous injection of GnRH. The present study tested the proposition that female-induced LH secretion, in male rats, depends upon the activation of GnRH secreting neurons. Immunoreactive LH and PRL were measured in 100µl samples of blood withdrawn via an intravascular cannula at intervals of 5-10 min before and during the time sexually experienced males were exposed to females. Female exposure occasioned a rapid, 3-fold elevation in plasma LH and PRL levels among sexually experienced control males treated with nonimmune serum. In sharp contrast, LH, but not PRL, secretion was abolished when male rats were given GnRH immune serum 30 min before they were exposed to a receptive female. LH release was also blocked by treating males with a 30-mm subdermal testosterone-filled Silastic capsule, whereas males treated with an empty capsule exhibited a prominent rise and a gradual decrease in peripheral LH and PRL levels. Thus, testosterone may block female-induced GnRH secretion and/or pituitary LH release. These findings, taken together, offer the first evidence that pericopulatory LH secretion is mediated by the acute activation of neurons which transfer GnRH into the pituitary portal circulation. (Supported by NIH Research Grant HD-13470)

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α-ADRENERGIC RECEPTORS PARTICIPATE IN OPIATE ANTAGONIST-INDUCED GONADOTROPIN SECRETION.
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To examine the extent to which monoamines are involved in opiate regulation of pituitary hormone secretion, we studied the influence of monoamine receptor blockers, administered systemically, on the luteinizing hormone (LH) releasing effect of naloxone, an opiate antagonist, in immature female rats. We also studied the influence of the dopamine antagonist, domperidone, which does not readily cross the blood brain barrier, on the prolactin (PRL) inhibiting effect of naloxone. The α-adrenergic blocker, phentolamine (10 mg/kg BW) but not the β-blocker, pronethalol, attenuated naloxone (2.5 mg/kg BW) induced release of LH. Neither adrenergic antagonist affected the pituitary response to exogenous LHRH (8 ng/100 g BW). Serotonin antagonists (methysergide or metergoline, 3-10 mg/kg BW) had no influence on naloxone or LHRH-provoked release of LH. Acute treatment with domperidone prevented naloxone-triggered declines in serum PRL but longer exposures to domperidone were less effective. These results suggest noradrenergic involvement in opiate regulation of LH secretion but do not rule out the possibility of separate sites of norepinephrine and endogenous opiate action in regulating gonadotropin secretion. These data are also consistent with the view that injections of naloxone reduce circulating levels of PRL by stimulating endogenous release of dopamine. (Supported in part by a McCandless Grant, Emory University and NIH Grants RR00165 and HD15073).

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NEUROENDOCRINE REGULATION OF PROLACTIN SECRETION AFTER HYPOPHYSIAL STALK TRANSECTION IN PIGS.
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Yorkshire gilts, 211 ± 5 (mean ± SE) days old, were fitted with cannula in anterior vena cava to determine profiles of prolactin (PRL) secretion. PRL was quantified in 200 µl aliquots of serum by RIA, and concn expressed in terms of NIH reference (SP-162C, 16IU/mg). Eight gilts were hypophysial stalk-transectioned (HST); nylon disc prevented vascular regeneration. Five gilts served as sham-operated controls (SOC). During preoperative period (120 min) and period of anesthesia-surgery (210 min) blood was collected every 15 min; during postoperative period (190 h) it was obtained every 4 h. PRL remained consistently low (2.3 ± 0.30 ng/ml) in 13 gilts during preoperative period. During 105 min of anesthesia (thiamylal sodium; halothane and O_2) PRL increased (8.2 ± 1.87 ng/ml). Peak PRL averaged 10.7 ng/ml at HST or SOC, and then declined steadily in both groups during last 105 min surgery. PRL remained elevated ($P<0.002$) in HST gilts as compared with SOC throughout postoperative period from 6 to 190 h (3.7 ± 0.40 *vs* 1.9 ± 0.18 ng/ml). These results indicate that regulation of prolactin secretion in the pig depends primarily upon hypothalamic inhibition. (Supported by USDA, Cooperative Agreement no. 58-519B-9-863, projects 2228, 2443 and 2444).

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A ROLE OF THE ENDOGENOUS OPIOID PEPTIDES IN THE STRESS-INDUCED FALL IN THYROTROPIN.

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The endogenous opioid peptides (OP) are postulated to be involved in the secretion of anterior pituitary hormones. We have studied the role of OP in the secretion of thyrotropin (TSH) in female Sprague-Dawley rats under basal and stress conditions. The opiate receptor antagonist naloxone (NAL) (0.02 or 1.25 mg/100 g BW ip or iv) had no effect on TSH (basal or thyrotropin releasing hormone stimulated) in rats sampled via cardiac puncture or jugular catheter. Restraint stress resulted in a 40% fall in TSH at 20', 60', and 120' post saline ($p < .01$) that was blocked by NAL (1.25 mg/100 g BW iv) 20' and 60' following the drug injection ($p < .05$). NAL (1.25 mg/100 g BW iv) had no significant effect on the rise in corticosterone associated with restraint (350%, $p < .01$). Bilateral microinjections of saline into the posterior hypothalamus of anesthetized rats (1 µl/side) resulted in a 30% fall in TSH at 15' and 30' ($p < .05$) while similar injections of NAL (50 µg/side) increased TSH by 40% at 15' and 60% at 30' ($p < .01$). NAL (100 µg) microinjected into the anterior pituitary had no effect on TSH. Conclusions: 1) The OP play no role in basal TSH secretion. 2) The OP decrease TSH during stress via NAL sensitive receptors located in the hypothalamus. 3) The NAL effect on the stress-induced fall in TSH is not mediated via changes in corticosterone levels. (Supported by NIH Grant AM 21348)

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INHIBITION OF METHIONINE ENKEPHALIN DEGRADATION BY CATECHOLAMINES. James L. Caffrey and Donald M. Hodges*. NTSU/TCOM, Fort Worth, Tx. 76107

Stress releases brain catecholamines (CAs) and produces a coincident analgesia that is apparently mediated by brain enkephalins. To determine if these neurochemical events might be linked, we investigated the effects of CAs on the degradation of methionine enkephalin (met-enk) in vitro. Met-enk metabolism was evaluated by incubating tissue homogenates with radiolabeled met-enk (10^{-4}M) followed by Porapak Q chromatography. Enzyme activity from rat brain had an estimated Km of 70-80µM. About 80% of the crude homogenate enzyme activity was recovered in the 28,000 x g x 20 min supernatant and was inhibited 95% by puromycin (10^{-4}M). CAs ($5x10^{-5}$M) clearly inhibited the enzyme activity: dopamine 66% inhibition, norepinephrine 25% inhibition, and epinephrine 4% inhibition, and subsequent dose response curves confirmed the inhibitory order of the three CAs. In contrast, their O-methylated metabolites at $5x10^{-5}$M failed to inhibit the enzyme. Dopamine (10^{-4}M) also was observed to inhibit like-enzyme activities from the small intestine (70% inhibition) and the adrenal glands (24% inhibition). The inhibition of enkaphalin degradation by CAs may provide a mechanism by which the adrenergic nervous system regulates the enkephalinergic nervous system. Supported by AOA Grant #79-11-172.

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TYROSINE HYDROXYLASE ACTIVITY IN LIMBIC AND HYPOTHALAMIC REGIONS OF FEMALE RATS. A. E. Jimenez*, D. C. Meyer, L. A. Carr*. Univ. of Louisville, Lou., Ky. 40292.

An increase in tyrosine hydroxylase (TH) activity in the whole hypothalamus of prepubertal female rats occurred between 10 and 30 days of age, followed by a decrease at 40 days of age (Physiologist 22: 3, 1979). Serum prolactin was significantly increased at 30 days compared to 10 or 20 days, then decreased at 40 days. Serum LH was low in most rats at 10-40 days of age. TH activity was measured in the preoptic area (POA), suprachiasmatic nucleus (SCN), median eminence (ME) and amygdala (AMYG). In the POA and SCN, significant peaks of TH activity occurred at 20 days and declined to baseline levels at 25 days. In the ME, the peak TH activities were at day 20 and persisted until day 40 while the AMYG showed a peak of activity at 25-30 days with a return to baseline levels at 35 days. These results show that significant changes in TH activity are occurring within discrete nuclear regions of the hypothalamus prior to the onset of puberty and these changes are temporally different from observations in the whole hypothalamus. Changes in TH activity may represent a synchronized maturation of catecholaminergic systems prior to the anticipated hormonal changes of puberty. (Supported in part by NIH, HD 12886-01 and the University of Louisville Medical School Research Committee Grant.)

SPLANCHNIC CIRCULATION

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EFFECT OF PERFUSION PRESSURE ON THE DISTRIBUTION OF 9µm AND 15µm SPHERES IN THE INTESTINAL WALL. L.C. Maxwell, A.P. Shepherd, and G.L. Riedel. Dept. of Physiol., Univ. of Texas Health Science Center, San Antonio, Texas 78284

We have previously shown that (a) the apparent intramural distribution of intestinal blood flow depends upon microsphere (µS) size, (b) the percentage of 9µm spheres that "shunt" to venous blood is inversely related to the mucosal-to-submucosal ratio of trapped spheres, and (c) previously lodged spheres migrate following perfusion pressure (Pa) elevation. In this study we have determined the effect of Pa upon µS distribution. Isolated loops of canine small bowel were vascularly perfused at pressures of 90, 120, and 150 mmHg. Radioactive 9µm and 15µm spheres were injected into the loops which, following each experiment, were dissected into mucosal, submucosal and muscularis tissues. The accumulations of µS in each tissue and in venous blood were quantitated in a gamma counter. Compared to loops perfused at a Pa of 120 mmHg, those perfused at either 150 or 90 mmHg had (a) lower percentages of µS in submucosa, (b) greater proportions of µS in mucosa and muscularis, and (c) an unaltered percentage shunting. We conclude that the distribution of µS within the intestinal wall is markedly affected by Pa within the range from 90 to 150 mmHg but that the shunting of µS to venous blood is not. These data demonstrate the necessity of knowing the perfusion pressures when comparing µS studies of intestinal blood flow. (Supported by grant HL-23435 and grants from the American Heart Association).

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DETERMINANTS OF THE OPTIMAL HEMATOCRIT FOR INTESTINAL OXYGEN TRANSPORT. A.P. Shepherd and G.L. Riedel*. Department of Physiology, University of Texas Health Science Center, San Antonio, Texas 78284

In a recent study we found that the ability of the intestine to regulate its oxygen uptake in response to changes in perfusion pressure was impaired if the hematocrit of the perfusate was either above or below the normal range. Therefore, to determine if there is an optimal Hct for intestinal oxygenation, we perfused isolated canine gut loops at a constant pressure (120 mmHg) and varied hematocrit (Hct) from 80 to 10%. As Hct fell, blood flow rose while arterial oxygen content fell. The regression of blood flow on Hct was linear while the relationship between oxygen uptake and Hct was parabolic, showing a maximal oxygen uptake at an hematocrit of 48.7%. To determine whether the optimal Hct for intestinal oxygenation could be altered by changes in vasomotor tone, we performed two other series of experiments. Raising perfusion pressure to 180 mmHg did not significantly alter the optimal Hct for oxygen uptake. However, during the hypermetabolic state induced by placing transportable solutes within the intestinal lumen, the optimal Hct for oxygen uptake increased markedly. We conclude that the optimal Hct for intestinal oxygenation is slightly higher than the normal range, a finding that could possibly be explained by the plasma skimming known to occur in the intestinal mucosa (supported by HL-23435).

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BLOOD FLOW-LIMITED INCREASES IN INTESTINAL OXYGEN CONSUMPTION Joseph D. Fondacaro and Eugene D. Jacobson Department of Physiology, College of Medicine University of Cincinnati, OH 45267

Mesenteric vasodilation induced by intraarterial infusion of dilator agents generally produces a rise in intestinal oxygen consumption (V_{O_2}), possibly reflecting a stimulation of intestinal metabolism, although the arteriovenous oxygen content difference (A-V_{O_2}) does not increase. We examined the relationship between intestinal blood flow (BF), A-V_{O_2} and V_{O_2} during infusion of increasing doses of prostacyclin (PGI_2). In anesthetized dogs we measured BF and A-V_{O_2} across a segment of small intestine during PGI_2 infusion. Intestinal V_{O_2} increased proportionally with BF but to a lesser magnitude until BF had doubled when V_{O_2} plateaued at the elevated level despite further increases in BF, suggesting that PGI_2 was not stimulating metabolism. Furthermore, during control periods, spontaneous variability yielded a V_{O_2}/BF relationship that was not different from the V_{O_2}/BF relationship seen during PGI_2 infusion, again suggesting that intestinal metabolism was not altered by PGI_2. When control A-V_{O_2} was above 3.0 ml O_2/min·100ml, there was a greater decline in this parameter during dilator hyperemia than when control A-V_{O_2} was below 3.0. It appears that the increase in V_{O_2} observed during PGI_2 induced mesenteric hyperemia is flow-limited and that PGI_2 increases intestinal oxygen uptake well below the point of maximal dilation. We conclude that PGI_2 increases intestinal blood flow either by increasing the caliber of perfused vessels or by opening new vessels rather than by stimulation of intestinal metabolism. (Supported by a grant from the American Heart Association).

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MEFANAMIC ACID (MA) INCREASES OXYGEN CONSUMPTION ($\dot{V}O_2$) DURING THE POSTPRANDIAL INTESTINAL HYPEREMIA (PIH). R.H. Gallavan, Jr.* and C.C. Chou (SPON: L.F. Wolterink) Departments of Physiology and Medicine, Michigan State University, East Lansing, MI 48823

We have shown that both i.v. and i.a. infusion of MA markedly enhances the hyperemic effect of digested food plus bile in the jejunum. In the current study we measured the effect of food on $\dot{V}O_2$ and blood flow (BF) in the isolated jejunal loop before and one hour after i.v. MA (10mg/kg) infusion. The results are as follows (N=6):

Before MA	NS	FOOD	FOOD-NS	%Δ
BF	41.5 ± 5.7	49.1 ± 7.2	7.6 ± 1.9*	17.7 ± 4.1*
$\dot{V}O_2$	1.5 ± 0.2	1.8 ± 0.2	0.3 ± 0.1*	16.1 ± 4.6*
After MA	**NS**	**FOOD**	**FOOD-NS**	**%Δ**
BF	20.7 ± 2.4	33.6 ± 4.3†	12.9 ± 2.1*†	61.1 ± 5.4*†
$\dot{V}O_2$	1.4 ± 0.1	1.9 ± 0.2	0.5 ± 0.1*†	34.9 ± 7.4*†

NS=normal saline in the segment; *=p< 0.05; † = p< 0.05 relative to the corresponding value before MA. Thus, MA decreases resting blood flow but this is not associated with a decrease in resting $\dot{V}O_2$. The enhancement of the food-induced jejunal hyperemia is associated with an enhancement of the food induced increase in jejunal $\dot{V}O_2$. There is a significant correlation between ΔBF and Δ$\dot{V}O_2$ (p< 0.05) both before and after MA. It appears that the enhancement of the PIH by MA may be related to its metabolic effects. (Supported by NHLI Grant HL-15231)

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GASTRIC OXYGEN UPTAKE AND BLOOD FLOW IN THE ISOLATED PERFUSED STOMACH. Gregory B. Bulkley, Michael A. Perry*, Peter R. Kvietys, and D. Neil Granger, Department of Physiology, University of South Alabama, Mobile, Alabama 36688.

The relationship of gastric oxygen uptake to blood flow was compared in two different canine stomach preparations, one perfused via the celiac artery (total perfusion), one via the left gastroepiploic artery (partial perfusion). Total flow, arterovenous O_2 difference, and local arterial and venous pressures were continuously monitored while flow was altered over a wide range (5-110 ml/min/100g) by pump perfusion. Oxygen uptake in the partially perfused preparation was flow limited over the entire range studied: Even at apparent flow rates of 110 ml/min/100g, apparent O_2 uptake had risen steadily to 6 ml/min/100g. This is similar to other reports from partially perfused stomach preparations. Total (celiac) perfusion produced flow limitation of O_2 uptake only at flows below 30 ml/min/100g. At higher flows, O_2 uptake was diffusion limited (constant at 1.5 ml/min/100g). Intra-arterial isoproterenol did not alter this relationship. Pentagastrin infusion caused O_2 uptake to become diffusion limited at a higher level (2.5 ml/min/100g) with blood flows above 40 ml/min/100g, and was associated with hydrochloric acid secretion. These results show that O_2 uptake is autoregulated over a wide range in the fully perfused stomach, and suggest that the apparent flow limitation of O_2 uptake seen in partially perfused (ischemic) stomach preparations is an artifact reflecting recruitment of previously nonperfused areas at higher flow rates.

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SECRETIN INDUCED VASODILATION AND O_2 CONSUMPTION IN THE EXOCRINE CANINE PANCREAS. HJM Beijer* AHJ Maas* and GA Charbon* (SPON: AP Shepherd) Exp Lab Thoracic Surg, Univ Hosp, Utrecht Holland.

In the exocrine canine pancreas secretin induced an increased secretion, combined with an increased O_2 consumption ($\dot{V}O_2$), an increased blood flow (q_a) and a varying O_2 extraction (O_2E) response. It was questioned whether these phenomena could be explained in the model of the functionally different sections of the terminal vascular bed. In pentobarbital anesthetized dogs we measured pancreatic q_a with electromagnetic flow probes and exocrine secretion flow (q_s). Blood gas analysis yielded arterial and pancreatic venous O_2 conc. Secretin (Karolinska), 1 U/kg was injected as i.v. bolus. q_a was maximally increased at 2 min and then gradually decreased to basal level at 32 min. q_a was maximally increased at 2 min and then rapidly decreased to basal level between 8 and 16 min. O_2E was significantly lowered at 2 min and then gradually increased until significantly higher than basal level at 16 min. $\dot{V}O_2$ was increased to a constant level between 1 and 16 min and then decreased to basal level at 32 min. Data may be explained as follows: during the first 2 min the precapillary resistance vessels are opening, while the capillary density essentially is not changed. This induced a faster passage of the blood through the capillaries and consequently extraction was diminished. From 2 to 16 min blood flow is decreasing to its basal level, while capillary density is increasing continually: the exchange area, and consequently the O_2 extraction, is continually increased. The underlying assumptions to this explanation will be discussed.

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EFFECT OF CARDIAC TAMPONADE ON COLONIC HEMODYNAMICS AND OXYGEN UPTAKE. P. R. Kvietys, G. B. Bulkley, M. A. Perry*, and D. N. Granger. Dept. of Physiology, University of South Alabama, and Dept. of Surgery, Johns Hopkins Hospital, Baltimore, Md.

Cardiac tamponade (CT) is frequently employed as a model for nonocclusive mesenteric ischemia. In this study, we assessed the effects of CT on blood flow and oxygen uptake of innervated autoperfused dog colon preparations. While measuring cardiac output (CO), arterial pressure (AP), colonic blood flow (BF) and oxygen extraction, graded CT was induced by repeated injections of 10% dextran into the pericardial sac. Cardiac tamponade reduced CO and BF. Arterial pressure was decreased when CO was decreased ≥ 32%. The increase in colonic vascular resistance was greater than the increase in total peripheral resistance, indicating selective constriction of the colonic vasculature. Colonic oxygen uptake was not affected by graded CT due to compensatory increases in oxygen extraction. When BF was reduced to ≤ 20 ml/min x 100g oxygen uptake decreased. The changes in oxygen uptake during CT were similar to those observed during graded reductions in colonic arterial inflow, indicating that CT did not alter the normal relationship between colonic blood flow and oxygen uptake.

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THE ROLE OF HISTAMINE IN POSTPRANDIAL INTESTINAL HYPEREMIA. H. Siregar*, and C.C. Chou. Departments of Physiology and Medicine, Michigan State University, East Lansing, MI 48824

To assess if histamine plays a role in the postprandial intestinal hyperemia, the vascular and metabolic effects of luminal placement of predigested food (17% carbohydrate, 33% fat, and 41% protein) in the jejunum of the anesthetized dog were compared before and after intra-arterial infusion of tripelennamine (T), metiamide (M), and a combination of both antagonists (M+T). Venous outflow (BF) and A-VO_2 difference of the jejunal segments were measured. BF and $\dot{V}O_2$ were not altered after infusion of M (10^{-5}mol/min), T (10^{-5}mol/min) or M+T for 10 min. The increases in BF and $\dot{V}O_2$ produced by histamine (0.5 μg/kg/min) were attenuated by either M or T, but were blocked by M+T. The percent changes in BF and $\dot{V}O_2$ from control produced by food, before and after blockades were:

	Blood Flow			Oxygen Consumption		
	Before	After	B-A	Before	After	B-A
M	+24.8*	+24.7*	0.1	+16.0*	+14.5*	1.5
T	+30.3*	+14.3*	16.1†	+11.8*	+ 2.0	9.8†
M+T	+25.1*	+ 7.5	17.6†	+11.7*	+ 3.9	7.8†

*p<0.05; †Difference between the values before and after blockades were significant. Thus, histamine receptor blockades with T and T + M, but not M, attenuate the food-induced increase in BF and abolish the increase in $\dot{V}O_2$. The study suggests that histamine plays a role in the postprandial increases in intestinal BF and $\dot{V}O_2$, and the responses appear to be mediated by H_1-receptors. (Supported by NHLI Grant HL-15231)

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LIVER VASCULAR CAPACITANCE RESPONSES TO NERVE STIMULATION, CHANGES IN FLOW, OR HISTAMINE. Carl F. Rothe, Tom D. Bennett and Carol L. MacAnespie*. Department of Physiology, Indiana University School of Medicine, Indianapolis, IN 46223.

Active changes in hepatic vascular capacitance during hepatic nerve stimulation or infusion of histamine or epinephrine were studied in isolated pump-perfused dog livers. The hepatic venous outflow was controlled by a servo system to keep the hepatic venous pressure at 0 or 5 mmHg. Changes in hepatic volume were determined by continuous analog integration of the difference between hepatic artery plus portal venous inflow and the hepatic venous outflow. Hepatic nerve stimulation at 5 pps expelled 84 ± 34 (SD) ml of blood per kg of liver and decreased the apparent hepatic compliance 36%. Stopping the hepatic and portal venous inflow caused a 173 ± 31 ml/kg passive reduction in liver blood volume. Histamine, i.a., dramatically reduced the hepatic venous compliance, decreased the portal venous conductance, and caused the apparent hepatic blood volume to double in some cases. Epinephrine (0.05 mg/liter blood, i.a.) caused hepatic artery constriction and the active expulsion of 71 ml/kg of blood. We conclude that the canine liver can be stimulated to produce active venoconstriction. (Supported in part by USPHS NIH grant HL07723.)

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VASCULAR COMPLIANCE OF THE FETAL SHEEP LIVER. Gordon G. Power, C. C. Genstler*, P. S. Dale*, and Raymond D. Gilbert. Loma Linda Univ., Loma Linda, California 92350

To estimate the importance of the liver as a fetal blood reservoir, we measured the compliance of the liver in 8 lambs in utero. Balloon-tipped catheters were positioned above and below the entry of the hepatic vein into the inferior vena cava, the hepatic artery and portal vein were ligated, and a flow probe placed around the common umbilical vein, the only remaining blood supply to the fetal liver. Then to determine compliance, the balloons were inflated for about 10 seconds to momentarily block hepatic outflow while volume flow into the liver and pressure at the outflow of the liver were measured continuously. The procedure was repeated an average of 5 times with 10 minute intervals allowed for recovery. Compliance was obtained from the pressure-volume curves and averaged 3.7 ± .5 (SEM) ml/mmHg/100 grams liver or 1.0 ± .1 ml/mmHg/kg body weight. In a second group of 9 fetal lambs, whole body vascular compliance was estimated by measuring the average venous pressure rise following the infusion of 60 ml of warm saline over a 10 second interval. Whole body compliance averaged 3.7 ± .4 ml/mmHg/kg body weight. We conclude that the hepatic vascular bed is responsible for about 27% of the whole body compliance in the fetal lamb and, therefore, could function as a significant blood reservoir.

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EFFECTS OF ALTERED INTESTINAL BLOOD FLOW AND PRESSURE ON Na AND H_2O FLUXES. D. Mailman, Biol. Dept., Univ. Houston, Tx 77004.

Previous work suggested that certain hormones change gut absorption partly through a cardiovascular effect because absorptive site blood flow (ASBF) and estimated capillary pressure were correlated with absorptive and secretory fluxes, respectively, of Na and H_2O. To test this possibility more directly, mesenteric artery (AO) and vein (VO) occlusion and IA nitroprusside (NP) were used to alter canine ileal blood flow and pressure. Fluxes were measured with luminal tracers and ASBF estimated as ^3H_2O clearance. Net Na and H_2O absorption was decreased by all three procedures. AO reduced ASBF and absorptive fluxes more than secretory fluxes. VO increased secretory fluxes and decreased ASBF and absorptive fluxes. NP decreased absorptive fluxes with little effect on secretory fluxes and increased or decreased ASBF depending on local resistance and systemic blood pressure. NP enhanced the effect of AO on net and absorptive fluxes but reduced the effects of VO. At comparable decreases of 65% in ASBF and 55% in absorptive fluxes, secretory Na fluxes decreased by 45% after AO to 40 mm Hg and increased by 65% after VO to 40 mm Hg. H_2O fluxes paralleled the Na fluxes. It was concluded that cardiovascular effects on gut fluxes are physical due to washout by ASBF and ultrafiltration due to capillary pressure. (Supported by NSF 7825867).

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INTESTINAL VASCULAR RESPONSE AND INTERSTITIAL SODIUM CONCENTRATION DURING GLUCOSE ABSORPTION. H. Glenn Bohlen. Dept. Physiology, Indiana University School of Medicine, Indianapolis, IN 46223

Coupled absorption of glucose and sodium may create a hyperosmotic mucosa and submucosa which influences the intestinal vasculature. Sodium concentration, $[Na^+]$, was measured in vivo in the bowel of rats with ion-selective microelectrodes during rest and glucose absorption (25-100 mg%). Tissue osmolarity was calculated based on $[Na^+]$ and an assumed related anion. At rest, $[Na^+]$ in the upper half of villi is 200-225 mM; in the submucosa, 140-150 mM. After one minute of glucose exposure, $[Na^+]$ in villi increases to and stabilizes at 250-400 mM; in three minutes, the submucosal $[Na^+]$ is 165-190 mM and for a given animal, remained constant. The time course of vasodilation and $[Na^+]$ event in the submucosa are equal. Projected osmolarity increase in the submucosa of 40-100 mosm would be vasoactive and contribute to absorptive hyperemia. Supported by PHS grant HL 20605.

CONTROL OF BREATHING: RESPIRATORY PATTERNS

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TRANSIT TIME ANALYSIS OF THE RESPIRATORY PATTERN IN NORMALS AND PATIENTS WITH AIRWAYS OBSTRUCTION. M.M.Grunstein, C.G.Irvin*, N.Berend* and K.S.Greve*. Univ.of Colo.School of Med. and Nat. Jewish Hosp. Denver, CO 80206

To assess airways obstruction during spontaneous breathing we analyzed spirometric and end-tidal CO_2 tracings in terms of the distribution of transit times during inspiration and expiration in 5 asthmatic subjects,before and after inhaled histamine,and in 10 normal and 9 patients with COPD. After 5 min of CO_2 rebreathing,to minimize volitional modulation of respiration, subjects were suddenly exposed to room air and each subsequent breath was analyzed for: a)mean transit time of inspiration (MTT_I)and expiration(MTT_E), representing the average of the distribution of transit times required for air entry and exit from the lung; b)coefficient of variation of transit times during inspiration(VTT_I) and expiration(VTT_E); c)mean transit time of expired CO_2(MTT_{CO_2}). In every subject,values of MTT_I, MTT_E, MTT_{CO_2} varied little between breaths and were independent of changes in tidal volume or P_ACO_2. In the 5 asthmatics, after histamine MTT_I rose by 15 to 45%, with greater increases in MTT_E(+65 to +140%) and MTT_{CO_2}(+60 to +180%). VTT_I was little affected, while VTT_E rose by 35 to 94%. Using FEV_1(% predicted) as a conventional index of airflow limitation, data from all subjects showed significant inverse relationships between: 1) $VTT_E$and FEV_1(r= -.82), 2)MTT_{CO_2}/MTT_E ratio and FEV_1(r= -.81), and 3)ratio of MTT_{CO_2} to expiratory duration (MTT_{CO_2}/T_E) and FEV_1(r= -.81). These data indicate that transit time analysis of the spirometric or CO_2 tracing during spontaneous breathing provides new and useful measures of lung function.

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EFFECTS ON RESPIRATORY TIMING OF VENTILATION WITH HIGH FREQUENCY OSCILLATION. Enid R. Kafer, H. Michael Marsh,* Kai Rehder and Thomas J. Knopp. Mayo Clinic and Foundation, Rochester, MN 55905 and University of North Carolina, Chapel Hill, NC 27514

Inspiratory duration (T_I) and total respiratory cycle time (T_{TOT}) were examined in 10 dogs (11-16 kg) anesthetized with halothane (1.2 to 1.6%) in oxygen during spontaneous breathing (SB) through an endotracheal tube, with and without respiratory system motion resulting from high frequency oscillation (HFO) of gas (frequency 20-22 Hz, stroke volume 2.5-4.2 ml/kg). Mean airway pressure (MAP) was adjusted by varying outflow resistance while $PaCO_2$ was controlled by adding CO_2 to the fresh gas. At comparable $PaCO_2$ levels and end-expiratory lung volumes close to functional residual capacity, neither T_I nor T_{TOT} were significantly different between SB with (T_I=0.97± 0.14 S, T_{TOT}=5.82±1.30 S, M±SE) and without (T_I=0.91±0.08 S, T_{TOT}=5.50±1.30 S) HFO. Increases in MAP (0 to 5, 10 or 15 cm H_2O) during HFO (6 dogs) caused a usually temporary suspension of SB (Hering-Breuer inflation reflex) at a constant $PaCO_2$. This inflation reflex was abolished by bilateral cervical vagotomy. Before vagotomy $1/T_{TOT}$ was negatively correlated with MAP ($P<0.05$) and 3 dogs became apneic at MAP=15 cm H_2O. It was concluded that respiratory timing during HFO in anesthetized dogs is dependent on lung volume and chemical drive, while effects of high frequency respiratory system motion appear minimal. (Supported by HLBI-71314, HLBI-00218, and HL-21584.)

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ANALYSIS OF THE RESPIRATORY RESPONSE TO ASPHYXIA IN NEWBORN RABBITS. Enrique Fernandez,* Charles G. Irvin *and Michael M. Grunstein. Univ. of Colo. Sch. of Med. and Natl. Jewish Hosp., Denver, CO, 80206.

To quantitatively assess the mechanisms leading to primary apnea and gasping during asphyxia, studies were conducted measuring the respiratory response in five rabbits (age range 13 to 15 days). The animals were anesthetized, tracheotomized and placed in a 2.5 liters pressure plethysmograph. Tracheal pressure, tidal volume and diaphragamatic EMG (EMG_{di}) were recorded and analyzed to determine peak end-inspiratory mouth pressure (P_{max}), ratio of inspiratory to total duration (Ti/Tot), and high/low ratio (H/L) of EMG_{di} as an index of diaphragmatic fatigue. During continuous airway occlusion at FRC, prior to primary apnea, there occurred: 1) an initial progressive increase in P_{max} followed by a decrease 2) a progressive decrease in Ti/T_{tot}, 3) an initially constant H/L ratio of the EMG_{di} followed by a rise, and 4) a constancy in the relationship between P_{max} to peak integrated EMG_{di}. After primary apnea, during gasping respiration: 1) P_{max} and EMG di increased above previous levels, 2) H/L ratio remained elevated and 3) Ti/T_{tot} continued to fall along the same time course established prior to apnea. Despite both the presence of an infinite elastic load and the severe metabolic compromise of asphyxia, there was no indication of diaphragmatic fatigue as evidenced by both the H/L ratio and P_{max} parameters. The respiratory changes during asphyxia in the newborn rabbit are therefore attributed solely to alterations in the behavior of the central mechanisms regulating the drive and timing of breathing.

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AUGMENTED BREATH IN KITTENS. Teresa Trippenbach. Dept. of Physiol., McGill University, Montreal, Canada H3G 1Y6.

The characteristics of the augmented breaths were studied in kittens, aged 1-21 days, anaesthetized with pentobarbital. 'Integrated' phrenic activity and esophageal pressure of the augmented breath were biphasic. The relationship between the esophageal pressure and 'integrated' phrenic activity had two slopes, the first was steep, for the initial part of the augmented breath, the second had a considerably lower slope for the augmented part of inspiration. The following postnatal changes in the characteristics of the augmented breaths were observed. 1) less variability in duration, peak amplitude and rate of rise of the 'integrated' phrenic activity during the initial phase. 2) less increase in the maximal amplitude of the 'integrated' phrenic activity with age. 3) increased duration of the total augmented inspiration due to both an increase of inspiratory time with age and a prolongation of the augmented phase. 4) decreased prolongation of expiration following the augmented breath. It is suggested that spontaneous changes in FRC of newborns may provoke inspiratory augmenting reflex. Decreased number of augmented breaths with age indicates increased stability of the peripheral respiratory system with maturation. (Supported by the MRC of Canada).

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CONTROL OF RESPIRATION AT INCREASED LUNG VOLUMES IN ANESTHETIZED CATS. Joe Finkler* and Steve Iscoe* (SPON. C.K. Chapler) Dept. of Physiology, Queen's University, Kingston, Ontario, Canada K7L 3N6.

The neural control of respiratory pattern at elevated lung volumes is incompletely understood. We studied the tidal volume (V_T) - inspiratory duration (T_i) relationship in 14 pentobarbital anesthetized, spontaneously breathing cats. Measurements were obtained either at functional residual capacity (FRC) or at elevated lung volumes. The sensitivity of the inspiratory off-switch mechanism to changes in lung volume was defined by the slope of the V_T-T_i relationship between normal and occluded breaths. At control FRC, the sensitivity was 26.3±2.8 (SEM) ms/ml (N=23). At elevated lung volumes of 23±3 ml (N=11) and 42±3 ml (N=12), the sensitivities were reduced ($P<.05$) to 10.4±2.9 ms/ml and 15.5±3.1 ms/ml respectively. The reductions in sensitivity indicated that greater changes in inspired volume were required to produce a given change in T_i at elevated lung volumes. In an attempt to identify the source of this decreased sensitivity, we also studied the responses of 41 pulmonary stretch receptors (PSR) to elevations of FRC (54±3 ml, N=41) for 10 min. All PSR increased their peak discharge frequencies by 75% and their end-expiratory frequencies by 30%. These results suggest that changes occurring centrally (brainstem respiratory neurons), and not peripherally (PSR), account for the decreased sensitivity of the inspiratory off-switch mechanism when breathing occurs at elevated lung volumes. (Supported by the Medical Research Council of Canada)

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RELATIONSHIP BETWEEN EXPIRATORY DURATION (Te) AND THE FOLLOWING INSPIRATORY DURATION (Ti) IN THE DOG. **E.J. Zuperku, F.A. Hopp*, and J.P. Kampine.**
Med. Col. of Wisconsin and Wood VA Ctr., Milwaukee, WI 53193

These studies were carried out to characterize the central effect of Te on the Ti values of subsequent breaths in anesthetized (thiopental sodium), paralyzed, vagotomized dogs. The Te of test breaths was lengthened by electrical stimulation of the largest A fibers in the central end of the vagus nerve during expiration (E) only. The phrenic neurogram was used to measure Ti and Te and to synchronize the stimulator. Mechanical ventilation had no noticable effect on Ti and Te, and it was possible to maintain blood gases constant, independent of the breathing pattern. Simulated "volume feedback" was used to establish a nonvagotomized control breathing pattern. The following sequence was commonly used: 4-6 control breaths, test breath, 1-4 unstimulated breaths. The study shows that: 1) A linearrelationship exists between Te and the following Ti(slope: 50-100 msec/sec) 2) The "volume threshold" curve for the inspiration following a prolonged Te is increased 3) The effect of a prolonged Te decays and manifests itself by increased Ti'sin 1-4 subsequent breaths 4) A linear relationship exists between Ti and the following Te. These studies suggest that the central organization of the respiratory centers contains mechanisms which allow information from previous breaths to be passed on into following breaths. Supported by VA Medical Research Service.

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CONTROL OF EXPIRATORY DURATION DURING TRANSIENT HYPOXIA AND HYPERCAPNIA IN CONSCIOUS DOGS. L.-Y. Lee, R.F. Morton*, and L.K. Yu*. Univ. of Kentucky, Lexington, Kentucky 40536

We previously reported that the expiratory duration (T_E) shortened progressively as the ventilation increased during transient hypoxia (HPX) and hypercapnia (HPC); the shortening of T_E persisted even after cold blocking of both vagi, suggesting a role of chemical drive in the control of T_E (Fed. Proc. 39:830, 1980). To examine the relationship between T_E and the inspiratory drive, we performed 49 studies on 5 awake dogs which rested quietly and breathed through endotracheal tubes. Transient HPX and HPC were induced with 4-7 consecutive breaths of N_2 and 15% CO_2 in air, respectively. Breath-by-breath responses were analyzed continuously, and the inspiratory drive was measured as the mean inspiratory flow ($\bar{V}_I$). As chemical drive increased progressively during transient HPX, T_E exhibited a significantly higher ($p < 0.01$) linear correlation with $\bar{V}_I$ of the following breath ($\bar{V}_I$) than with $\bar{V}_I$ of the same breath: in the 5 dogs studied, the mean correlation coefficient (r) between T_E and $\bar{V}_I$ was -0.790, whereas the r between T_E and $\bar{V}_I$ was -0.646. Similar results were found during transient HPC. These results suggest that the progressive shortening of T_E during transient HPX and HPC may result from a progressive increase in inspiratory drive which terminates the expiration of the preceding breath at an earlier time. (Supported by NIH Grants HL-25089 and BRSG RR-05374.)

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THE EFFECT OF POSTURE ON THE RESPONSE TO CO_2 Brian Abraham*, Charles Weissman*, Jeffrey Askanazi, J. Milic-Emili and John M. Kinney. College of Physicians & Surgeons of Columbia University, New York, NY 10032.

Studies of breathing patterns are often performed in the supine position in ill patients and either seated or supine in normal subjects. This study examines the effect of posture (seated vs supine) on the pattern of breathing at rest and during stimulation (steady state CO_2, 2 and 4%) in 9 normal subjects. A canopy-computer-spirometer system was used to non-invasively measure minute ventilation ($\dot{V}_E$), tidal volume (V_T), frequency (f), inspiratory and expiratory times (T_I,T_E), mean inspiratory flow (V_T/T_I), inspiratory duty cycle (T_I/T_{TOT}), O_2 consumption ($\dot{V}O_2$), and CO_2 production, $\dot{V}CO_2$. Arterial PCO_2 was measured in 5 subjects. At rest $\dot{V}_E$ was 21% ($p < .005$) higher in the sitting position while O_2 consumption was 7% greater when seated (NS). With administration of 4% carbon dioxide minute ventilation was 13.9 l/m and 20.0 l/m in the supine and seated position respectively. The relationship between $\dot{V}_E$ and V_T was parallel in both cases. For any given level of $\dot{V}_E$, inspiratory flow was higher in the seated position. At all levels of V_T, inspiratory time was lower in the seated position. The ventilatory response to CO_2 as measured by $\Delta\dot{V}E/\Delta PaCO_2$ was identical in both cases, while ventilatory sensitivity was increased when seated. Changes in position from supine to sitting are associated with an alteration in breathing pattern and sensitivity to CO_2 while the ventilatory response to CO_2 is unchanged.

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INVOLVEMENT OF THE PNEUMOTAXIC CENTER IN THE MEDIATION OF INSPIRATORY INHIBITORY REFLEXES (IIR) FROM INTERCOSTAL AND ABDOMINAL MUSCLES. R. Shannon, D.L. Freeman* and B.G. Lindsey. Department of Physiology, College of Medicine, University of South Florida, Tampa, FL 33612.

Stimulation of intercostal and abdominal muscle proprioceptor afferents (Group I) has been shown to result in medullary inspiratory neuron inhibition. Inspiratory-expiratory (IE) and expiratory (E) neurons in the pneumotaxic center (PC) region are facilitiated by the muscle afferents (MA). Experiments were conducted to determine if the PC IE and E neurons mediate the IIR from the MA to the medulla. Decerebrated, vagotomized, paralyzed, artificially ventilated cats were used. Stimulus-response latencies of phrenic (PA) and rostral pontine respiratory unit activities were measured during electrical stimulation of intercostal nerve afferents.

NEURONS	n	NEURON LATENCY mean (range)	PHRENIC LATENCY mean (range)
IE	17	23.7ms (12.9-62.5)	15.6ms (12.9-21.8)
E	5	28.9ms (25-31.7)	14.9ms (12.9-16.3)

The results show that inhibition of PA preceded the facilitation of IE and E neurons. It is known that the inhibition of PA is secondary to medullary I neuron inhibition; the results therefore suggest that the PC IE and E neurons are not the primary neurons mediating the IIR from the muscle afferents. (Supported by NIH Grant HL-17715).

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THE ROLE OF THE LARYNX IN THE REGULATION OF BREATHING DURING HYPOXIA IN SLEEPING LAMBS. P. Johnson* & J.E. Fewell, Nuffield Institute for Medical Research, University of Oxford.

Expiratory laryngeal resistance plays a role in ensuring an adequate lung volume and respiratory rhythm during quiet sleep in lambs (Central Nervous Control Mechanisms in Breathing, Ed. C von Euler, Pergamon Press,337,1979). Hypoxia increases activity of the laryngeal adductor muscles in adult rats (Resp Physiol 39:335,1980). The role of this increased expiratory resistance on the respiratory response to hypoxia is unknown. We therefore investigated the cardiorespiratory effects of hypoxia in 7 unanaesthetized young lambs with and without their upper airway intact. The response to acute hypoxia (F_IO_2.10-.07) was an increase in minute ventilation, heart rate and blood pressure followed by arousal if the lambs were in quiet sleep. In contrast, arousal usually preceded the respiratory response to hypoxia, if the lambs were in REM sleep although this occurred at a lower P_aO_2. When hypoxia was sustained for 60 to 70 minutes, a quiet sleep-like high voltage state usually followed. If the lambs were breathing through a tracheostomy, with no expiratory resistance, breathing frequency decreased and often became irregular. Re-introducing the upper airway by closing the tracheostomy or adding an expiratory resistance sufficient to produce a subglottic pressure of 8 cm H_2O pressure rapidly restored a regular breathing pattern and increased frequency. Thus an intact functional upper airway is important in maintaining regular breathing during hypoxia in sleeping lambs. (Supported by Wellcome Trust 9594-1.5, Foundation for Study of Sudden Infant Death and HL 07159).

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VOLUME-TIMING RESPONSES TO SUSTAINED ELEVATION OF FRC. S.R. Muza*, D.T. Frazier, C.P. Pan* & F.W. Zechman, Dept. of Physiology and Biophysics, Univ. of Ky., Lexington, KY 40536

We have described the response of slowly adapting pulmonary stretch receptors (PSR's) to sustained elevations of FRC in cats. These studies have been repeated to examine the effect of elevated FRC on the volume-timing relationships. In 7 spontaneous breathing dial-urethane anesthetized cats a negative pressure was produced around the thorax and abdomen to increase FRC by about 1 tidal volume for up to 60 minutes. Body temperature was maintained ± 0.3°C of control. A tracheal cannula was connected to a resistive manifold for selective loading of inspiration or expiration. Two resistive loads and tracheal occlusion were presented six times each at control FRC (FRC_C), at elevated FRC (FRC_e) and 30 minutes after return to FRC_C. (T_i) and (T_e) were measured from a diaphragm EMG. We observed T_i at FRC_e (.88±.3 sec) was slightly shorter than T_i at FRC_C (1.06±.4 sec). Tracheal occlusion at FRC_e caused a shorter T_i (1.37±.4 sec) than at FRC_C (1.79±.5 sec) ($p<.05$). At FRC_e the slope (m) of the V_i-T_i relationship was steeper (m=-65±18) and shifted upward from the V_i-T_i curve at FRC_C (m=-50±17) ($p<.05$). 30 minutes following return to FRC_C, T_i was still slightly shorter (.96±.3 sec) than the initial FRC_C T_i. The V_e-T_e relationship at FRC_e was not significantly changed from control. We conclude that the V_i-T_i relationship does not exactly follow a predicted function based on total lung volume because of a partial adaptation of PSR's. (Supported in part by NIH Grant HL 24412.)

LUNG FLUID BALANCE II

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EFFECT OF DIAPHRAGMATIC LYMPH CONTAMINATION ON CAUDAL MEDIASTINAL NODE, CMN, LYMPH FLOW IN UNANESTHETIZED SHEEP. Robert Gunther* and Robert Demling. U.C. Davis, Davis, CA 95616.

Standard CMN lymph fistulae were prepared in 9 sheep. Residual diaphragmatic lymphatics (D.L.) entering the CMN proximal to node transection were removed by cauterizing the right diaphragm along the edge of the node. After 3 days steady state lymph flow, $\dot{Q}_L$ and L/P protein ratios were measured. Animals then underwent a similar cautery procedure for removal of D.L. on the left side and similar measurements obtained. In 5 animals a large D.L. was cannulated and $\dot{Q}_L$ and L/P measured in the unanesthetized steady state. Results for $\dot{Q}_L$ and L/P after the right cautery procedure were 5.2 ± 1.2 ml/hr and .65 respectively and after the left side were 5.1 ± 1.4 and .66 respectively. These compare well with values after the last 30 standard CMN procedures of 5.4 ± 1.6 and .66. Mean $\dot{Q}_L$ and L/P for D.L. were 0.3 ± .12 ml/hr and .62. The L/P for D.L. was always less than for CMN. Residual D.L. do not contribute significantly to caudal mediastinal node lymph flow or protein content in the unanesthetized steady state. (Supported by NIH HL-25403.)

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REMOVAL OF SUBDIAPHRAGMATIC CONTAMINATION OF CAUDAL MEDIASTINAL NODE (CMN) EFFERENT LYMPH IN ANESTHETIZED SHEEP. P. Roos*, J. Wiener-Kronish*, K. Albertine*, M. Matthay* and N. Staub. Cardiovascular Res. Inst. and Depts. of Physiol., Med. & Anat., Univ. of California, San Francisco, CA 94143.

Contamination of CMN efferent lymph by aberrant diaphragmatic lymphatics may be significant (FED. PROC. 40:403, 1981). In 4 anesthetized, ventilated sheep we measured CMN efferent lymph flow and albumin concentration before and after adding 10 ml/kg of isosmotic 5% albumin solution containing ^{125}I-albumin to the abdominal cavity just below the diaphragm. We stimulated both phrenic nerves at 30/min to maximize contamination. To try to eliminate any contamination, we cauterized the pleura along the esophagus and diaphragm on both sides. The data are summarized in the table (mean ± 1 S.D.).

Contamination	Peak	Steady State
Lymph Specific Activity (as % of abdominal fluid)		
Control	21.3±16.8	11.3±9.6
After Cautery	8.6± 6.3	4.2±3.5

Peak contamination (1h) ranged between 0-38%, then fell by half in the steady state (2-3h). Systemic contamination of CMN efferent lymph can be reduced to low levels by careful, thorough node resection and cauterization along the esophagus and diaphragm to ablate aberrant lymphatics. [Supported by HL25816 (Program Project), HL07159 (PFTP), HL06168 (NRSA)].

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EFFECTS OF VENTILATION ON LYMPH FLOW FROM THE ISOLATED PERFUSED LAMB LUNG. W. Mitzner, J.T. Sylvester, S. Permutt. The Johns Hopkins Medical Institutions, Baltimore, MD. 21205

Although external compression of lymphatic vessels is a major mechanism of lymph clearance from systemic tissues, the relative contribution of this clearance mechanism in the lung is not well characterized. To study the effect of ventilation by itself in an intact animal is difficult because of the many concurrent systemic vascular and neural effects. In the present investigation we have studied this question utilizing the isolated perfused lamb lung with intact lymphatic drainage from the caudal mediastinal node. Following cannulation of the duct and recording of lymph flow in the intact animal, we established an in situ perfusion of the lung maintaining normal flow, arterial gases and ventilation. Lymph flow stabilized to a mean steady value of 3.2 g/h within 1 h. The viability of the lymphatics in the isolated lung was confirmed by the observation of active pulsations in lymphatic pressure. Stopping the ventilation caused a 58% fall in lymph flow in 10 min. Over the next 30 min the lymph flow would return to near control. Resuming ventilation then caused a marked overshoot in the lymph flow, suggesting that during the decreased lymphatic clearance with no ventilation, there was an increase in active lymphatic pumping and/or an increase in interstitial pressure. High frequency ventilation (15 Hz) also caused an acute decrease in lymphatic flow, though not as severe as cessation of ventilation. We conclude that ventilation plays an important role in lung lymphatic clearance.

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EVALUATION OF LUNG FLUID BALANCE CHANGES IN SHEEP: LYMPH FLOW VS DUAL DILUTION. D.G.Niehaus*, H.van der Zee* and T.M.Saba. Dept. Physiology, Albany Medical College, Albany, NY 12208.

Reticuloendothelial system (RES) phagocytic defense is modulated by plasma opsonic fibronectin. Experimental depletion of fibronectin limits reticuloendothelial function in sheep. In previous studies (JAP 49:693,1980) with the sheep lung lymph fistula preparation, it was demonstrated that fibronectin deficiency exaggerated the increased lung vascular permeability during sepsis. Since the surgical trauma required for the preparation of the lung lymph fistula alters RES function this invasive approach limits studies on the influence of altered RES function, and fibronectin deficiency on lung fluid balance in sheep. The current study evaluated the ability of the dual-dilution technique to detect alterations in lung water as compared to matched steady-state lymph flow determinations. Anesthetized sheep were tested in both the supine (n=3) and prone (n=3) positions. The thermal lung water space was calculated as: (thermal mean transit - cardiogreen mean transit time) x cardiac output. In the prone position, changes in lung fluid balance as indicated by both techniques were positively correlated. There appeared to be no correlation between the techniques in the supine position. In additional sheep (n=6) the gravimetric lung water (13.9±1.5 g/kg) was identical to the thermal lung water space (13.9±1.4 g/kg). These data suggest that the dual-dilution technique provides a sensitive, non-invasive method for evaluation of changes in lung fluid balance in sheep. (GM-21447 and BRSG SO7RR05394-19)

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HYPOPROTEINEMIA INCREASES LYMPH FLOW IN SHEEP LUNG INDEPENDENTLY OF CHANGES IN STARLING FORCES. GC Kramer*, BA Harms*, BI Bodai*, RH Demling and EM Renkin, Human Physiology and Surgery, Univ. of California, Davis, CA 95616

We studied the effects of a sustained decrease in plasma oncotic pressure on pulmonary fluid balance in 6 unanesthetized sheep. Initial plasma protein concentration, 58.9± 5.2 mg/ml, was quickly reduced to 33.2±1.8 mg/ml via plasmapheresis and held at this value for 24 hrs. Lactated Ringers was infused at a rate adjusted to maintain baseline central venous pressure; cardiac output and pulmonary vascular pressures also remained at baseline. New steady state lymph flows (232% baseline) and lymph-plasma protein concentration (L/P) ratios (62% baseline) were reached in 4 hrs. Decreased lymph protein resulted in reestablishment of baseline plasma-to-lymph oncotic gradient. The increased lymph flow was not the result of increased filtration forces, since all vascular pressures and the oncotic gradient were unchanged; nor was it due to increased surface area since L/P ratios were decreased. Elevation of microvascular pressure (left atrial balloon) during hypoproteinemia caused a greater increase in lymph flow (1.33 ml/hr·mmHg) than with normal plasma protein concentrations (0.68 ml/hr·mmHg). The greater response with hypoproteinemia resulted from 1) an apparent increase in blood to lymph fluid conductivity, 2) reduced fluid viscosity, and 3) diminished oncotic feedback due to minimal interstitial protein concentration. (NIH grants 18010 and 27619)

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PROTEASE-INDUCED INCREASE IN PULMONARY VASCULAR PERMEABILITY. M.V.Tahamont*, P.S.Barie*, F.A.Blumenstock* and A.B.Malik.

Pulmonary vascular injury after acute pancreatitis may be associated with the release of proteases from the injured pancreas. In order to test this hypothesis, we compared the effects of pancreatitis and i.v. protease (trypsin) infusion (mean 4.5 mg/kg/h for 2 h) on lung fluid and protein exchange in sheep with lung lymph fistulas. Pancreatitis was induced by injection of 2 mg/kg trypsin and 1.5 ml/kg 5% Na taurocholate into the pancreas.

	Qlymph	L/P	Clearance (C_L)	Pmv
Baseline(n=5)	5.4±1.5	.80±.03	4.3±1.2	7.6±0.5
Trypsin	11.8±7.4*	.90±.03*	10.6±1.8*	8.7±1.3
Baseline(n=8)	4.4±1.3	.73±.05	3.4±1.2	6.3±1.1
Pancreatitis	7.4±1.0*	.76±.05	5.4±1.5*	5.9±1.4

*p<.05; L/P=lymph/plasma prot. conc. ratio; C_L=Qlymph x L/P; Pmv=pulm. microvasc. pressure = $P_{\overline{la}}$ + 0.4 ($P_{\overline{pa}}$ - $P_{\overline{la}}$); Qlymph = pulmonary lymph flow

Protease release during pancreatitis was confirmed by measurement of a 27% decrease in plasma anti-protease activity. Both trypsin infusion and pancreatitis increased Qlymph and C_L without a change in Pmv, indicating an increase in vascular permeability. Therefore, the pulmonary vascular injury observed during pancreatitis may be mediated by proteases released from the inflamed pancreas. (HL-26551; HL-00363; Parker B. Francis Foundation)

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DIFFERENTIAL EFFECT OF HISTAMINE ON PROTEIN PERMEABILITY IN THE DOG LUNG AND FORELIMB M.B. MARON, Physiology Program, NE Ohio Univ. College of Medicine, Rootstown, Ohio 44272.

The effects of histamine on the vascular permeability of a perfused canine isolated left lower lung lobe (LLL) and a perfused canine forelimb preparation were evaluated by comparing the apparent filtered volumes (FV) calculated from the increases in hematocrit (hct) and plasma protein concentration (pr). In the LLL and forelimb, elevation of venous pressure (P_v) to 16 torr resulted in a ratio of filtered volumes (FV_{pr}/FV_{hct}) of 0.97 ± 0.03 (SE) and 0.99 ± 0.04, respectively. In the LLL, histamine (2.3 µg/ml blood) did not significantly alter this ratio (1.02 ± 0.03), while the addition of methylene blue (5mg), an agent which increases pulmonary vascular permeability, significantly reduced it to 0.62 ± 0.08 indicating that protein permeability had increased. In the forelimb, histamine (2.1 µg/ml) transiently decreased FV_{pr}/FV_{hct} to 0.23 ± 0.04. After recovery from histamine, elevation of P_v caused further filtration without significant protein leakage as evidenced by a ratio of 0.94 ± 0.05. In conclusion, the ability of histamine to increase protein permeability in the forelimb but not the LLL indicates that intrinsic differences in the regulation of vascular permeability exist between blood vessels of the lung and forelimb. Supported by NIH Division of Research Resources Grant #5S08RR09026 and grants from the American Lung Association, and the American Heart Association, Akron District Chapter.

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HEPARIN DOES NOT PREVENT INCREASED LUNG VASCULAR PERMEABILITY AFTER MICROEMBOLI IN UNANESTHETIZED SHEEP. M.R. Flick * and J. Hoeffel* (SPON: J.F. Murray). Dept. of Medicine and Cardiovascular Research Inst., Univ. CA, San Francisco 94143.

We tested heparin's effect on increased lung microvascular permeability during air emboli. In 4 unanesthetized sheep we measured lung lymph ($\dot{Q}$lym) and protein ($\dot{Q}$prt) flow, pulmonary arterial (Ppa) and left atrial (Pla) pressures, and cardiac output ($\dot{Q}$b). We calculated pulmonary vascular resistance (PVR). After a 2h baseline we infused air i.v. at a constant rate to increase PVR 3-4 fold. We repeated the experiment in the same sheep pretreated with heparin (3000 units/kg i.v.). The mean data are summarized in the table:

Condition	Ppa cm H_2O	Pla cm H_2O	$\dot{Q}$b l/min	PVR dyn-s-cm^{-5}	$\dot{Q}$lym ml/h	$\dot{Q}$prt mg/h
Untreated						
baseline	13	1	5.7	123	10.4	263
emboli	31	-7	4.6	494	38.7	1019
Heparinized						
baseline	14	1	5.5	135	10.7	304
emboli	32	-6	4.7	488	40.6	1168

Heparin had no effect on lung fluid balance or hemodynamics during the baseline period; during air emboli, heparin did not effect hemodynamics or attenuate increases in $\dot{Q}$lym and $\dot{Q}$prt. Intravascular coagulation and pulmonary thromboembolization do not play a role in this increased permeability pulmonary edema. [Supported by HL-26913 (Young Investigator Research Award) and HL-19155 (Pulmonary Vascular SCOR)].

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EFFECT OF CONCENTRATED ALBUMIN ON PULMONARY EDEMA AFTER HCL ASPIRATION IN ISOLATED PERFUSED DOG LUNG. S. Nanjo*, J. Bhattacharya and N.C. Staub, Cardiovascular Research Institute and Dept. of Physiology, University of California, San Francisco, CA 94143.

Although concentrated albumin is reported to attenuate edema after HCl instillation in isolated, perfused dog lung, we found no beneficial effect of albumin in open thorax, intact dog lung (PHYSIOLOGIST 23:44b, 1980). In 8 isolated, blood-perfused dog lobes, we measured weight change (ΔWt) and pulmonary arterial pressure (Ppa) at venous pressure = 0 and constant flow. After 1h we instilled 0.4 ml/kg of .1N HCl. In 4 lobes we added 37 g of 25% albumin to the perfusate 5 min after HCl to increase calculated colloid osmotic (Πmv) fourfold. The data are summarized in the table (mean ± 1 S.D.).

Condition	No.	Ppa (cmH_2O)	Πmv (cmH_2O)	ΔWt (g/h)
Baseline	8	14.2±0.5	17.5± 3.3	3.2±1.9
HCl	4	15.5±0.9	18.7± 2.2	22.2±7.9
HCl + Albumin	4	16.9±2.3	78.5±14.5	23.4±8.7

Albumin was of no benefit. In 5 additional lobes we measured ΔWt vs Ppa. After HCl the slope (ΔWt/Ppa) increased dramatically, averaging 5-6 times baseline. Albumin did not affect the increased slope after HCl. The increased alveolar capillary permeability after HCl aspiration is not affected by albumin. It may appear to be so, however, if Ppa decreases slightly. (Supported in part by HL25548).

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ACCURATE DETERMINATION OF LUNG WATER IN TWO MODELS OF PULMONARY EDEMA. Gordon R. Neufeld, University of Pennsylvania, School of Medicine, Philadelphia, PA 19104.

A recent workshop on lung water measurements concluded that all the available methods applicable to man were limited to accuracies of 20 to 30 percent. Traditional measurements of pulmonary extravascular water volume (PEWV) by indicator dilution fall in this range of precision. The primary difficulty has been the inability to discriminate between recruitment, derecruitment effects and real changes in water content. In twenty-five anesthetized and mechanically ventilated dogs, indicator dilution data were obtained in a control group, an alloxan permeability edema group and a hydrostatic edema group. Following each study, the lungs were dried and water content determined. A multiple linear regression incorporating PEWV and the extracted fraction of water in the tracer bolus yielded superior results to PEWV alone:

$$\text{LUNG WATER} = 1.59 + 3.21\ (E_x) + 0.264\ (\text{PEWV/kg})$$
$$r = .883$$

The root mean square error from the line of identity was 8.2% for all groups combined. Equally significant was the fact that the regression equation reliably estimated the control period lung water in all the groups. The analysis appears to be sufficiently precise to follow edema formation in individual cases. A three compartment model is sufficient to explain the result. (Supported in part by USPHS Grants HL 23730 and HL 16916).

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ECHIS CARINATUS VENOM LEADS TO FIBRIN MICROEMBOLI AND PULMONARY EDEMA IN DOGS. R.C. Schaeffer, Jr., T. Hadden*, F. Hosner*, R. McClelland* and R.W. Carlson. Depts. Med., Mt. Carmel Mercy Hospital and Wayne State University, Detroit, MI 48235

Anesthetized ventilated mongrel dogs (n=6, 20.5-27.3 kg) were given an IV (iliac vein) infusion (30 min, 1.0 ml of 0.9% NaCl) containing 0.1 mg/kg of saw-scaled viper (E. carinatus) venom; a toxin that activates prothrombin. Systemic arterial and left ventricular end-diastolic pressure were unchanged, although cardiac index declined from $\bar{x}$=160±30 sd to 100±20 ml/min/kg ($p<0.05$) by mid-infusion. In contrast, pulmonary vascular resistance increased from 178±35 to 648±65 dynes sec cm^{-5} ($p<0.05$). These changes persisted for 120 min after the end of venom infusion. At this time hypoxemia (PaO_2 = 64±11 torr) was seen in three animals, but p_aH $PaCO_2$ and blood lactate were little affected. In one animal pulmonary edema fluid (EF) was collected and the EF/plasma oncotic pressure ratio was 0.79. At autopsy the lung wet/dry weight ratio uncorrected for lung blood was 6.5±1.5. Light microscopy revealed fibrin microemboli throughout terminal arterioles of the lung, as well as perivascular edema of extra-alveolar vessels and hemorrhage in dependent lung regions. These data suggest that E. carinatus stimulates intravascular coagulation to produce fibrin microemboli, pulmonary hypertension and edema. Use of this venom may be a technic to study endogenous microembolization of the lung. (Supported in part by a grant from Mount Carmel Research and Education Corporation #223-208)

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TREATMENT OF LOW PRESSURE EDEMA IN DOGS. G.R. Long*, F.W. Santman*, L. Oppenheimer*, and L.D.H. Wood*. (SPON: H.S. Goldberg). Depts. of Med. and Surg., U. of Manitoba, Canada.

In canine oleic acid edema, lowering the pulmonary capillary wedge pressure (Ppw) by phlebotomy significantly reduced edema. Conceivably, plasmapheresis (P) and ultrafiltration (U) reduce Ppw and edema without reducing hematocrit, and vasoactive drugs (V) maintain cardiac index (CI) at reduced Ppw. We administered oleic acid to 28 anaesthetized ventilated dogs having Ppw of 7.5 mmHg. One hour later, venous admixture (Qva/Qt) had increased ($p<.01$) from .03 to .17 and extravascular lung liquid (EVLL, thermal indicator dilution) had increased ($p<.01$) from 2.6 to 5.9 ml/g dry bloodless lung. Then the dogs were randomly divided into 4 equal groups: control (C) where Ppw was maintained at 7.5 mmHg; groups P and U, where Ppw was reduced from 7.5 to 2.5 mmHg; and group V, where dopamine or dobutamine was infused (10μg/kg/min) while P reduced Ppw from 7.5 to 2.5 mmHg. Four hours later the measurements were repeated, and EVLL was determined gravimetrically in the excised lungs:

	C	P	V	U
EVLL	7.4 ± .6	6.4 ± .3*	6.7 ± .5*	6.6 ± 1.21
CI	3.3 ∓ 1.6	2.0 ∓ .5*	3.4 ∓ 1.0	2.3 ∓ 0.7*

In groups P and V, edema was reduced by 25% compared to control dogs (*=$p<.05$). In groups P and U, CI decreased with Ppw, and the vasoactive drugs maintained CI at reduced Ppw. We conclude that combined plasmapheresis and vasoactive therapy reduces low pressure edema without reducing cardiac output.

EPITHELIAL TRANSPORT

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EVIDENCE FOR A SYMPATHOMIMETIC EFFECT OF NUCLEOTIDES ON SHORT CIRCUIT CURRENT (Isc) IN ISOLATED TOAD URINARY BLADDER (TUB) EPITHELIA. Carl L. Thurman, James T. Higgins and Anne M. Trinchero*, Dept. of Medicine, The Medical College of Ohio, Toledo, OH 43699

Adenyl cyclase activity in TUB cells couples hormonal stimulation with Na^+ transport. In some systems the activity of the enzyme is dependent upon cytoplasmic concentrations of both ATP and GTP. We have found that an exogenous analog of the guanosine nucleotide increases Na^+-dependent Isc through adrenergic receptors in TUB epithelia.

Epithelia were mounted in an Ussing apparatus to isolate control and experimental portions of the tissue. Isc was stimulated by serosal 10^{-3}M dibutryl cAMP, 10^{-3}M NaF and 5 x 10^{-5}M 5'-guanylylimidodiphosphate (GppNp) but not by 5 x 10^{-5}M methylene guanosine 5'-triphosphate. Baseline Isc was reduced by 30% with 10^{-4}M trifluoperazine (TFP). TFP completely eliminated the TUB response to GppNp. Post-TFP addition of cAMP produced a transient increase in Isc which lasted about 20 minutes. Pre-treatment with the α-adrenergic antagonist prazosin completely abolished the GppNp response and suppressed cAMP stimulation by 52%.

These data support the view that adrenergic stimulation increases Na^+ transport in TUB epithelia. GppNp activity is coupled to increased Na^+ flux by a serosal α-adrenergic receptor. Blockage of this receptor with prazosin reveals a cAMP-sensitive sympathetic component in addition to the well documented intracellular effect of cAMP in the TUB cell.

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CELL CALCIUM AND THE REGULATION OF TRANSEPITHELIAL SODIUM TRANSPORT: ROLE OF PROSTAGLANDINS. David Erlij, Lewis Gersten* and Gary Sterba* Depts. of Physiol. and Med., Downstate Medical Center, S.U.N.Y., Brooklyn, NY 11203 USA.

Stimuli that elevate cytoplasmic calcium may increase or reduce the transepithelial transport of sodium depending on specific circumstances. We have examined the transepithelial transport of sodium in the frog skin in response to Ionomycin, ionophore A23187 and the use of a sodium-free solution in the serosal side of the frog skin. The ionophores, A23187 and Ionomycin, and the elimination of sodium in the serosal side are known to elevate cytoplasmic calcium. Ionomycin and ionophore A23187 increase the transport of sodium in frog skin. On the other hand, a sodium-free solution can increase or decrease the transport of sodium depending on the species and variety of frog used.

We found that when we use any of the three procedures to increase cytoplasmic calcium, after treating the skins with indomethacin, sodium transport is either not affected or reduced. Moreover, the stimuli that increase cytoplasmic calcium also increase the rate of release of prostaglandin by the tissue into the basal solution by more than ten-fold.

These data indicate that calcium-induced prostaglandin release is a major cause of variation in the transport response to elevation of cytoplasmic calcium. (Supported by grants from the N.I.H. and the New York Heart Association).

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SODIUM CURRENT ACROSS APICAL BORDER OF THE FROG SKIN IS DESCRIBED BY THE GOLDMAN CONSTANT FIELD EQUATION. Howard F. Schoen* and David Erlij. Downstate Med. Ctr., State Univ. of New York, Brooklyn, N.Y. 11203.

One of the most specific models for Na movement across the apical membrane of frog skin epithelial cells suggests that Na current moves through pores following the predictions of the Goldman constant field equation (Fuchs, Larsen & Lindemann 1977, J. Physiol. (London) 267: 137). Since this view has been questioned by some workers we have reexamined this problem using microelectrode techniques. We measured the current-voltage relationship of the apical membrane using the assumption that the amiloride-sensitive current is equal to the trans-cellular sodium current. The data fit the constant field equation over the range of about -8 to +50 mV (outside solution zero). Moreover, the intercept where current equals zero is usually in the range predicted by the Nernst equation for the known intracellular levels of sodium in this preparation (8 to 25 mM when short circuited in a normal Ringer's solution). (Supported by grants from the NIH and New York Heart Association).

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INDUCTION OF AN ELECTROGENIC LUMINAL ALKALINIZATION CURRENT BY A PHOSPHODIESTERASE INHIBITOR IN TURTLE BLADDER. Noriko Sataka,*J.H. Durham*and W.A. Brodsky. Depts. of Physiology and Biophysics, Mt. Sinai School of Medicine, NY and Osaka Medical College, Osaka, Japan.

The short-circuiting current (Isc) in ouabain-treated bladders, removed from turtles 6 days after the final feeding, is carried by HCO_3 reabsorption (or H secretion) when such bladders are bathed on both surfaces by an identical Cl-free, Na-free, HCO_3-rich Ringer solution equilibrated with $CO_2 + O_2$. Serosal addition of a disulfonic stilbene (SITS) reverses the orientation of the PD and Isc which reach +8mV and +4ua respectively and which are doubled by the serosal addition of theophylline. The serosal addition of isobutyl methyl xanthine (IBMX), a phosphodiesterase inhibitor, and/or cyclic AMP decreases but does not reverse the PD and Isc. The Isc across bladders removed from turtles 1 day after feeding or from bicarbonate-loaded turtles was small but positive (+4ua) to be begin with. The serosal addition of IBMX and cAMP increased Isc to +40ua and doubled the transepithelial conductance. Finally, pH statting of a HCO_3-free, Cl-free luminal fluid at pH, 4.0 was used to estimate the rate of alkali secretion or $J_{HCO_3}(s)$ while serosal pH and HCO_3 were 7.4 and 20 mM. Under these conditions, IBMX and cAMP induce parallel increases in $J_{HCO_3}(s)$ and positive Isc, while acetazolamide induces parallel decreases in these parameters. It is concluded that the acid-base excretory function of the turtle bladder is modulated by the intracellular cyclic nucleotide level. (NIH & NSF support).

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INTRACELLULAR Na^+ AND K^+ ACTIVITIES IN PERFUSED RAT LIVER. R. Wondergem, J.F. Garcia-Diaz,* L.M.Baxendale,* and W. McD. Armstrong, Depts. Physiol., ETSU-Coll. of Med., Johnson City, TN 37614; and I.U. Sch. Med., Indpls., IN 46223.

The transmembrane potential (E_m) in rat liver increases following partial hepatectomy (Wondergem and Harder, J. Cell. Physiol. 102:193, 1980). As an initial step toward determining whether changes in intracellular cation activities accompany this hyperpolarization, we have measured intracellular activities of Na^+ (a^i_{Na}) and K^+ (a^i_K) in isolated rat livers. Livers were perfused via the portal vein at 15-20 ml/min with Krebs' salt solution equilibrated with 95% O_2 - 5% CO_2. To measure the E_m, the cells were impaled with open-tip microelectrodes filled with 3M KCl. Intermittent current (0.5 nanoamp) was passed to continuously monitor microelectrode resistance, which ranged from 12 to 18 megohms. In 31 impalements (6 animals) the E_m ranged from -19 to -42 mV (mean ± S.D. = -27 ± 6 mV). K^+ and Na^+-selective liquid ion-exchanger microelectrodes were used to measure a^i_K and a^i_{Na}. In 21 impalements (2 animals) the a^i_K ranged from 76 to 91 mM (mean ± S.D. = 84 ± 4 mM), and in 31 impalements (4 animals) the a^i_{Na} ranged from 5 to 14 mM (mean ± S.D. = 9 ± 2 mM). (Supported by SREB; USPHS 1 S08 RR09171-02 and USPHS grants AM-12715 and HL 23332).

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EFFECT OF cAMP ON TIGHT JUNCTIONAL PERMEABILITY IN NECTURUS GALLBLADDER. M.E. Duffey*, C. Palant*, S. Ho*and C.J. Bentzel. Departments of Physiology and Medicine, SUNY/Buffalo and Buffalo VA Medical Center, Buffalo, N.Y. 14214.

Mechanisms for regulation of tight junctional permeability may be important to salt and water transport by "leaky" epithelia. We examined the role of cAMP in alteration of tight junctional structure and function in Necturus gallbladders mounted in an Ussing-type chamber. When the mucosal surface was exposed to 10^{-4}M 8-Bromo-cAMP, transepithelial resistance increased from 86 to 127 Ωcm^2 and NaCl diffusion potentials (half mucosal NaCl replaced with sucrose) decreased from 15.3 to 12.0 mV. Transepithelial electrical potential difference and short-circuit current increased significantly. In addition, the electrical potential difference across the mucosal cell membrane rapidly depolarized from -50 to -38 mV and the intracellular potassium activity, measured by potassium-selective microelectrodes, gradually declined from 85 to 72 mM. Freeze fracture electron microscopy revealed a reorientation and increase in depth of intramembranous tight junctional fibrils in the cAMP treated tissues. All changes were reversible and concentration-dependent. We conclude that: 1) cAMP reduces the ionic permeability of tight junctions; 2) this reduced ionic permeability is associated with alteration in the structure of tight junctions; and 3) cAMP may increase the mucosal and/or basolateral cell membrane potassium permeability. (Supported by SUNY BRSG 2-S07-RR05400 and VA Research Fund.)

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Ca^{++} MEDIATION OF ACETYLCHOLINE-INDUCED PANCREATIC ACINAR SECRETION: DIRECT MEASUREMENTS OF CYTOSOLIC Ca^{++}. J. O'Doherty* and R. J. Stark*, (SPON: E. E. Selkurt) Dept. Physiol. Indiana Univ. Sch. Med., Indpls., IN 46223

In the exocrine pancreas, acetylcholine (ACh) decreases the membrane potential (Em) while stimulating fluid and enzyme release. Ca-selective and conventional microelectrodes were used to examine the relationship between the electrical response, secretory response and cytosolic Ca^{++} concentration ($[Ca]_i$) in acinar cells of the mouse pancreas. By continuously measuring the ACh-induced changes in intracellular potentials during the secretory process, we determined the effect of varying the conc. of the stimulus. Stimulation with ACh at concentrations ranging from 10^{-8} to 10^{-5}M, depolarized Em by 2.6 to 10.5 mV and increased $[Ca]_i$ from 0.4 µM to between 0.5 and 1.0 µM indicating that the induced changes in Em and $[Ca]_i$ are directly related to the stimulus conc. Ach-stimulation of amylase secretion also followed a definite dose response curve. Amylase release (measured as a percentage of the basal secretory rate) reached a maximum at 10^{-7}M ACh stimulation and progressively decreased at higher concentrations of stimulus. Increasing the stimulus above an optimal conc. appears to reduce or inhibit enzyme release. These results demonstrate the ability of $[Ca]_i$ to actively regulate pancreatic enzyme secretion within a narrow range of cytosolic Ca^{++} activities, and therefore to act as a primary intracellular mediator. Supported by USPHS NIH grant 26246.

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EFFECT OF CHOLINERGIC STIMULATION ON IONIC PERMEABILITY OF THE BASAL CELL MEMBRANE OF THE SECRETORY CELL OF THE ISOLATED ECCRINE SWEAT GLAND. Kenzo Sato. University of Iowa Hospitals, Iowa City, IA 52242

The detailed electrophysiological events following cholinergic (MCH) stimulation of the eccrine sweat gland are still poorly understood. The present study was designed to clarify the change in ionic permeability across the basal (secretory) cell membrane during MCH stimulation. A short segment of the secretory coil was dissected out from an isolated monkey palm eccrine sweat gland and was immobilized by gentle suction between two constriction pipets in Krebs' Ringer solution at 37°C. Membrane p.d. was measured using a standard glass microelectrode technique. The mean membrane p.d. was -73 mV. Stimulation of secretory cells with local iontophoresis of MCH caused a biphasic change in p.d.: an initial transient depolarization followed by repolarization to plateau at a few mV less negative than the resting p.d. A local ionic replacement study showed that the basal membrane p.d. is made up mainly of K^+ and partially of Cl^- diffusion potentials. Permeability sequence of ions across the basal membrane is: $K^+ >> Cs^+ > Tris^+ > Li^+ > Na^+$, and $Cl^- > Isethionate^- > SO_4^{2-}$ in resting cells, and $K^+ >> Cs^+ > Tris^+ \approx Li^+ \approx Na^+$ and $Cl^- > Ise^- > SO_4^{2-}$ during the steady state after MCH stimulation. Since the total conductance of the secretory cell membrane does not change significantly during MCH stimulation, the above data is interpreted to indicate that permeability of Na^+, but not of K^+ or Cl^-, increases during cholinergic stimulation (to the level of $Tris^+$ or Li^+).

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MUSCARINIC ACETYLCHOLINE RECEPTOR CHARACTERIZATION IN THE AVIAN SALT GLAND. Seth R. Hootman* and Stephen A. Ernst. Univ. of Michigan, Ann Arbor, MI 48109

Fluid and ion secretion by the avian salt gland is regulated primarily by muscarinic cholinergic receptor (MAChR) activation. We have characterized these receptors in salt glands of domestic ducks adapted to low (FW) and high (SW) salinities, using the tritiated antagonist quinuclidinyl benzilate ([^{3}H]QNB). Specific QNB binding to MAChR in homogenates from salt glands of both FW- and SW-adapted ducks revealed a single population of saturable high affinity sites (K_dFW = 40.1 ± 3.0 pM; K_dSW = 35.1 ± 2.1 pM). Following SW adaptation, total gland receptor populations increased from 1.41 ± 0.09 to 9.03 ± 0.86 pmol/gland. The average number of binding sites per cell increased by 2.4-fold, demonstrating that proliferation of MAChR accompanies the salt gland response to functional demand. The receptor exhibits typical pharmacological affinities for muscarinic antagonists (QNB, atropine, scopolamine) and agonists (oxotremorine, carbachol, methacholine). In addition, the diuretics furosemide and bumetanide competitively inhibit [^{3}H]QNB binding to salt gland MAChR, with K_i's in the millimolar range. In parallel studies, furosemide also inhibited QNB binding to MAChR in homogenates from rat exorbital lacrimal gland but had no effect on binding to rat atrial or brain receptors. These results suggest that MAChR in avian salt gland and in other secretory epithelia may be intimately associated with the furosemide-sensitive Na^+ and Cl^- uptake mechanism. Supported by USPHS grant AM 27559.

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ASSOCIATION OF MICROELECTRODE IMPALEMENT POTENTIALS WITH MORPHOLOGICALLY DISTINGUISHABLE CELL TYPES IN INSECT MIDGUT. James T. Blankemeyer. Dept. of Physiological Sciences, College of Veterinary Medicine, Oklahoma State University, Stillwater, Ok. 74078

The insect midgut actively transports potassium from the hemolymph to lumen when chamber mounted. The net K flux accounts for the ISC and both the ISC and trans-epithelial PD diminish with reduced K on the hemolymph side. There are three electrically distinguishable impalement potentials in the midgut. One of these the LPD, was identified, on the basis of the voltage divider ratios, as the site of trans-epithelial K active transport (Blankemeyer and Harvey (1978, JEB 77, 1-13). The other major cell type, the HPD, was determined to be uninvolved in trans-epithelial K active transport. In an attempt to associate the microelectrode impalement potential with one of the morphologically distinguishable cell types, a fluorescent dye, Lucifer Yellow CH, was ionophoretically injected into midgut cells. Injection of HPD impalements produced recovered dye in 4 of 6 midguts with all 4 showing dye in columnar cells. Although recovery of dye from LPD impalements has been unsuccessful, identification of the columnar cell as the HPD implies that the LPD impalement is the goblet cell since the replacement cell is rare in some lepidopteran species. (Supported in part by USPHS grant AMR-21890).

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EMF'S OF ACTIVE ELECTROGENIC ANTIPORTS AND SYMPORTS. W.S. Rehm, G. Carrasquer, T.C. Chu* and M. Schwartz. Depts. of Medicine and Physics, Univ. of Louisville, Louisville, KY 40292.

Spangler and Goodall presented an equation for the emf of a passive electrogenic Na-K antiport (Biophysics J 21:216a, 1978). Herein we consider active electrogenic cotransport systems. Consider an active antiport with monovalent cations involving for 1 cycle the transport of n moles of P across a membrane from side 1 to side 2 and m moles of Q from side 2 to side 1, with ATP → ADP + P_i as the energy source. With the model in isolation (no return circuit), the Gibbs free energies would be given by:

$-\Delta G_P = nRT \ln (P)_1/(P)_2 + nF (V_1 - V_2)$

$-\Delta G_Q = mRT \ln (Q)_2/(Q)_1 - mF (V_1 - V_2)$

$-\Delta G_{ATP} = RT \ln[k(ATP)/(ADP)(P_i)]$ where k is the equilibrium constant for ATP hydrolysis, V the potential and R, T and F have their usual meanings. Let $E = (V_2 - V_1)$. In equilibrium, the sum of the ΔG's = 0. These equations yield:

$$E = E^* + \frac{RT}{(n-m)F}\left[n \ln \frac{(P)_1}{(P)_2} + m \ln \frac{(Q)_2}{(Q)_1}\right]$$

where $E^* = (RT/(n-m)F)(\ln[k(ATP)/(ADP)(P_i)])$. With $n > m$, a decrease of $(P)_2$ gives an increase in E (a normal response same as for simple conductive limb for P) and a decrease in $(Q)_2$ yields the opposite response (an anomalous one). With P and Q as univalent anions, the changes in E will be opposite to those for cations. Equations for the emf's of electrogenic symports will be considered. (NIH and NSF support)

COMPARATIVE PHYSIOLOGY OF CIRCULATION AND RESPIRATION

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HERMIT CRAB LOCOMOTION: ENERGETIC COST OF CARRYING A SHELL. Clyde F. Herreid II, Robert J. Full* and Sandra M. Woolley*. SUNY, Buffalo, NY 14260.

Coenobita compressus from Panama were run on a minature treadmill enclosed in an airtight lucite respirometer while O_2 consumption ($\dot{V}_{O_2}$) was monitored. The $\dot{V}_{O_2}$ rapidly increased from a resting value (0.14 $ml O_2/g hr$) to a steady-state $\dot{V}_{O_2}$; the $t_{\frac{1}{2}}$ on-response was 3 min. After the 20 min. run, recovery was also rapid; $t_{\frac{1}{2}}$ off response was 3.5 min. This response was different from other species of land crabs previously studied, but it was similar to mammals and cockroaches. $\dot{V}_{O_2}$ during steady-state running was a direct linear function of velocity (V): $\dot{V}_{O_2} = .29 + 1.98$ V. The minimum energetic cost of transport was comparable to quadrupedal and bipedal vertebrates. When crabs were removed from their shells and run "nude", the total cost of locomotion was greatly reduced but the minimum cost of locomotion remained the same: $\dot{V}_{O_2} = .12 + 2.00$ V. At low velocities (.05 km/hr), the $\dot{V}_{O_2}$ running with a shell was about twice that of a "nude" crab, while at high velocities the relative cost was only about 1.3 times higher. Hermit crabs were run with shells of different masses to evaluate the effect of load-carrying. With small loads, the relative increase in $\dot{V}_{O_2}$ increased directly with the relative size of the load; however, once the load was equal to the animal's mass or larger (up to 2-5 times the crab mass) there was no further change in $\dot{V}_{O_2}$. This suggests an increase in mechanical efficiency with heavy loads. Kinematic analysis will be discussed. (Supported by NSF grant PCM 79-02890.)

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ACID-BASE DISTURBANCES DURING EXERCISE IN THE BLUE CRAB, CALLINECTES SAPIDUS. C.E. Booth* and B.R. McMahon. Univ. of Calgary, Alta., Canada T2N 1N4.

Enforced swimming activity (1 hr) resulted in a mixed respiratory and metabolic acidosis in the hemolymph of C. sapidus. Posthranchial pH dropped (7.63 to 7.24) during the first 15 min, then increased slightly over the duration of the exercise. PaO_2 remained high (65-75 torr), but $PaCO_2$ increased from 2-3 torr at rest to 4-6 torr at 30 min, then decreased with further exercise. Hemolymph lactate (LA) showed a log increase with time, rising from 1 to 14 mM over 60 min, while HCO_3^- decreased from 5.7 to 3.4 mM in the first 30 min and then stabilized. During recovery, $PaCO_2$ returned to resting levels within 3 hr, and by 6 hr was further reduced by 0.5 torr. Hemolymph pH, LA, and HCO_3^- were not fully recovered at 6 hr, but all variables had returned to pre-exercise levels by 24 hr post-exercise. Metabolic acidosis accounted for over 80% of the increase in H^+, but analysis of metabolic and respiratory components was complicated by an altered acid-base, equilibrium, as indicated by an increase in the calculated pK_1 (= 6.005 at rest and 6.147 at 30 min of exercise); as a result, measured PCO_2 values during exercise exceeded those calculated from the Henderson-Hasselbalch eq. by up to 1.5 torr. This discrepancy was eliminated by 1 hr recovery, at which time pK_1 had returned to its control value. The calculated base-deficit (4.96 mM) accounted for only 40% of the LA produced, suggesting that additional buffers were available, possibly including $CaCO_3$ from the exoskeleton. (Supported by NSERC Grant # A5762).

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REGULATION OF GILL VENTILATION AND ACID-BASE STATUS IN HYPEROXIA-INDUCED HYPERCAPNIA IN THE LARGER SPOTTED DOGFISH (Scyliorhinus stellaris). N. Heisler*, G.F. Holeton* and D.P. Toews* (SPON: J. Piiper). Dept. Physiol. Max Planck Inst. Exp. Med., D-3400 Göttingen, FRG; and Dept. of Biol., Univ. of Toronto, Ontario, and Dept. of Biol., Acadia Univ., Wolfville, Nova Scotia, Canada

Dogfish were exposed to environmental oxygen tensions of up to 530 mmHg in a closed sea-water recirculation system for measurement of bicarbonate transfer processes (Heisler, Resp. Physiol. 1978). pH, PCO_2 and PO_2 were determined in dorsal aortic blood and gill ventilation was measured by means of electromagnetic flow probes connected to openings in rubber fingerlings, which were glued around the gill slit areas, collecting the expired water. Initiation of hyperoxia caused gill ventilation to fall to 30-40% of the control value within 5 min. Thereafter ventilation was gradually further reduced, reaching 15% of the control after 24 h, when the resultant respiratory acidosis (usually not exceeding - 0.15 pH-units throughout the experiment) was compensated by accumulation of bicarbonate taken up from the environment. PCO_2 rose from about 2 mmHg in normoxia to 7-9 mmHg after 1 day and 9-11 mmHg after 5 days of hyperoxia. At these times of exposure arterial pH was almost completely restored to control values. These results suggest that gill ventilation in hyperoxia is less reduced than expected from the oxygen demand of the organism until the ensuing respiratory acidosis is compensated by uptake of bicarbonate from the environment.

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VASCULAR ORGANIZATION OF THE GILLS AND PULMONARY ARTERY OF LARVAL AMBYSTOMA TIGRINUM. Gary Malvin* (SPON: S.C. Wood). Univ. of New Mexico, Dept. of Physiol., Albuquerque, NM 87131

The larval form of the amphibian, Ambystoma tigrinum, possesses both gills and lungs. The complex vascular organization of these two respiratory organs was investigated using corrosion casts made by methyl methacrylate infusion into the bulbous arteriosus. Casts were examined by both light and scanning electron microscopy. Three distinct anatomical perfusion pathways were apparent within the gill: 1) a respiratory route which allows blood to flow through filamental capillaries, 2) another intrafilamental path which bypasses the capillaries by directing blood around the periphery of the filament, and 3) an extrafilamental route which shunts blood through anastomoses between the afferent and efferent branchial arteries. Blood leaving the gill may enter either 1) the systemic circulation or 2) the pulmonary artery via an anastomosis. This latter connection could also allow pulmonary artery blood to bypass the lung and be shunted instead to the systemic circulation. Proximal to this anastomosis, the pulmonary artery breaks up into a 5-10 mm long structure of anastomosing vessels which then reforms into a single vessel. Although the function of this structure is not known, some possibilities are to 1) regulate lung perfusion, 2) sense blood gas levels, or 3) serve in ionic regulation. The existance of these vascular structures provide the morphological basis for possible control of perfusion within and between the gill and pulmonary artery. (Supported by NSF Grant PCM-7724246).

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THE "MIXING-METHOD" IN VIVO: ARTERIAL PO2 AS A FUNCTION OF SATURATION IN ANIMALS WITH SHUNTS. S.C. Wood. University of New Mexico, School of Medicine, Albuquerque, N.M., 87131

The oxygen equilibrium curve of blood (O2EC) is conventionally drawn as % Sat. = f(PO2). However, when the O2EC is determined in vitro by the "mixing-method", PO2 = f(% Sat). The principle of this method should also apply in vivo if venous admixture occurs. Therefore, PO2, the independent variable of open systems (tonometers or pulmonary capillaries), becomes the dependent variable in closed systems (mixing syringes or central shunts). Furthermore, arterial PO2 (PaO2) for a given % Sat. should be inversely related to Hb-O2 affinity. For a given reduced % Sat. due to shunt, a right-shifted O2EC will provide increased PaO2. This, in turn, could increase the rate of O2 diffusion to tissues. Limiting factors of this hypothesis are environmental PO2 and lung (or gill, skin) O2 diffusing capacity. The presence of low Hb-O2 affinity in many amphibians and reptiles (the "shunt" vertebrates) is indirect support of the hypothesis. Direct support is limited but shows increasing PaO2 (at constant % Sat.) with decreasing Hb-O2 affinity due to species differences or increased temperature.

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PLASMA ION BALANCE OF SUBMERGED ANOXIC TURTLES AT 3 C: CALCIUM-LACTATE INTERACTION. Donald C. Jackson and Norbert Heisler. Div. Biol. & Med., Brown Univ., Providence, RI 02912 and Dept. Physiol., Max Planck Institute Exp. Medicine, D-3400 Göttingen, FRG.

Freshwater turtles, Chrysemys picta bellii, were submerged in O_2-free water at 3 C. Groups of turtles (7/group) were tested at intervals of 0, 1, 2, 4, 8 and 12 weeks for plasma concentrations of lactate, Na^+, K^+, Cl^- and HCO_3^-. Also, calcium ion activity was determined anaerobically at 3 C, and total calcium was measured by atomic absorption spectrophotometry. As previously observed (The Physiologist, 23:71, 1981), plasma lactate rose markedly during anoxia to 145 ± 5 mM (mean ± SE) after 12 weeks, and an apparent net excess of anions progressively accumulated to a final mean value of 66 mEq/l. Ionized calcium, which was part of the ion balance calculations, rose from 4.0 to 25.0 mEq/l, while total calcium rose from 5.4 to 77.2 mEq/l. To test the hypothesis that some of this non-ionized calcium was bound to lactate, the calcium activity was measured in aqueous solutions containing 80 mEq/l calcium and with either 145 mM NaCl or 145 mM NaLactate. Calcium activity in the presence of lactate fell to about 25 mEq/l, similar to the activity/concentration ratio observed in vivo after 12 weeks of anoxia. It is concluded that a significant fraction of plasma lactate is bound to calcium in turtles subjected to prolonged anoxia at low temperature, and this largely accounts for the apparent anion excess observed.

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MECHANISM FOR THE PRODUCTION OF ORIENTATION CLICKS BY AN ECHOLOCATING BIRD. Roderick A. Suthers and Dwight H. Hector*. Indiana Univ., Bloomington, IN 47405

The swiftlet, Collocalia spodiopygia, nests in dark caves where it produces echolocating clicks for navigation. Clicks are typically emitted in pairs with about 25 msec between the members of each pair and at repetition rates of up to 15 or more pairs/second. Most of the acoustic energy lies between 4 and 9 kHz. We have monitored pressure and airflow in the respiratory system and the electrical activity of muscles acting on the syrinx during click production. Clicks are generated in the syrinx. Immobilizing the tongue or sealing the glottis does not affect click production, providing a tracheal cannula permits airflow through the syrinx. Just prior to sound emission, expiratory effort causes sternal air sac pressure to rise and airflow through the syrinx to increase. The first member of the click pair is produced when the sternotrachealis muscles contract drawing the syrinx caudad. This relaxes the external and internal tympaniform membranes which begin to vibrate as they fold into the syringial lumen before making contact with each other and obstructing the airway. Immediately after the first click, tracheal airflow and pressure go to zero. The tracheolateralis muscles then become active, pulling the syrinx craniad and abducting the syringial membranes which are again set into vibration, producing the second member of the click pair. (Supported by NSF Grant BNS 79-13968)

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BLOOD CARBON DIOXIDE DISSOCIATION CURVES OF DEVELOPING CHICK EMBRYOS AND CHICKENS. H. Tazawa*, M. Tamura* and M. Mochizuki*. (SPON: A. L. Kunz). Yamagata Univ. Sch. of Med., Yamagata 990-23, Japan

In avian embryos during a late period of incubation, the carbon dioxide accumulates due to a fixed diffusive conductance across the eggshell coupled with an increase in CO_2 production during development. When the convective ventilation begins, the CO_2 elimination from the egg and the chicken is raised. To investigate the changes in CO_2 transport by blood before and after hatching, the CO_2 dissociation curves of oxygenated and deoxygenated bloods were determined in embryos developing during the last half period of incubation and in chickens during an early postnatal period. The Natelson micro-blood analyzer was employed to measure CO_2 and O_2 concentrations. The oxygenated blood CO_2 concentration at Pco_2 40 Torr (T_{40}) steadily increases from 13 mMol/L at the 10th day of incubation to 24 mMol/L at day 18, but it markedly decreases to 17 mMol/L at hatching and begins to increase in the first 2-3 days of postnatal period. The change in T_{40} is proportional to that in plasma [HCO_3^-] at Pco_2 40 Torr and runs parallel with an increase in blood O_2 capacity. The slope of the dissociation curve between 30 and 40 Torr (capacity coefficient) and the Haldane effect factor (ratio of CO_2 difference between deoxygenated and oxygenated bloods at Pco_2 40 Torr to O_2 capacity) increase with development, suggesting an improvement of CO_2 transfer by blood in older embryos which undergo diffusion limitation to CO_2 elimination.

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Cardiac muscle cell hyperplasia induced by neonatal carbon monoxide exposure. Fred. J. Clubb, Jr.* and Sanford P. Bishop*, Dept. of Path., Univ. of Alabama, Birmingham, AL 35294, and David G. Penney and Michael S. Baylerian*, Dept. of Physiol., Wayne State Univ., Detroit, MI 48201.

Cardiomegaly was produced in newborn male and female rats using CO inhalation for 32 days, thereafter returning to room air. Hearts were perfused with collagenase, minced and isolated cells quantitated. At 500 ppm CO, whole heart (H) myocyte (M) numbers exceeded controls (C) at 7, 32, 65 and 105 days of age by an ave. of 11%. Right ventricle (RV) M numbers exceeded C at 24, 32, 65 and 105 days of age by an ave. of 20%. Differences in left V plus interventricular septum (LV+S) were smaller. DNA content in H, RV and LV+S exceeded C by similar %'s. Rate of binucleation was depressed between 4-9 days of age at both 200 and 500 ppm CO relative to C suggesting that CO stimulates continued cytokinesis. 85-95% of M were binucleate after 12-14 days of age in all groups. Whole M vol. exceeded C only at 14 days of age, M vol.: body weight (BW) ratio was much greater than C at 14, 24 and 32 days of age. At 105 days of age there were no differences in M vol. or M vol.: BW ratio between CO and C LV+S or RV. There were also no differences in hydroxyproline conc. between CO and C H, LV+S or RV. RV M vol. of both CO and C groups was 82% of that in LV+S. These data suggest that M hyperplasia contributes to CO-induced cardiomegaly in the neonate, and accounts for the persistence of cardiomegaly (see other Abstr.) in previously CO-exposed adults. (Supported by NIH Grants HL-23255 and HL-22859).

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Does the species dependent ("starting") P_{50} affect the hematological response to long-term carbon monoxide (CO) exposure? Randall N. Gatz, Eoma S. Dissanaike* and Steven C. Wood. Battelle-Geneva Research Centers, 1227 Geneve, Switzerland.

Carbon monoxide deleteriously affects O_2 transport to tissues by reducing O_2 capacity and increasing Hb-O_2 affinity. We have tested the hypothesis that species differences in Hb-O_2 affinity (P_{50}) will influence the hematological response to long-term (CO) exposure. Sprague-Dawley rats and Golden Syrian hamsters were exposed to 500 ppm CO for 6 weeks. Continuous O_2 equilibrium curves (O2EC's) were measured on blood from untreated animals. Discontinuous O2EC's for both untreated and CO exposed groups were constructed using data from tonometered blood samples. The major hematological changes before and after CO exposure were:

	T Hb g%		P50		2,3 DPG		% COHb	
	Before	After	Before	After	Before	After	Before	After
Rat	14.6	19.0*	33.9	21.3*	1.47	1.22*	<1%	38.0
n = 16			$\Delta P50 = 12.6$					
Hamster	11.3	19.4*	25.3	15.2*	1.00	1.07	<1%	40.0
n = 15			$\Delta P50 = 10.1$		*P < 0.05 Before vs. After			

The change in P_{50} was 2.5 Torr greater in the rat than in the hamster. The molar ratio of 2,3-DPG/Hb decreased in the rat and did not change in the hamster. These species differences may be related to natural biology (hamster is a burrower, hibernator; rat is not) and may affect the large difference in maximal tolerated COHb (hamster, 80%; rat, 65%). (Supported by Battelle Memorial Institute & NSF grant PCM 74-24246.)

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LUNG MECHANICS AND PERIPHERAL AIRWAY STRUCTURE OF THE WEST INDIAN MANATEE. Michael Bergey* and Horst Baier. Rosenstiel School of Marine Science and Division of Pulmonary Disease, Univ. of Miami School of Medicine, Miami, Fl.

Lung mechanics of marine mammals have been found to vary greatly from those of terrestrial mammals. Lungs of the harbor porpoises are capable of maintaining high expiratory flow rates even at low lung volumes, whereas expiratory flow rates in humans drop rapidly after their peak near total lung capacity. The excised lungs of two female manatees (accidental mortalities obtained through U.S. Fish and Wildlife Service) were investigated to see if the same flow-volume relationship is present in a less active marine mammal. Pressure-volume curves were obtained by enclosing the lungs in a chamber and varying the surrounding pressures. Volume changes were recorded with a spirometer attached to the bronchus. Maximum expiratory flow-volume (MEFV) curves were obtained by venting the inflated lungs into a "vacuum reservoir" while measuring volume changes with a plethysmograph. Manatee lungs were found to be more compliant than human lungs. In contrast to the human lung, MEFV curves revealed a convex profile with high flow rates even at low lung volumes. Histologic sections showed extensive cartilage and smooth muscle reinforcement of peripheral airways, likely to prevent collapse at low lung volumes thus preserving high flow rates during exhalation. This facilitates the exchange of a large percentage of the lung volume during the short (1.0sec) exhalation period in living manatees, and may be of adaptive significance for an aquatic mammal.

HYPERTENSION II

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ION TRANSPORT IN RAT TAIL ARTERY DURING DEOXYCORTICOSTERONE ACETATE (DOCA) HYPERTENSION. Purabi Dutta* and Allan W. Jones. University of Missouri, Columbia, MO 65212

The distribution of water and electrolytes and ion turnovers were studied in the tail arteries of DOCA hypertensive rats. There was no significant change in the total water or electrolyte contents in the arteries of DOCA animals. The steady state turnover rate (k, min^{-1}) of ^{36}Cl was significantly higher ($P<0.025$) and its maximum response (Δk_{max}) to norepinephine (NE; $6x10^{-6}$ M) was lower in the arteries of DOCA rats. However, neither k nor Δk_{max} was altered for ^{42}K, ^{45}Ca or ^{24}Na due to hypertension.

Ion	k(min^{-1})		Δk_{max} to NE	
	Control	DOCA	Control	DOCA
^{42}K	0.0064	0.0076	0.039	0.026
^{36}Cl	0.101	0.139	0.076	0.047
^{45}Ca	0.019	0.020	0.015	0.023
^{24}Na	0.159	0.164	—	—

The uptakes of Na and Ca at normal conditions as well as in the presence of NE or variable $[K]_o$ were also unchanged. We conclude that the distribution and premeability of electrolytes in the rat tail artery are not greatly altered in DOCA hypertension. This highly innervated artery may be partially protected from the transport changes observed in other vessels. (Supported in part by USPHS grants HL 15852 and IF HL 05773)

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EFFECT OF ATRIAL EXTRACT ON VASCULAR Na^+-K^+ PUMP ACTIVITY. W.T. Link*, M.B. Pamnani, S.J. Huot and F.J. Haddy. Dept. of Physiology, Uniformed Services University, Bethesda, MD 20014

We have previously reported the presence of a ouabain-like humoral factor and suppression of vascular Na^+-K^+ pump activity in acutely volume expanded animals and in animals with several forms of low renin experimental hypertension. In search of the source of the ouabain-like humoral factor, we examined an extract of rat atrial muscle (containing specific atrial granules) with potent natriuretic activity to determine whether it, like the humoral ouabain-like factor, inhibits vascular Na^+-K^+ pump activity. Fresh rat atria were homogenized in buffer saline, boiled for 5 minutes and supernates of boiled extracts were separated and assayed for natriuretic and ouabain-like activity. Similarly prepared ventricular supernates were used as controls. Atrial (but not ventricular) supernates infused into anesthetized non-diuretic rats caused more than a 9-10 fold increase in urine and sodium excretion within 10 min and the response was completed in 30 min. These findings are similar to those previously reported by Sonnenberg et al. (Physiologist 23:13, 1980). However, our assay for ouabain-like activity failed to show a difference in total ($\bar{d}\pm S\bar{d}$:496±1033, P>.5, N=8) and ouabain-insensitive ($\bar{d}\pm S\bar{d}$:21±112, P>.5, N=4) ^{86}Rb uptakes by normal tail arteries incubated in atrial or ventricular supernates. We conclude that the heat stable natriuretic factor present in atrial granules is probably not identical with the ouabain-like humoral agent present in hypertensive and volume expanded animals.

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CENTRAL EFFECTS OF INTRAVENTRICULAR 6-HYDROXYDOPAMINE (6OHDA) ON DEVELOPMENT OF REDUCED RENAL MASS (RRM) HYPERTENSION AND VASCULAR Na^+-K^+ PUMP ACTIVITY IN RATS. S. Huot, M. Pamnani, and F. Haddy. Dept. of Physiology, USUHS, Bethesda, MD 20014

We have shown that RRM rats develop hypertension (HT) accompanied by decreased vascular Na^+-K^+ pump activity and the presence of an ouabain-like factor in plasma. In this study we investigated the effect of intraventricularly administered 6OHDA on the development of RRM HT, vascular Na^+-K^+ pump activity (measured by ouabain-sensitive ^{86}Rb uptake) and the level of ouabain-like humoral factor. Male Wistar rats received two weekly injections of 6OHDA (200 µg each) into the lateral ventricle. Two weeks later all rats underwent four-fifth (4/5) nephrectomies, were fed a low (0.02%) Na^+ diet and were divided into control (C) and experimental (E) groups. C rats drank distilled water while E rats drank 1% saline. After five weeks tail arteries were excised under pentobarbital anesthesia for measurement of ouabain-sensitive (OS) and ouabain-insensitive (OI) ^{86}Rb uptakes, and plasma assayed for ouabain-like activity. Treatment with 6OHDA prevented development of HT in E rats. OS and OI ^{86}Rb uptakes by tail arteries of C and E rats were not significantly different (P>.5, N=7). Supernates of boiled plasma from E rats failed to show ouabain-like activity when applied to normal rat tail arteries. These studies indicate that intraventricular 6OHDA abolished depressed vascular Na^+-K^+ pump activity and circulating ouabain-like factor in E RRM rats which may explain why these animals failed to develop HT.

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APPARENT LOWER ACTIVE STRESS IN NOREPINEPHRINE STIMULATED AORTIC RINGS FROM SPONTANEOUSLY HYPERTENSIVE RATS (SHRs) COMPARED TO WISTAR-KYOTO (WKY) RATS. J.M. Price, B. Hall,* and D.L. Davis. University of South Florida, College of Medicine, Department of Physiology, Tampa, FL 33612.

A mechanism for increased resistance to flow in hypertension proposes that cell permeability to calcium is increased resulting in a preexisting tone (1,2). This causes the decreased active response in SHR aortic strips. We measured ring width, circumference (length), and wall thickness on-line with a video analyzer prior to dose-response experiments at the length for maximum response. Force was also determined in a saline solution (PSS), free of calcium (Ca^{++}), containing 2mM ethylene glyco-bis-(ß-aminoethlether)N,N-tetraacetic acid. SHR rings (n=15) had a lower active force and lower active stress but the same ED_{50} and thickness in PSS with Ca^{++}. When active force was expressed as peak force minus force in calcium free PSS no difference was found. Active stress and ED_{50} were the same in SHRs and WKY rats. 50% SHR and 20% WKY rings relaxed in Ca^{++} free PSS. Relaxation as a % total active force was 4.0±0.7 in WKY rats and 14.0±2.6 in SHRs. Because active force is higher and tone is less than in previous work on SHR aorta, which used helically cut strips, the results suggest that tone is due to damage during experiments and that SHR vessels are more susceptible to damage.

1. Noon, et. al., Proc. Natl. Acad. Sci. 75:1605-1607, 1978.
2. Fitzpatrick et. al., Clin. and Exp. Hyper. 216:1023-1037 1980. Supported by NIH HL21103 and Am. Heart Assoc. (Florida).

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ARTERIAL CONNECTIVE AND NON-CONNECTIVE TISSUE PROTEIN ALTERATIONS IN EXPERIMENTAL MALIGNANT (MHY) AND BENIGN (BHY) HYPERTENSION. RE Chatelain*, PM DiBello*, BN Dardik* and CM Ferrario, Research Division, Cleveland Clinic, Cleveland, OH.

Aortic ligation between the renal arteries in the rat results in the development of either the MHY or BHY forms of hypertension (Br J Exp Path, 61: 401, 1980). When compared to sham-operated controls, MHY and BHY animals sacrificed 9 days after ligation showed a marked increase in the total amounts of the non-connective tissue proteins of the intima-media of the thoracic aorta (MHY: 1.73 ± 0.05; BHY: 1.82 ± 0.04; SHAM: 0.89 ± 0.04 mg; $p < 0.001$). In BHY animals this increase coincided with a parallel increase in the connective tissue (collagen and elastin) protein content (BHY: 3.90 ± 0.30 mg). On the contrary, this increase was lacking in MHY whose values remained similar to controls (MHY: 3.49 ± 0.20; SHAM: 3.45 ± 0.16 mg). Thus, the unaltered non-connective tissue protein content of MHY animals suggest that the impaired arterial hypertrophy observed in these animals (J Lab Clin Med 97: 700, 1981) is restricted to defects in the metabolism of collagen and elastin. In this connection, a marked plasma corticosterone elevation was observed in MHY animals (MHY: 52 ± 6, BHY: 19 ± 4; SHAM: 21 ± 4 µg/dl, $p < 0.001$). Glucocorticoids are known to impair connective tissue metabolism. Therefore, elevated corticosterone in malignant hypertension may contribute to the development of arterial lesions by inducing alterations in proteins involved in the maintenance of the arterial structure. (Supported by HANEO and NHLBI #HL-6835 grants.)

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CORRELATIONS BETWEEN PULSE WAVE VELOCITIES (PWV) AND TOTAL PERIPHERAL RESISTANCE (TPR). Phyllis A. Neef*, Mary Anne Bassett Frey, Alice Faryna*, Margaret M. Mullins, Dept. of Physiology and Cox Heart Institute, Wright State University School of Medicine, Dayton, Ohio 45435

Noninvasive methods for assessment of cardiac function are established. However, the need for a reliable method of evaluating vascular function still exists. Measurement of PWV may be an effective noninvasive technique for examining vascular status. 12 men and women ages 22-59 yrs with blood pressures (BP) from 98/74-150/100 participated. At seated rest, BP, cardiac output (CO) by impedance cardiography, TPR and PWV's were monitored over 10 beats. PWV's were determined from the heart to the carotid in the neck, to the radial at the wrist and to the dorsalis pedis over the instep. Mean values ± SD for the group were:

PWV:	carotid	9.2±4.5 m/sec	BP:	systolic	125.0±17.3mmHg
	radial	7.7±1.9 m/sec		diastolic	85.2± 9.3mmHg
	dorsalis	9.6±1.3 m/sec		mean	98.6±11.6mmHg
CO:		4.4±1.6 L/min	TPR:		27.8±18.6 mmHg/L/min

Each PWV was significantly correlated with TPR with the following r values: carotid 3.96 ($p<0.05$), radial 2.17 ($p<0.05$), dorsalis pedis 3.04 ($p<0.05$). As TPR increases and vessels appear to become less distensible, PWV also increases. We conclude that PWV shows promise as a useful technique for evaluating vascular function as it relates to changes in TPR. (Supported in part by the Dayton Area Heart Association)

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CENTRALLY ADMINISTERED ANGIOTENSIN II ALTERS CATECHOLAMINE TURNOVER IN RAT BRAIN. C. Sumners* and M.I. Phillips Dept. of Physiology, University of Florida, Gainesville, FL 32610.

Studies have implicated a role for catecholamines (CA) in pressor and drinking responses to centrally administered angiotensin II (AII) in rats. We have investigated whether AII injected into lateral brain ventricles (i.v.t.) can alter catecholaminergic transmission in the brain, as indicated by alterations in CA turnover. Turnover of norepinephrine (NE) and dopamine (DA) was examined in α-methyl-p-tyrosine (α-MT) treated rats, where CA synthesis has been inhibited. Chronic cannulae were implanted into the right lateral cerebroventricle of male 250g rats, for i.v.t. injections of AII. Hypothalamic NE and striatal DA levels were compared in control (no α-MT, 0.9% saline i.v.t.), α-MT treated (200 mg/kg i.p., 4 hrs before death), and α-MT plus AII (500ng i.v.t., 5 mins before death; a dose which causes drinking and a rise in blood pressure) treated animals. Rats were sacrificed, brain areas dissected and assayed for catecholamines by an enzymatic isotopic technique. α-MT treated rats exhibited a lowering of both striatal DA (2.5 +0.23 µg/g,n=5) and hypothalamic NE (0.98+0.07 µg/g,n=5) compared with controls (7.76 +0.31 µg/g DA;1.65+0.09 µg/g NE,n=5). Rats injected with α-MT plus AII showed a further decrease in NE (0.73 +0.06µg/g,n=5, and an attenuated fall in DA (4.2 +0.22 µg/g, n=5) indicating changes in CA turnover. The results show that a pressor/dipsogenic dose of AII i.v.t. increases NE and decreases DA turnover. Supported by NIH:RIHL27334A-01

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INHIBITION OF ANGIOTENSIN I CONVERTING ENZYME (KININASE II) WITH A NONSULFHYDRYL INHIBITOR (MK-421) IN SODIUM DEFICIENT DOGS. M.E. Olsen* and R.E. McCaa. Dept. of Physiology and Biophysics, Univ. of Miss. Sch. of Med., Jackson, Mississippi 39216

The response of the renin-angiotensin-aldosterone and kallikrein-kinin systems was evaluated during long-term inhibition of angiotensin I converting enzyme (kininase II) with a new non-sulfhydryl inhibitor, MK-421, N-(1-S-carboxy-3-phenylpropyl)-L-Ala-L-Pro, in sodium deficient dogs. In response to oral MK-421 administration (4 mg/kg/day) in sodium deficient dogs plasma renin activity increased from 3.89 ± 0.58 to 17.3 ± 2.6 ng/ml/hr, arterial pressure decreased from 102 ± 3 to 65 ± 2 mm Hg, plasma aldosterone concentration decreased from 43.6 ± 8.3 to 13.7 ± 3.2 ng/dl, renal blood flow increased from 131 ± 8 to 160 ± 9 ml/min, and urinary kallikrein activity decreased from 27.3 ± 3.6 to 6.9 ± 1.8 E.U./day. During the first day of MK-421 administration urinary sodium excretion increased markedly from 0.62 ± 0.37 to 19.3 ± 4.3 mEq/day. During long-term MK-421 administration urinary sodium excretion averaged 6.4 ± 1.5 mEq/day. In sodium deficient dogs maintained on MK-421 administration, angiotensin II infusion (3 ng/kg/min) restored urinary sodium excretion, renal blood flow, plasma aldosterone concentration, and arterial pressure within three days to levels observed in untreated sodium deficient dogs. These data indicate that the long-term hypotensive and natriuretic actions of inhibitors of angiotensin I converting enzyme are mediated by inhibition of angiotensin II formation. (Supported by USPHS NIH Grant HL 09921).

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BODY FLUID VOLUMES IN NEONATAL SPONTANEOUSLY HYPERTENSIVE RATS (SHR). Margaret M. Mullins, Manh van Trinh* and Bernadette L. Plair*. Wright State University, Dayton OH 45435

We have previously reported elevated plasma aldosterone in 10 day-old SHR compared to age-matched Wistar-Kyoto (WKY) controls (Federation Proc.38:1285,1979). We have now measured body fluid volumes at that age in order to determine the possible role of aldosterone in the initiation of hypertension in SHR. Plasma volume (PV, RISA space), extracellular fluid volume (ECFV, $Na_2{}^{35}SO_4$ space) and total body water (TBW, by dessication) were measured and interstitial fluid volume (ISFV) calculated as (ECFV - PV). TBW, ECFV and ISFV (ml/100gm wet body weight) were greater in SHR (p's<.02), while PV's did not differ. When body weight was corrected for fat content (8.7% WKY vs 3.3% SHR) ECFV and ISFV were still greater in SHR (p's<.02) while now TBW's were the same. Treatment of SHR with spironolactone (SP) caused all volumes to fall to or below those of untreated WKY and a small but significant decrease in TBW and PV occurred in treated WKY. We conclude that 1)aldosterone excess is associated with preferential expansion of ISFV and 2)this expansion may contribute to the subsequent development of hypertension in SHR.

($\bar{x}\pm$sem)

	SHR			WKY		
	Untreated	SP	Fat-free	Untreated	SP	Fat-free
TBW	76.1±0.7	72.7±0.8	78.7±0.7	73.6±0.4	71.1±0.8	80.5±1.7
ECFV	57.1±1.6	48.0±1.2	59.7±2.0	47.0±3.0	45.2±2.0	52.4±1.7
ISFV	47.6±2.1	40.3±1.2	49.3±2.2	38.0±2.8	37.9±2.0	41.7±0.3
PV	10.0±0.6	7.7±0.4	10.4±0.6	8.9±0.3	7.5±0.4	9.7±0.4

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INDICES OF EXPERIMENTAL PRE-ECLAMPSIA IN RATS FOLLOWING INFUSION OF EXTRACT OF PRE-ECLAMPTIC PLACENTA. Silvana Brianceschi* and John J. Curry. Dept. of Physiology, Ohio State Univ., Columbus, Ohio 43210

Acute infusion of toxemic placental extract (TPE) into pregnant rats results in an increase in systolic and diastolic pressure similar to that previously shown to follow its administration to nonpregnant rats and in vasospasms. These vasospasm effects are reversed by administration of the angiotensin II receptor blocker saralasin and were not seen following administration of normal placental extract. Chronic infusion of TPE into third trimester pregnant rats via implanted osmotic minipumps, resulted in a significant increase in systolic pressure by day 18 of pregnancy. By day 19 pressure in all groups had decreased to pre-parturition levels. There were no significant differences between groups in plasma renin activity or in plasma angiotensin I or aldosterone levels at this time. Chronic administration of TPE also resulted in a significant decrease in the size of Bowman's space in renal glomeruli. These data suggest that the effects of TPE administration are consistent with the clinical signs of pre-eclampsia and that TPE might be useful in creating rat model for the disease. The results further suggest that the vascular effects of TPE are not manifested by stimulation of the renin-angiotensin system, but act upon angiotensin II receptors either by binding to these receptors or by altering their numbers, or affinity for circulating levels of angiotensin. (Supported in part by es American Heart Assoc., Central Ohio Chapter.)

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THE EFFECTS OF PREDICTABLE AND UNPREDICTABLE SHOCK ON CARDIOVASCULAR AND ADRENAL FUNCTION IN RATS. J.E. Lawler, G.F. Barker,* J.W. Hubbard,* R.H. Cox,* and V.H. Bachuss.* University of Tennessee, Knoxville, TN 37916.

Rats prefer to receive predictable (signalled) electric shock but little is known about the physiological responses to predictable vs unpredictable shock. Twenty-seven Long-Evans rats received 40, 1 sec duration, .4 ma tail shocks, once each minute for 6 daily sessions. Animals differed in how predictable the shocks were. Group 100% (N=9) received the most predictable shock, followed by Group 75% (N=10), and Group 50% (N=8), which received shock half the time a tone was on, and half the time in its absence. On the 6th day, blood pressure was monitored via an aortic cannula, and blood was withdrawn within 3 mins of the end of a session for assays of corticosterone, epinephrine and norepinephrine. The most predictable group had the highest systolic pressure (155 mmHg), while the other 2 groups were between 140-145 mmHg. In all groups, heart rate was 40 beats/min higher during the session than in a subsequent 20 min rest period. Corticosterone levels were significantly higher in the 100% and 75% groups (48.19±6.14 ug/100ml & 48.44±8.18) compared to Group 50% (30.39±4.88). Finally, plasma catecholamines were highest in the 100% group (E=480 pg/ml, NE=613) followed by the 75% group (E=402, NE=577), and the 50% group (E=346, NE=513). Contrary to expectations, the most unpredictable situation does not lead to the greatest elevations in cardiovascular and adrenal function. (Supported by NIH Grant HL-19680)

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ENHANCED CELL COMMUNICATION DURING DIASTOLIC DEPOLARIZATION IN HEART. W. C. De Mello. Department of Pharmacology, UPR Medical Sciences Campus, G.P.O. Box 5067, San Juan, P. R. 00936.

Studies on cell-to-cell communication performed on canine Purkinje fibers beating spontaneously, showed that the coupling coefficient (V_2/V_1) is relatively low at the point of maximal depolarization (0.54 S.E. ± .02; n = 15) but gradually increases during diastole reaching an average value of .79 (S.E. ± 0.03; n = 15) immediately before the start of the action potential. Determination of space constant and input resistance performed throughout diastole showed that λ and V_o/I_o are enhanced during diastolic depolarization. Calculation of the intracellular resistance per unit length (r_i) and membrane resistance per unit length (r_m) showed that r_m was increased by about 65% and r_i was reduced by about 29% during diastolic depolarization. The fall in r_i means that the junctional resistance is spontaneously reduced in diastole leading to an optimal degree of coupling immediately before the firing of the action potential. The possible mechanisms involved in the reduction of r_i will be discussed. (Supported in part from a grant from American Heart Association - P.R. Chapter, and the Angel Ramos Foundation).

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THE DIFFERENTIAL AND RATE DEPENDENT EFFECT OF THE ISOMERS OF VERAPAMIL ON SINUS NODE AND AV JUNCTIONAL AUTOMATICITY. Hans O. Cloor*, Ferdinand Urthaler and Thomas N. James*. UAB Medical Center, Birmingham, Alabama 35294

L and D-Verapamil (VPML) were selectively perfused into the sinus node artery (SNA) and atrioventricular node artery (AVNA) of 30 dogs. In the sinus node (SN) the threshold concentration was 0.5 for L-VPML and 5 µg/ml for D-VPML. In the AV junctional region (AVJ) the threshold concentration was 1 for L-VPML and 10 µg/ml for D-VPML. During sinus rhythm (n=20) L-VPML .5, 1, 2 and 5 µg/ml into SNA caused a sinus bradycardia of 13 ± 8, 16 ± 7, 23 ± 9 and 28 ± 11 beats/minute respectively ($p<0.05$). During AVJ rhythm (n=10) L-VPML (1 to 5 µg/ml) into AVNA caused similar AVJ bradycardia. Although L-VPML AVJ bradycardia, expressed in beats/minute, was always significantly less than the sinus bradycardia elicited by the same concentration of L-VPML, the percent slowing of SN and AVJ rhythms were identical. Norepinephrine (NE) (.0125, .025, .05 and .1 µg/ml) into SNA (n=10) caused sinus rate increases of 25, 36, 42 and 45 percent respectively. After L-VPML, 2 µg/ml, sinus rate was 16 ± 6 percent lower than control but the same concentrations of NE caused similar 24, 34, 46 and 55 percent sinus rate increases. Thus, L-VPML causes little or no β-adrenergic blockade. L-VPML is approximately 10 times more powerful than D-VPML on both the SN and AVJ pacemakers. The negative chronotropic effect of L-VPML is inversely related to intrinsic rates of SN and AVJ.

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ROLE OF CALCIUM IN THE RESTITUTION OF ACTION POTENTIAL DURATION AND CONTRACTILE FORCE. Hirotsugu Atarashi*, Gangaiah Natarajan* and Borys Surawicz. Univ. of Kentucky Med. Ctr., Lexington, KY. 40536

Calcium $(Ca^{2+})_o$ is known to affect the restitution (Res) course of action potential duration (APD) and contractile force (CF) during progressive increase in premature cycle length in mammalian myocardium (Bass, Am. J. Physiol. 228: 1717, 1975), but previous studies have been conflicting. We studied this problem in isolated guinea pig papillary muscles at 37°C within $(Ca^{2+})_o$ range of 0.3-7.2mM/L, recording simultaneously APD and CF at the peak of staircase at a basic stimulation rate of 0.2Hz. Premature APD longer than basic APD was designated as APD overshoot (OS), and premature CF greater than basic CF as CF OS. CF OS was present in 12/14 experiments with APD OS $\leq$5% and in 3/14 experiments with APD OS >5% ($p<0.005$). At 0.3-1.8mM/L $(Ca^{2+})_o$ (n=17) when premature APD OS was 6.7±2.7%, premature CF was 91.6±17.4% and postextrasystolic (PES) CF 150.4±36.7% of basic value. At 3.6mM/L $(Ca^{2+})_o$ (n=5) when premature APD OS was 2.4±1.5%*, premature CF was 122.5±15.2%* and PES CF 264.8±56.1%**. At 5.4-7.2mM/L $(Ca^{2+})_o$ (n=6) when premature APD OS was 0.4±1.9%**, premature CF was 156±15.7%** and PES CF 355.6±77.3%** (*$p<0.01$, **$p<0.001$). The Res times of APD and CF were inversely related ($r<-0.63$, $p<0.01$). Our results show a significant inverse correlation between Res or APD and Res of CF, and suggest that Res of APD is controlled by intracellular Ca^{2+}, presumably via time-independent K^+ outward current. (Supported by grant from Ky. Heart Assoc.)

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DIFFERENTIAL DISTRIBUTION OF VAGAL FIBERS TO SINOATRIAL AND ATRIOVENTRICULAR NODAL REGIONS OF THE CANINE HEART. W.C.Randall, L.E.Rinkema and S.B.Jones, Loyola Med. Ctr., Maywood,IL 60153

Little definitive information is available concerning differential distribution of autonomic cardiac nerves to sinoatrial (SAN) and atrioventricular (AVN) regions of the heart. Selective responses to reflex excitation indicate such restricted distributions are functionally significant. In open-chest, pentobarbitalized dogs, right (RCV) and left (LCV) cervical vagi were electrically stimulated (20 Hz, 5 msec, 5-7 v) before and after each of 6 to 8 carefully painted phenol (90%) strips (2-3 mm width) over the superior right atrium (RA), ultimately to surround the SAN. Most parasympathetic nerves reach SAN via the superior vena cava (SVC) and from the posterior RA, with additional projections across the lateral surface of SVC. Phenolization of the circumference of the SAN ablates many of these pathways, leaving vagal distribution to AVN virtually unimpaired. Phenol painting at the junction of the inferior VC and the atria dramatically ablates vagal inhibition of conduction across the AV junction. These studies illustrate clearly distinct vagal distribution to the SAN and AVN regions. After all responses to vagal stimulation have been abolished, sympathetic alterations in heart rate, and atrioventricular conduction remain, thus revealing important differentiation in sympathetic fiber distribution to these key regions of automaticity and conduction. Interventions are available to selectively ablate these autonomic inputs. (Supported by Bane Charitable Trust and DePauw Funds.)

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EVIDENCE THAT TRANSMURAL INFARCT ABLATES ELECTROPHYSIOLOGIC RESPONSES TO SYMPATHETIC NERVE STIMULATION OUTSIDE THE INFARCT. Michael J. Barber, Thomas M. Mueller and Douglas P. Zipes. Krannert Inst. of Cardiol., Indiana U. Sch. Med. and VA Med. Ctr., Indianapolis, Indiana 46223

We reported that epicardial application of phenol produced sympathetic denervation (SD) that prevented effective refractory period (ERP) shortening at epicardium and endocardium during stellate stimulation (SS). In this study, we tested whether transmural infarction (TI) produced SD in noninfarcted areas. Sympathetic innervation was determined in 5 open chest dogs by measuring left ventricular ERP shortening during left SS. ERP was measured at multiple endocardial and epicardial sites with bipolar stimuli at twice diastolic threshold using the extrastimulus technique. Basic cycle length was constant. TI was produced by injecting a rapidly hardening vinyl latex solution into the first diagonal branch of the LAD. Prior to TI, SS shortened ERP (144±2 to 134±3 msec, mean ± SE; $P<.05$) at all (38) sites. After TI, SS shortened ERP (152±3 to 142±4 msec; $P<.05$) in all sites (14) proximal or very lateral to the distribution of the latex injection. SS did not decrease ERP in the TI or in 14/16 sites of noninfarcted myocardium distal (apically) to TI, so that mean ERP did not change (147±4 vs. 150±3 msec). Norepinephrine (0.5 µg/kg/min i.v.) in 4 dogs shortened ERP (156±4 to 142±4 msec) in previously nonresponsive sites distal to TI. We conclude that intracoronary latex injection produces TI that results in SD to regions within the TI, as well as to distal noninfarcted myocardium.

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ELECTRICAL CHANGES OF CANINE PURKINJE FIBERS FOLLOWING ALCOHOL AND ALTERED CALCIUM. W.H. Thies and K. Greenspan, Ind. U. Med. School, Terre Haute Ctr. Med. Ed., Terre Haute, IN 47809. Ethanol markedly alters the electrical and mechanical properties of cardiac tissue. The mechanism(s) of such alterations appear to be correlated. The present studies were performed to assess the changes following alteration of Ca^{++} conc. in normal Tyrode's as well as Tyrode's containing 70mM ethanol. Standard intracellular electrophysiologic techniques were utilized with excised canine cardiac Purkinje fibers. Following control recordings, the tissue was superfused with Tyrode's containing altered Ca^{++} conc. After equilibration the tissue was exposed to solutions with varied Ca^{++} and Ethanol (70mM). At 10mM Ca^{++} conc. and higher, a marked triangularization of the action potential occurred with a decrease in the time necessary to reach -60mV repolarization. Simultaneously phase 2 demonstrated a significant increase while phase 3 showed a slight decrease in the rate of repolarization. But, low Ca^{++} conc. (1mM) shows an increase in the time to -60mV repolarization and a decrease in the rate of repolarization of phase 2. The addition of ethanol (70mM) results in an exacerbation of the effects of high Ca^{++} and appears to be antagonistic to the effects of low Ca^{++} conc. The data obtained in the media containing the low Ca^{++} are perhaps due to diffusion barriers. The study strongly suggests that some of the effects of ethanol are mediated by changes in Ca^{++} movement across the cardiac membrane.

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BLOOD CALCIUM ACTIVITY AND CARDIAC FUNCTION. B. W. Allen* (SPON: G. G. Somjen). Dept. Physiol., Duke Univ., Durham,NC 27710

Calcium activity in circulating blood was measured in anesthetized cats with a calcium-selective flow cell electrode (Ionetics, Inc.) in a carotid artery loop. EKG, arterial pressure, and end-expiratory % CO_2 were recorded, and PO_2, PCO_2 and pH were measured in arterial blood samples. Blood Ca^{2+} was lowered by the injection of pH-adjusted citrate, or raised by the injection of $CaCl_2 \cdot 2H_2O$. A single injection of 100 µM citrate/Kg lowered blood $[Ca^{2+}]$ from its control level of 1.1 to 0.6 mM. Recovery of blood calcium level was complete in less than an hour. When Ca^{2+} was raised, recovery was only partial after an hour, and successive doses had a cumulative effect. Lowering blood $[Ca^{2+}]$ caused lengthening of corrected Q-T interval; then disappearance of T-waves (0.8 mM); then pulsus alternans (0.6 to 0.7 mM); then reversible loss of pulse with preserved rhythmic EKG. Signs of tetany were not seen; perhaps because of general anesthesia or brevity of the period of lowered Ca^{2+}. Raising blood $[Ca^{2+}]$ caused increased pulse pressure and minor increase of P-R interval. We conclude that changes of blood $[Ca^{2+}]$ have more effect on cardiac contractility (and perhaps arteriolar resistance) than on electrical activity of the heart. (Supported in part by NS 11933).

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KINETICS OF BLOOD LACTATE APPEARANCE DURING A PROGRESSIVE INCREMENTAL EXERCISE TEST. L.B. Gladden, J.W. Yates,* R.W. Stremel, B.A. Stamford. Exercise Physiology Lab. and Dept. of Physiology and Biophysics, Univ. of Louisville, Louisville, KY 40292.

Recently, the relationship between blood lactate concentration (LA) and work intensity has been described by noting the point at which an abrupt increase in LA occurs (anaerobic threshold). However, the relationship between LA and work intensity appears to be exponential; therefore, we thought it would be informative to describe the kinetics of this curve. Six subjects pedaled a cycle ergometer while work rate was increased by 30 watts each minute until they were unable to continue. Arterialized blood samples were taken at 15 sec intervals and later analyzed for LA. LA did not increase during the first two minutes for any of the subjects. After the first 2 min, LA rose monoexponentially (doubling times of 2.3 and 2.4 min) in 2 of the subjects. For the other 4 subjects, the LA response was best described by the sum of a slow exponential (doubling times, 2.7-4.1 min) and a fast exponential (doubling times 0.9-1.2 min) after the first 2 min. These results suggest that simply characterizing the LA response to incremental exercise by a breakpoint is an oversimplification.

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THE EFFECT OF ALTERING THE INSPIRED OXYGEN FRACTION ON LACTATE ACCUMULATION DURING PROGRESSIVE EXERCISE. M.C. Hogan*, R.H. Cox*, and H.G. Welch. University of Tennessee, Knoxville 37916

These experiments were designed to investigate differences in plasma lactate accumulation during progressive bicycle ergometer exercise while breathing hypoxic, normoxic, or hyperoxic gas mixtures. Six subjects rode to exhaustion on 3 different occasions while breathing mixtures of 17%, 21%, or 60% O_2. After a 10-minute rest period, the subject rode for 3 minutes at a work rate of 60 W followed by 15-W increases until exhaustion. Inspired and expired gas fractions, ventilation, heart rate, and arterialized venous lactate were measured. Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output were calculated for the last minute of each work rate while lactate samples were drawn during the last 10 seconds. $\dot{V}O_2$ was not significantly different at any work rate among the 3 different conditions. The rate of lactate accumulation was significantly greater during hypoxia as compared to either normoxia or hyperoxia. Total lactate accumulation was significantly less during hyperoxia than normoxia or hypoxia. Although lactate accumulation during each of the three tests was best described by a curve, a breaking point at which lactate increased above resting levels was determined. This occurred 30 W higher in hyperoxia than normoxia or hypoxia. We conclude that these variations in lactate concentration cannot be explained on the basis of differences in $\dot{V}O_2$, and that other factors must be considered. (Supported in part by American Heart Association, East Tennessee Chapter)

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KINETICS OF BLOOD LACTATE APPEARANCE DURING CONSTANT LOAD WORK. R. W. Stremel, J. W. Yates*, L. B. Gladden, B. A. Stamford. Exercise Physiology Laboratory and Dept. of Physiology and Biophysics, Univ. of Louisville, Louisville Ky. 40292.

Observations of blood lactate (LA) change during constant load exercise are well documented in the literature, while the kinetics of the LA appearance have not been considered. To characterize these kinetics, five male subjects performed 20 minutes of six different constant load work tests ranging 300 to 2100 kpm/min at 300 kpm/min intervals. Arterialized blood samples were obtained from a hand vein at 15 sec. intervals and fluorometrically analyzed for LA. For the first minute of each test, there was no significant change in LA, regardless of work intensity or subject fitness. The time of peak lactate appearance occurs later in the test as exercise intensity is increased. Associated with this is a slowing of the kinetic rise of LA to that peak ($T\frac{1}{2}$ of 2.06 ± 0.16 min at 600 kpm/min and 3.51 ± 0.52 min at 1800 kpm/min). A range of work intensities exists in which no significant change in LA occurs and at the highest work rates, LA increased throughout the test. However, this increase was still well described by a first order exponential. These results suggest a balance between blood LA appearance and disappearance during 20 min of exercise until severe intensities are reached. (Supported by the University of Louisville Graduate Research Council.)

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FATIGUING EXERCISE EFFECTS UPON THE HUMAN ACHILLES TENDON REFLEX. Gary Kamen, Indiana University, Bloomington, In. 47405

While the patellar tendon reflex is usually reduced in amplitude and total reflex time slowed by the effects of muscular exercise, several investigators have reported heightened Achilles tendon reflexes following muscular exertion. In an effort to examine this phenomenon further, 12 male subjects performed either isometric or rhythmic exercise at either a low intensity (25% MVC) or a high intensity (50% MVC). Four bouts of each exercise task were administered on each of four test days. Results showed little change in electromyographic latency following exercise. However, in several conditions, contraction time and half-relaxation time were enhanced. Reflex force increased following the 50% MVC isometric condition, but was reduced in amplitude following the 25% MVC isometric condition. It is suggested that the observed facilitation of the Achilles tendon reflex occurs due to exercise-induced activation, which may precede the fatigue state.

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THE EFFECT OF RHYTHMIC EXERCISE ON MUSCLE TEMPERATURE AND ISOMETRIC ENDURANCE. M.D. Hoffman*, C.A. Williams, and A.R. Lind. St. Louis Univ. Dept. of Physiology, St. Louis, MO 63104.

Three males volunteered in a series of experiments using bicycle ergometry in order to examine the relationship between the muscle temperature of the quadriceps and the endurance of a subsequently held isometric contraction. The experiment consisted of exerting a max. voluntary contraction (MVC) on a leg dynamometer, one bout of cycling for 1,3 or 10 min at levels of 20%,60% or 80% V_{O2} max followed by a MVC and a isometric contraction of the quadriceps at 40% MVC. There was a 15 sec interval between the end of cycling and the positioning of the leg on the dynamometer during which quadriceps temperature was measured. Isometric endurance was reduced by 30% after 1 min cycling at all 3 workloads. Endurance did not decline further after cycling at 20% V_{O2} max for 3 or 10 min but did progressively decrease with longer bouts of rhythmic exercise at the higher workloads, the greatest decrease seen following 10 min of work at 80% V_{O2} max. Muscle temp. increased as the workload and duration of cycling increased. There was an inverse relationship between endurance and muscle temp. described by the regression line, y= -20.5x + 839 ± 5.3. This relationship also held when the muscle was artificially cooled or heated by submersion of the lower body in a water bath. Muscle temperature, workload and MVC were not strongly correlated. These data suggest that the encorachment on isometric function by rhythmic exercise is due to changes in muscle temperature. (This work was supported by AFOSR Grant # 76-3804.)

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THE EFFECT OF MUSCLE MASS ON THE BLOOD PRESSURE RESPONSE TO ISOMETRIC EXERCISE. D. Hendershot,* J.S. Petrofsky, Chandler A. Phillips and R. Glaser. Departments of Engineering and Physiology, Wright State University, Dayton, Ohio 45435.

The blood pressure response which occurs throughout the duration of fatiguing isometric contractions was examined in four male and female college aged subjects during fatiguing contractions at tensions of 25, 40, and 70 percent of each person's maximum voluntary contraction. In all subjects isometric contractions were exerted with the adductor pollicis muscle, handgrip muscles, biceps muscles, toe muscles, calf muscles, and quadriceps muscles. Two series of experiments were performed on each subject and with each muscle group; in one series of experiments the circulation was occluded by an arterial cuff inflated to 300 mm Hg. The two largest muscle groups, the quadriceps and biceps muscles were found to have a larger blood pressure response than the other four groups; the increase in blood pressure in these two muscles was about 20 mmHg higher than in the other four muscle groups throughout the duration of fatiguing contractions at all three tensions. This project was supported in part under a grant from the National Heart and Lung Institute #1 R01 HL25977-01

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METABOLIC AND CIRCULATORY RESPONSES TO THREE WHEELCHAIR PROPULSION MODES. R.M. Glaser, D.P. Beal*, J.S. Petrofsky, P.A. Smith*, E.L. Fox, and A.G. Suryaprasad*. Wright State Univ. Sch. of Med., Dayton, OH 45435 and VA Med. Ctr., Dayton, OH 45428

The purpose of this study was to compare metabolic and circulatory responses elicited by three types of wheelchair propulsion systems: 1-conventional synchronous handrim (SH), 2-asynchronous handrim (AH), and 3-arm crank (AC). For this, 10 volunteers exercised on a combination wheelchair-arm crank ergometer at four given submaximal power output (PO) levels and at their max PO for each propulsion mode. Exercise bouts were 5 min in duration and physiological data were collected during the 4th and 5th min. Oxygen uptake ($\dot{V}O_2$) and pulmonary ventilation ($\dot{V}E$) were determined by open circuit spirometry, whereas heart rate (HR) and cardiac output ($\dot{Q}$) were determined by impedance cardiography. In comparison to SH propulsion, AH and AC propulsion enabled higher max PO's to be achieved (374, 399 and 474 kpm·min^{-1}, respectively). Peak $\dot{V}O_2$, $\dot{V}E$, HR and $\dot{Q}$ were similar for the three modes of propulsion. At given submaximal PO levels, $\dot{V}O_2$, $\dot{V}E$, HR and $\dot{Q}$ were generally lowest for AC propulsion. Although $\dot{V}O_2$ and $\dot{V}E$ were generally lower for AH than for SH propulsion, HR and $\dot{Q}$ were similar for these modes of locomotion. These data indicate that wheelchair designs which incorporate asynchronous modes of wheelchair propulsion may be advantageous. They appear to permit greater locomotive capability and elicit lower metabolic and circulatory stresses. (Supported in part by the Rehabilitative Engineering R&D Service of the VA)

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PEAK PERFORMANCE OF THE 1980 NATIONAL INTERCOLLEGIATE WHEELCHAIR BASKETBALL TEAM FOLLOWING TRAINING. R.J. Durbin*, R.M. Glaser, S.W. Wilde*, D.S. Miles*, G.W. Gayle*, and R.W. Gotshall. Wright State Univ. Sch. of Med., Dayton, OH 45435

Peak metabolic and cardiopulmonary responses of members of the 1980 National Intercollegiate Wheelchair Basketball Team (N=9) were determined prior to and following a 6-week (3x per wk) interval training program (ITP) using wheelchair ergometer (WERG) exercise. The ITP consisted of 2 portions: 1-aerobic--two 10 min exercise bouts at 80% maximal heart rate (HR max), each followed by 5-min rest periods, and 2-anaerobic--four 2-min work bouts at 95% HR max, each followed by a 2-min rest period. HR was continuously monitored during training to set WERG power output to maintain target HR. Prior to (pre-) and following (post-) the ITP, subjects performed a progressive intensity exercise test on the WERG. Peak responses to max effort exercise were as follows:

	$\dot{V}O_2$ (l·min^{-1})	$\dot{V}E$ (l·min^{-1})	HR (bpm)	LA (mM·l^{-1})	PWC (kpm·min^{-1})
Pre-	2.08	94.7	172	8.5	455
Post-	2.63	125.2	177	10.3	592
%Δ	+26	+32	+3	+21	+30
P<	0.01	0.01	NS	NS	0.01

It thus appears that an intense ITP on the WERG can markedly increase peak performance of these wheelchair athletes. (Supported in part by the Rehabilitative Engineering R&D Service of the VA)

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$\dot{V}_{O_2}$ MAX OF NORMAL WHITE, MESTIZO AND BLACK COLOMBIAN BOYS 6-16 YEARS OF AGE: ABSENCE OF RACIAL DIFFERENCES. G.B. Spurr, J.C. Reina,* M. Barac-Nieto* and M.G. Maksud. Departs. Physiol., Med. Col. of Wis., Milwaukee and Physiol. Sci. and Pediatrics, Univ. del Valle, Cali, Colombia.

When comparing $\dot{V}_{O_2}$ max of groups of children, differences in racial composition appear as a possible confounding variable. $\dot{V}_{O_2}$ max was measured in 106 white, 217 mestizo and 70 black boys using a Balke-Ware treadmill procedure. The children were considered nutritionally normal and free of past undernutrition by selection within ± 5% of Colombian norms of weight and height for age and weight for height. In 5 age groups of 2 yr intervals, younger boys showed no differences in weight or height among the races. In older boys, white children were heavier and taller than mestizo boys. In general, black boys fell between white and mestizo subjects in average weight and height and no consistent pattern of differences was observed. Average max heart rates ranged from 201 to 209/min with mestizo boys tending toward slightly higher values than others. $\dot{V}_{O_2}$ max (L/min, or ml/kg/min) was not significantly different among races in each of the 5 age groups. Average $\dot{V}_{O_2}$ max varied from 49 to 56 ml/kg/min. Regression analysis of $\dot{V}_{O_2}$ max (L/min) on body weight resulted in almost superimposable regression lines with slopes and intercepts which were not significantly different. We conclude that there is no racial difference in $\dot{V}_{O_2}$ max during this period of growth of white, mestizo and black boys. Supported by NIH Grant No. 10804.

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INTERRELATIONSHIPS AMONG POWER OUTPUT, PEDAL FREQUENCY, OXYGEN UPTAKE, AND HEART RATE DURING BICYCLE ERGOMETER EXERCISE. D.B. Reynolds, J.S. Petrofsky and R.M. Glaser. Wright State Univ., Dayton, OH 45435

Four young (20-24 yrs) male subjects pedaled at 30, 60, or 90 RPM on a bicycle ergometer in 4 min bouts at power outputs (PO) corresponding to 20, 40, 60, 80, 100% of their previously determined maximum oxygen uptake (max $\dot{V}O_2$). Max $\dot{V}O_2$ was determined for each RPM by a progressive intensity exercise test. Heart rate (HR), surface electromyogram of the right quadricep and right pedal force (RPF) were also measured. Position and speed of the crank was accurately determined with sensors utilizing movement of the crank sprocket wheel. Average max $\dot{V}O_2$ for 90 RPM was 6.0% lower, whereas it was 24.5% lower for 30 RPM than for pedaling at 60 RPM. In two subjects, lower max $\dot{V}O_2$ at 30 RPM may have been partially due to their exercising at the 7 kp load limit of the bicycle ergometer. At given submaximal PO's, $\dot{V}O_2$ for 30 and 60 RPM were nearly equal, while it was greater for 90 RPM. The slopes of the submaximal $\dot{V}O_2$-PO curves were about equal, indicating that the higher $\dot{V}O_2$ for 90 RPM was due to a larger zero load offset. HR increased nearly linearly with $\dot{V}O_2$ with no dependence on RPM. RPF varied with crank position, with peak force occuring just below the forward horizontal position. Greater submaximal $\dot{V}O_2$ for 90 RPM probably results from internal ergometer friction, resistance in the visco-elastic tissues of the legs and inertial forces resulting from accelerations of the leg mass. (Supported in part by the Rehabilitative Engineering R&D Service of the VA)

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PHYSIOLOGICAL RESPONSES TO HANDRIM AND ARM CRANK WHEELCHAIR PROPULSION. P.A. Smith*, R.M. Glaser, J.S. Petrofsky, P.D. Underwood, Jr.*, G.B. Smith* and J.J. Richard*. Wright State University School of Medicine, Dayton, OH 45435

The handrim propulsion system of most manual wheelchairs has been shown to be inefficient and stressful to the cardiovascular and pulmonary systems. Arm crank propulsion has been suggested to reduce these stresses. In order to compare conventional handrim wheelchair propulsion to arm crank type wheelchair propulsion, 16 volunteers (9 able-bodied, 7 wheelchair-dependent) operated both wheelchairs over level tiled and carpeted test courses at 3 km·h^{-1}. The arm crank propelled wheelchair was operated in 3 gear ratios--low, medium and high. Exercise bouts were 5 minutes in duration. During the final minute of each test oxygen uptake ($\dot{V}O_2$), pulmonary ventilation ($\dot{V}E$), and heart rate (HR) were monitored. Subjects exhibited significantly lower magnitude of these physiological responses during arm crank wheelchair propulsion relative to handrim wheelchair propulsion for all gear drive ratios. Average percent differences were: 30% and 33% for $\dot{V}O_2$; 27% and 34% for $\dot{V}E$; and 16% and 19% for HR on the tiled and carpeted test surfaces, respectively. From these data we conclude that arm crank wheelchair propulsion is less strenuous than conventional handrim wheelchair propulsion and that arm crank propulsion systems should be considered as a possible means to improve wheelchair design. (This study was funded in part by the Rehabilitative Engineering Research and Development Service of the VA and the VA Rehabilitation Engineering Center)

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CHANGES IN LUNG VOLUMES AND FLOW RATES AFTER A MARATHON. C.E. Doerr*, S.A. Schonfeld*, R.W. Gotshall, D.E. Sinks*, and D.S. Miles*. Wright State University, Dept. of Physiology, School of Medicine, Dayton, Ohio 45435 and The Ohio State University Col. of Med., Pulmonary Disease Division, Columbus, OH 43210.

Recent studies have reported reductions in forced vital capacity (FVC) after marathon racing with simultaneous increases in residual volume (RV), with no changes in total lung capacity (TLC). It has been speculated that the underlying mechanism was the early closure of peripheral airways. In order to further characterize the mechanism(s), we tested 8 male runners ($\bar{x}$ age = 38, range 29-53) before, immediately after, and the day following competition in the Columbus Bank One Marathon ($\bar{x}$ run time = 3 hr. 30 min.) Subjects completed maximum expiratory flow-volume maneuvers in triplicate, breathing (1) air; (2) 80% He/20% O_2; and (3) air, following administration of a bronchodilator (isoproterenol). Lung volumes were determined by nitrogen washout and single breath He dilution. There were no changes in FVC, RV, or TLC after the marathon. No changes occurredin FEV_1, FEV_3, FEF_{50}, FEF_{25}, or peak flow. The $\Delta\dot{V}max_{50}$, $\Delta\dot{V}max_{25}$, and isoflow values were also similar pre- to post-race. Isoproterenol had no effect upon FVC and flow rates. In conclusion, these results indicate that small airways obstruction does not occur and there is no enhanced bronchial smooth mucle tone post-marathon racing. In contrast to previous reports, we failed to demonstrate any change in lung volumes using two independent methods.

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CHANGES IN DIFFUSION CAPACITY AND CLOSING VOLUME AFTER A MARATHON. D.S. Miles*, C.E. Doerr*, S.A. Schonfeld*, D.E. Sinks*, and R.W. Gotshall. Wright State Univ., Dayton, OH 45435 and The Ohio State Univ., Columbus, OH 43210

The purpose of this study was to elucidate the possible mechanism(s) responsible for a reduction in diffusion capacity of the lung (D_{LCO}) after marathon racing. Eight male subjects were tested before, immediately after, and one day post completion of the Columbus Bank One Marathon. Closing volumes(CV) were measured using a single breath O_2 test and D_{LCO} was measured with the single breath technique. Pulmonary capillary blood volume (V_c) and membrane diffusing capacity (D_M) were calculated based upon measurement of D_{LCO} at two different O_2 tensions.

	D_{LCO}	D_M	V_c	D_M	CV/VC
	ml/mmHg/min	ml/mmHg/min	ml	% Total Resistance	%
Before	31.3	59	112	57	12
Post	28.6	46	116	65	16
1-Day Later	31.3	54	115	61	13

There were significant decreases in D_{LCO}, D_M and increases in CV post-race. Since D_{LCO} reflects the sum of its series components (V_c, D_M), the observed reduction in D_{LCO} must be explained by a decrease in D_M given no change in V_c. This increase in membrane resistance ($1/D_M$) may reflect the occurrence of perivascular and/or peribronchial edema. Such a change would increase lung elastic recoil and could explain the increase in CV. Our speculation is consistent with the results we have reported elewhere that no simultaneous reduction in small airway caliber occurred post-race.

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EFFECT OF PHYSICAL TRAINING ON AGE OF MENARCHE, BODY COMPOSITION AND THE MENSTRUAL CYCLE. Joel Stager,* David Robertshaw and Elizabeth Miescher.* Dept. Physiology and Biophysics, Colorado State University, Fort Collins, CO 80523.

Swimming, a sport which often involves the initiation of physical training before the onset of menarche can result in a low body fatness without a decrease in body weight. The hypothesis was tested that a critical body fat percentage is necessary for both the onset and continuation of menstruation in athletes. We investigated the effect of intensive prepubertal swimming on body composition and its relation to the age of menarche. The mean age of menarche of the swimmers was 13.6 yrs, 1.1 yr later than the national average. Measureements of body fatness calculated from measurements of body density indicated that the delay in onset of menarche may be related to a delay in achievement of a critical body fat percentage (17%). Frisch et al. (Human Biol 45; 469, 1973) have proposed that 22% body fat is necessary to maintain normal menstrual cycles. Only 7% of the collegiate athletes had attained this critical composition and yet 50% had normal menstrual cycles. College age athletes with irregular cycles (<7 menstrual cycles/yr) were older at menarche but not fatter than those with regular cycles (>10 menstrual cycles/yr). It was concluded that 1) the initiation of menarche may be related to the achievement of a critical body fatness, 2) that the Frisch hypothesis is not confirmed and 3) that a delay in age of menarche may be associated, in a college age population, with irregular cycles. (Supported by NIH grant #HD 13778).

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EFFECT OF EXERCISE TRAINING ON C-HDL LEVELS IN WOMEN: CONTINUOUS VS. INTERVAL PROGRAM. M.A.B.Frey, B.M.Doerr*, L.L.Laubach*, B.Mann*, and C.J.Glueck*. Wright State Univ., Dayton, OH 45435 and Lipid Research Clinic, Univ. of Cinn., Cincinnati, OH 45267

Exercise training of 7-10 wk increases plasma high-density lipoprotein cholesterol (C-HDL) levels in men. Our previously reported interval-type bicycle ergometer training program for women on oral contraceptives (OC) increased maximum oxygen uptake ($\dot{V}O_2$max) by almost 20% but did not change C-HDL. 16 women 18-30 yr of age and not taking OC participated in this study. Subjects exercised 30 min 3 times/wk for 10 wk at 70% maximum heart rate reserve: 10 in an interval program (5 min exercise, 2 min rest), and 6 for 30 min continuously. Variables significantly ($p<0.05$) changed were:

		INTERVAL		CONTINUOUS	
VARIABLE	UNITS	pre	post	pre	post
$\dot{V}O_2$max	ml/kg/min	27.5	32.3	30.2	34.4
Resting heart rate	beats/min	73.6	66.0	67.3	59.7
Body fat (hydro. wgt.)	%	27.4	24.8	30.2	28.0

Neither C-LDL, total cholesterol, nor triglycerides were changed significantly. C-HDL decreased significantly at 2 and 5 wk, and returned to control at 10 wk (pretrain=61.67 mg/dl, 2 wk=56.33, 5 wk=58.06, 10 wk=62.00). Successful exercise conditioning for a 10-wk period does not elevate C-HDL in women in comparison to men and suggests a sex-specific difference in factors that mediate exercise-induced increases in C-HDL. (Supported in part by grants from the Miami Valley Chapter, A.H.A., and by GCRC Grant #RR00068-19)

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HEART RATE RESPONSE TO REDUCED CORONARY BLOOD FLOW DURING SUBMAXIMAL EXERCISE. Delvin R. Knight* and H. Lowell Stone Dept. of Physiology, Univ. of Okla. HSC, Okla. City, OK 73190

Seven dogs were subjected to submaximal exercise tests to determine the effect of reduced coronary blood flow (CBF) on heart rate (HR). Dogs were chronically instrumented with a Doppler ultrasonic flow probe and hydraulic occluder around the left circumflex coronary artery (LCA). After 3 weeks, the dogs were submaximally exercised while measuring CBF velocity, ECG by telemetry and HR with a cariotachometer. The submaximal exercise tests were repeated while obstructing CBF with the hydraulic occluder to 20% of peak reactive hyperemic flow, previously determined by a 15 sec occlusion of the LCA. The HR responses were similar, except at the higher workloads when myocardial function appeared to be compromised by the reduced flow. At the highest workload of 6.4 km/h, 16% grade, HR increased from a resting level of 99±5 to 257±8 beats/min and CBF increased from 30±2 to 52±3 cm/sec. After the LCA had been stenosed to 14±3 cm/sec, HR increased from a level of 98±8 to 219±12 beats. Reduction of LCA flow to the same level during exercise also resulted in a reduction in existing HR. The relative bradycardia at the higher workloads suggests a reflex decrease in the sympathetic activity, or an increase in vagal activity during exercise when CBF was reduced. (Supported by NIH Grant #HL22154)

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ACTIVATION OF β_1-RECEPTORS ON THE CORONARY RESISTANCE FOLLOWING REPETITIVE EXERCISE. Isabella Y.S. Liang* and H. Lowell Stone. Dept. Physiol., Univ. of Okla. HSC, Oklahoma City, OK 73190

Selective β_1-adrenergic blockade (βB) was used to determine the changes in coronary resistance with repetitive exercise. Five conscious dogs were studied in the untrained (UT) and partially trained (PT) conditions during submaximal exercise. Myocardium oxygen consumption (MV_{O_2}) was measured. Left circumflex coronary blood flow velocity (CF), aortic pressure, heart rate (HR) and diastolic coronary resistance index (DCRI) were measured. Atenolol (βB 1 mg/kg) was used.

		DCRI (mm Hg/cm/sec)		
workload (kph/%)		0/0	6.4/8	6.4/16
control	UT	4.77	2.45	2.09
βB	UT	5.30*	3.06*	2.61*
control	PT	4.10	1.92	1.69
βB	PT	4.86*	2.67*	2.33*

*$P < 0.05$ compared to control at the same workload. There was, comparing to control values, a decrease in HR, MV_{O_2}, and CF during submaximal exercise with βB in both the UT & PT conditions. However, these values following βB were not significantly different in the UT & PT conditions. These data suggest that blockade of β_1-adrenergic receptors during submaximal exercise in both the UT & PT conditions resulted in no change in the coronary resistance. Thus, the difference in coronary resistance observed in previous studies was not due to alterations of the myocardial metabolic signal as a result of β_1-receptor activation. (Supported by NIH Grant # 22154).

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CORONARY VASCULAR ADRENERGIC RECEPTOR BLOCKADE DURING EXERCISE. Patricia A. Gwirtz and H. Lowell Stone. Dept. of Physiol. & Biophys., Univ. of Okla. HSC, Oklahoma City, OK 73190

The effects of sympathetic and parasympathetic nervous systems on coronary blood flow during exercise were determined by direct adrenergic blockade of myocardial adrenergic receptors. Five dogs were chronically instrumented to measure Doppler coronary blood flow velocity (CFV), mean left circumflex coronary artery blood pressure (CBP), ECG and heart rate (HR) during submaximal exercise. Intracoronary administration of atropine (Atr, 100-500 mg), phentolamine (Ph, 1 mg) or propranolol (Pr, 1 mg) was used to avoid systemic drug effects. CBP averaged 93±21 mm Hg at rest and 111±11 mm Hg during exercise.

	Rest		Exercise		Ex + Blockade	
	CFV	HR	CFV	HR	CVF	HR
Atr	47±14	106±25	71±12	190±10	71±16	190±10
Ph	35±14	119±12	66± 8	237±25	70±10	246±23
Pr	36± 2	109±10	68±11	235±20	54± 7	205±19

These data suggest (a) there is no cholinergic component controlling CF during exercise (b) α-blockade increases CFV indicating a neurally mediated vasoconstrictor tone on coronary vessels during exercise, and (c) β-blockade reduces CFV by a direct effect on coronary vessels and on myocardial metabolism. (Supported by NIH Grant HL22154, HL05835).

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SELECTED RESPONSES OF THE IMMUNE SYSTEM TO EXERCISE AND PASSIVE THERMAL STRESS. Lou A. Stephenson*, Margaret A. Kolka, J. E. Wilkerson. Human Performance Lab., Indiana Univ., Bloomington, IN 47405

Five adult males participated in 3 experiments in which core temperature (Tre) and venous plasma immunoglobulin (Ig) concentrations, leucocyte counts and differentials were determined. In one experiment, the subjects performed a short duration maximal work bout (E). In the other 2 sessions, the Ss sat in an 80 C. sauna for 30 min, with rehydration (PHR), or without rehydration (PHD). Tre increased in all cases (E: +0.5 C;PHD: +0.9 C;PHR: +1.8 C). A differential decrease in plasma volume was observed in the 3 procedures (E: -11.2%;PHD: -7.3%;PHR: -3.6%). This hemoconcentration accounted for the increases in the plasma concentrations of IgG, IgA, & IgM. All procedures elicited a leucocytosis (E: +67%;PHD: +16%;PHR: +40%), with a lymphocytosis noted in each. E and PHR elicited a neutrophilia and a monocytosis. PHD alone elicited an eosinopenia. These data suggest that cardiovascular status and not core temperature is the major factor influencing the leukocytosis of exercise and passive thermal stress.

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DOES HEAT ACCLIMATION LOWER THE RATE OF METABOLISM DURING PHYSICAL EXERCISE? Kent B. Pandolf, Michael N. Sawka, Barbara A. Avellini* and Yair Shapiro. U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760

Heat acclimation has been suggested to either lower or have no effect on the rate of metabolism (M) elicited by physical exercise. Our primary investigation (Study I) was conducted to determine if heat acclimation does indeed lower the rate of M ($W \cdot kg^{-1}$) during exercise. Two additional investigations were evaluated to determine if season (summer or winter) of acclimation (Study II) and gender (Study III) further influence the effect heat acclimation has on M during exercise. Volunteers for Studies I (n = 15 men), II (n = 8 men), and III (n = 10 men, + 9 women) completed treadmill walks (1.34 or 1.56 $m \cdot s^{-1}$, 0% grade, 100 min) in cool (20°C, 40% rh) and hot (40°C, 30% rh or 49°C, 20% rh) environments immediately before and after heat acclimation. Heat acclimation involved 6 (Study III) or 10 (Studies I and II) consecutive days each lasting 120 min (10' rest, 50' walk, 10' rest, 50' walk). After heat acclimation, a significantly ($p < 0.05$) lower M was observed for Study I (-7%) and II (-6%) in the cool exposure but no differences were found for the hot exposure. No difference in M was found between seasons (Study II). For Study III, a lower ($p < 0.05$) M was observed in both the cool (-6%) and hot (-3%) environments after acclimation; no difference was found between the sexes. These data indicate that M is generally decreased during exercise after heat acclimation. The observed percent decrease was greater in the cool than hot test environment. Physiological mechanisms which could contribute to this decreased M include an increased muscular efficiency and/or a lowered body temperature.

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A QUANTITATIVE EVALUATION OF NECK MUSCLE PERFORMANCE. Chandler Allen Phillips and Jerrold Scott Petrofsky. Wright State University, Dayton, OH. 45435.

A problem frequently reported by helicopter flight crew members is neck muscle soreness and weakness due to the loading of various electronic and optical devices on the standard Army flight helmet (SPH-4). Basically, the SPH-4 is designed and tested for impact protection with little or no consideration given to the physiological performance of the neck muscles. Consequently, a series of experiments were performed to evaluate the stresses imposed on the neck muscles during isometric contractions of these muscles in the forward, lateral and backward directions. A set of strength-endurance data points were generated by measuring the endurance time that the neck muscles could sustain tensions of 25%, 40%, 55%, 70% and 90% of the muscle's maximal strength (MVC). A series of curves were fitted to these data points using standard regression techniques and resulted in three inverse non-linear curves for the three directions tested. The characteristic equation which uniquely describes each strength-endurance curve can (in part) be used to optimize the physiological endurance of the neck muscles for a given helmet loading condition. (This work supported by U.S. Army contracts DAMD 17-80-C-0089 and DAMD 17-80-C-0089-P102).

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THE METABOLIC RESPONSES TO HELIUM-OXYGEN BREATHING DURING EXERCISE. Alan G. Brice* and Hugh G. Welch. University of Tennessee, Knoxville, TN 37916

Evidence exists that there are alterations in metabolic responses to standard exercise when the diluent gas is changed from nitrogen (air) to a gas with a differing density such as helium. To compare the metabolic responses of He-O_2 breathing during exercise with those of air breathing, 4 trained male cyclists performed exercise on the bicycle ergometer at 6 different intensities. Each subject was tested twice at each work rate, once while breathing air and once while breathing He-O_2. There were no significant differences between the gases for lactate or heart rate. Minute ventilation was greater ($p < .01$) when He-O_2 was the inspired gas. There was a significant interaction ($p < .001$) between work rate and gas for minute ventilation. Tests for simple main effects showed differences in ventilation between the gases only at the 2 highest work rates. When all 6 levels of work rate were analyzed together there were no significant differences ($p = .08$) between the gases for $\dot{V}O_2$. However, at the 2 most intense work rates where great differences in ventilation between the gases existed, the $\dot{V}O_2$ when breathing He-O_2 was significantly higher ($p < .01$) than that during air breathing. These results indicate differences in $\dot{V}O_2$ between air and He-O_2 breathing during intense exercise which may be related to the large differences in ventilation observed between the two gas mixtures. (Supported in part by American Heart Association, East Tennessee Chapter)

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COMPARISON OF THE CARDIOVASCULAR EFFECTS OF INHALED AND INJECTED CARBON MONOXIDE. Wayne E. Kanten*, David G. Penney, Michael S. Baylerian*, David A. Swastek* and David C. Szlag*. Dept. of Physiol., Wayne State Univ., Detroit, MI 48201.

Recent reports suggest that the cardiovascular (CV) effects of intraperitoneally (i.p.) injected CO differ from those when CO is inhaled. Conscious male rats inhaled 500 ppm CO for periods from 0-48 hrs. (INH), or received 100% CO (15ml/kg) i.p. by single injection (INJ). Measurements of heart rate (HR) and systolic blood pressure (P_{sys}) were taken by the tail-cuff method and carboxyhemoglobin saturation (COHb) determined spectrophotometrically. In the INH group, after two hrs, COHb had risen to 35-38%, P_{sys} had fallen to 48% of controls (C) and HR had risen 25% above C. HR remained elevated and P_{sys} remained depressed for 48 hrs. In the INJ group, HR rose sharply in the first 15 min. while P_{sys} fell more gradually. Within 1 hr, COHb reached 56%, P_{sys} fell to 55% of C and HR rose 29% above C. Beyond 1 hr, COHb fell, HR declined to C and P_{sys} returned to C as CO was lost through ventilation. COHb, P_{sys}, and HR were nearly normal after 4 hrs. Overall, in the INJ group, HR and P_{sys} changes closely paralleled changes in COHb. The results corroborate more extensive CV studies with anesthetized, open-chest rats inhaling CO (Fed. Proc., 40, 2899, 1981). It appears that regardless of the route of entry, CO produces profound peripheral vasodilation, fall in P_{sys}, and reflex tachycardia. The elevated cardiac output which results, re-establishes tissue oxygen delivery. (Supported by NIH Research Grant HL-22859).

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INTERACTION OF CARBON MONOXIDE AND NICOTINE ON THE RAT HEART. James J. McGrath and David Smith, Texas Tech University Health Sciences Center, Department of Physiology, Lubbock, Texas 79430.

Experiments were continued to assess the effects of carbon monoxide (CO) on the isolated spontaneously beating rat heart. Hearts removed from male, white laboratory rats were perfused via the aorta with oxygenated (95%O_2-5%CO_2) Kreb's Henseleit solution. Heart rate and pulse pressure were measured by a catheter inserted into the left ventricle and attached to a pressure transducer. Coronary flow was timed and collected in a calibrated vessel. After 30 minutes, the hearts were challenged with solutions containing CO (10%CO-85%O_2-5%CO_2), nicotine (10 ug/ml in 95%O_2-5%CO_2) or CO and nicotine (10 ug/ml nicotine in 10%CO-85%O_2-5%CO_2). The hearts were allowed to recover in oxygenated, nicotine-free perfusate for 10 min. Heart rate remained unchanged following perfusion with CO while coronary flow increased to 146 and 143% of control at 2 and 8 min., respectively. Heart rate and coronary flow were significantly depressed by nicotine. After 2 and 8 min. heart rate declined to 89 and 78% while coronary flow declined to 84 and 80% of control. When the hearts were perfused with CO and nicotine heart rate decreased to 93 and 83% of control at 2 and 8 min. Coronary flow initially increased at 2 min. to 114%. This was followed by a decrease after 8 min. to control levels. These results suggest that CO and nicotine may have opposite effects on coronary flow. Supported in part by American Heart Association, Texas Affiliate.

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Heart function in persistent cardiomegaly resulting from neonatal carbon monoxide exposure. David G. Penney and Michael S. Baylerian*. Dept. of Physiol., Wayne State Univ. School of Medicine, Detroit, MI 48201.

Newborn male and female rats inhaled 500 p.p.m. CO for 33 days. 2 ventricle (2V); body weight (BW) ratio peaked at 14 days of age. Left V + interventricular septum (LV+S) was 78% and right V free wall (RV) was 100% above predicted values at this time. After return to room air, relative 2V wt. declined, but persisted above pred. values: 16% in females and 13% in males at 92 and 103 days of age respectively, and 11% in females and 12.5% in males at 171 and 180 days of age, respectively. Persistence in the RV is about double that in the 2V. 2V/BW ratio was greater than controls (C) in all 4 groups. At these times the polycythemia present during CO exposure had declined, although hematocrit remained elevated 2-4% in 3 of the 4 groups. CV function was assessed using an open chest, chloralose-urethane anesthetized preparation. In the 92 and 103 day old rats there was no difference in card. output, stroke vol., str. work, peak aortic flow, 1st derivative of aor. fl., etc. when compared to C. However the 1st derivative of V pressure was elevated in the presence of higher systemic resistance. There were no differences when these parameters were normalized per g LV+S. Acute increases in preload resulting from 10% and 20% increases in blood volume produced the same changes in CV parameters as in C. Although heart mass remains abnormal, these studies reveal little alteration in pump or muscle function. (Support by NIH Grant HL 22859).

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WITHDRAWN

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ARTERIAL LACTATE AND PYRUVATE LEVELS AFTER EXERCISE AT 65.6 ATA. R.E. Moon*, E.M. Camporesi, B. Stolp* and J.V. Salzano. F.G. Hall Laboratory for Environmental Research, Duke University, Durham, N.C. 27710.

Graded 6 min exercise levels were completed by three trained volunteers on a bicycle ergometer inside a dry hyperbaric chamber: 1) at 1 ATA, up to 1440 kpm/min, breathing air, and 2) at a simulated depth of 65.6 ATA, up to exhaustion, breathing Trimix-10 (10% N2, .76% O2, balance He, density = 17.1 g/L). Blood samples (2 ml) were drawn from a radial artery cannula, during rest and 1 minute after termination of all exercise periods. Lactate (Lac) and Pyruvate (Pyr) levels were assayed by enzymatic techniques after precipitation with perchloric acid. Sample decompression (30 min) was shown not to affect the measured concentrations. Pyr levels increased with increasing work load both at 1 and at 65.6 ATA: the increase was greater at pressure for 2 subjects. At 1 ATA, Lac concentrations increased sharply with increasing work levels above 720 kpm/min. At 65.6 ATA, Lac concentration increased sharply above 360 kpm/min, while PaO2 measured during the last min of exercise was always in excess of 270 Torr. At pressure, Lac concentrations were always higher than 1 ATA values, both at rest (70% increase) and after exercise (over 200% increase). Significant differences ($p < .05$; paired t-test) could be demonstrated at 720 and 900 kpm/min. This increased lactic acidemia suggests a higher level of anaerobic metabolism for any given work rate completed at 65.6 ATA. The phenomenon may represent an additional factor limiting exercise performance at pressure.
(Supported in part by NHLBI grant # HL 07896-18.)

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BLOOD GLUCOSE AND OXYGEN TOXICITY. Daniel J. Crittenden*, David L. Beckman and Steven J. Blumenthal*, Dept. Physiol., Sch. Med., E. Carolina Univ., Greenville, NC 27834

Protection against toxic effects of O_2 at high pressure (OHP) is afforded by adrenalectomy, thyroidectomy, and hypophysectomy, all of which tend to reduce blood sugar. Adrenaline, which augments O_2 toxicity, tends to raise blood sugar. We attempted to determine the effects of increased blood glucose on O_2 toxicity by injection of glucose or alloxan. Fifteen male Sprague-Dawley rats were exposed 3 at a time to 6 ATA 100% O_2 in a hyperbaric chamber for 60 min or until all 3 severely convulsed. Immediately before being placed in the chamber, 6 control rats were sham treated by injection with 2 cc saline IP, 4 rats were given 2 cc 33% glucose IP, and 5 alloxan-pretreated diabetic rats were also sham treated. Control rats showed severe seizures after 28.3±3.3 min (mean±SEM), glucose-pretreated rats after 47.8±9.8 min, and alloxan-pretreated rats after 55.6±4.4 min ($P < 0.001$). Lung wet wt/body wt ratios x 10^3 were 7.0±1.4 for controls, 5.8±.8 for glucose-pretreated rats, and 7.4±1.1 for alloxan-pretreated rats. End-exposure blood glucose values determined by the glucose oxidase-O_2 depletion method were elevated from a control value of 272.7±59.5 mg% to 481.8±34.2 mg% in glucose-pretreated rats and to 495.8±20.4 mg% in alloxan-pretreated rats. Our data from glucose- and alloxan-pretreated rats suggest that elevated blood glucose may protect against seizures in OHP exposure.
(Supported by N.C. United Way.)

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TRANSCUTANEOUS DOPPLER ULTRASONIC DETECTION OF CIRCULATING BUBBLES IN THE SHEEP FETUS FOLLOWING HYPERBARIC DECOMPRESSION. Michael R. Powell, Mark T. Smith*, and Merrill P. Spencer. Institute of Applied Physiology and Medicine, Seattle, WA 98122

Lack of the pulmonary filter, which protects the mother from arterial gas embolism, renders every bubble in the fetal circulatory system a potential progenitor of neurologic decompression sickness. We used a transcutaneous bubble detection system as surgically implanted probes produce artifacts. A 5 cm focusing 5 MHz CW Doppler probe signal was displayed on a bidirectional FFT color 3-D spectral analyser which separated fetal from maternal and arterial from venous signals. Following a dive of 160'/12, Grade II maternal venous and Grade I fetal arterial bubbles were found. A different 160'/12 produced Grade III maternal and I fetal. With 160'/15, the grades were IV maternal and IV fetal. Recompression to 60 FSW (PO_2 = 2.0 ATA) eliminated both maternal and fetal bubbles; the treatment was insufficient as the lamb was born 2 days later with hind leg paralysis. Arterial gas embolization is postulated. Another gravid ewe, dived 160'/10 min., displayed Grade IV venous. She was treated at 160 FSW/45 min. (PO_2 = 2.63 ATA). Fetal embolization cleared and the lamb was born (6 days later) normal. Supported by US PHS Grant RR-05827.

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DECOMPRESSION GAS PHASE FORMATION FOLLOWING EXPOSURE TO DIFFERENT ENVIRONMENTAL STRESSES. Merrill P. Spencer and Michael R. Powell. Institute of Applied Physiology and Medicine, Seattle, WA 98122.

In a series of experiments to study the effects of environmental stress on decompression bubble formation, 12 divers made 72 man-dives in a dry chamber (100 fsw/50 min.). Gas phase formation was evaluated by means of the precordial Doppler ultrasonic flow meter. Results are given in the following table:

CONDITION	TIME-AVERAGE DOPPLER SCORE (I-IV)
1. wet-exercise	0.54
2. wet-resting	0.41
3. wet suit-resting	0.24
4. dry-exercise (2X)	0.25
5. dry-resting	0.41 (joint pain, 2 cases)

On a paired-t test, only the wet-exercise and dry-exercise condition was significant at the $p<0.05$ level. Gas phase formation was not provoked by either isometric or isotonic exercise in one arm when compared to the contralateral arm. Two cases of pain-only decompression sickness were encountered; both were in the dry-resting divers. One presented with Grade III and the other Grade IV. Insofar as table development and testing is concerned, wet-exercise is "bubble provoking" while dry-exercise mitigates gas phase formation. Supported by US PHS Grant HL 24321.

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HYPERBARIC PRESSURE CAN ALTER MYOCARDIAL CONTRACTION IN THE ABSENCE OF SYMPATHETIC NERVOUS ACTIVITY. T.J. Doubt and D.E. Evans. Naval Medical Research Institute, Bethesda, Md. 20014.

Our previous work has shown that cats exposed to a hyperbaric pressure of 1000 fsw developed a 12 ± 4% decrease in spontaneous heart rate (HR); a 16 ± 9% increase in excitation-contraction (E-C) delay measured from onset of QRS complex of the ECG to onset of left ventricular developed pressure (LVP); and a 17 ± 2% increase in +dP/P (ratio of +dP/dt to LVP at maximum +dP/dt). The present experiments examined cardiac responses to hyperbaric pressure during sympathetic nervous system (SNS) blockade. Cats were anesthetized with chloralose (100 mg/kg, iv). Beta adrenergic blockade with sotalol (4 mg/kg, iv) reduced HR by 24 ± 3% ($p < .01$), increased E-C delay by 18 ± 6% ($p < .05$), and decreased +dP/P by 9 ± 3% ($p < .05$). Compression with helium-oxygen (PO_2 = 0.35 atm) to 1000 fsw did not alter the degree of beta block, as tested by HR response to isoproterenol (1 µg/kg, iv). Increasing pressure from 1-1000 fsw, however, further reduced HR by 5 ± 1% ($p < .01$); resulted in no significant change in E-C delay (7 ± 6% increase); and increased +dP/P by 10 ± 3% ($p < .05$). These results indicate that helium pressure can decrease cardiac excitability and increase contractility independently of its action on the SNS. Further, these data suggest that the magnitude of a given cardiac response to elevated pressure will depend on the degree of sympathetic activity opposing the pressure-related changes. (Supported by NMRDC Work Unit No. M0099.PN002.9026).

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SYMPATHO-ADRENAL RESPONSES TO COLD EXPOSURE AND KETAMINE ANESTHESIA IN THE RHESUS MONKEY. Margaret A. Kolka, Reynaldo S. Elizondo and Robert P. Weinberg*. Indiana University School of Medicine, Physiology Section, Bloomington, IN 47405

The effect of cold exposure on the sympatho-adrenal system was studied in eight Rhesus monkeys with and without ketamine anesthesia. Monkeys were placed in a thermoneutral temperature (25°C) for 1 hr (control) followed by cold air exposure (12°C) for 3 hr, or placed in cold water (28°C) to induce a decrease in core temperature to 35°C and 33°C. Plasma catecholamines were analyzed by HPLC. The 3 hr cold air exposure was associated with a 175% increase in Norepinephrine (NE) and a 100% increase in Epinephrine (E). Decreases were evident in core temperature (T_{re}) (0.5°C), mean skin temperature ($\bar{T}_s$) (5.5°C) and in mean body temperature (T_b) (2.0°C). Continuous infusion of ketamine (0.65 mg/kg·min^{-1}) resulted in no change in the plasma levels of NE and E from the control. T_{re}, $\bar{T}_s$, and T_b all showed greater declines with the addition of ketamine infusion. Water exposure (28°C) under ketamine anesthesia resulted in a drop in T_{re} to 33°C within 1 hr. Plasma levels of NE and E were unchanged from control values at T_{re} = 35°C and T_{re} = 33°C. The data suggest that the unanesthetized catecholamine response to cold exposure is related to non-thermal inputs. (Supported by Grants PHS AM16703 and NASA OR335).

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RESPONSE TO NOREPINEPHRINE IN THE HYPOTHERMIC ISOLATED HEART. F. D. Romano* and S. B. Jones. Department of Physiology, Loyola University Medical Center, Maywood, IL 60153.

Although in situ hearts of hibernating animals are known to function in profound hypothermia, little is known of the adrenergic control of these hearts. The present experiments test the inotropic and cAMP changes of hypothermic hearts in response to norepinephrine (NE). Isolated hamster hearts were perfused at 90 mmHg with oxygenated KRB. Coronary flow (CF) was measured above the aorta. Generated ventricular pressure (GP) and heart rate (HR) were determined from the pressure pulse of a saline-filled balloon in the left ventricle. GP, HR and CF were recorded at 22°C, 17°C, 12°C and 7°C as the temperature was gradually lowered. Measurements were made when the hearts reached a steady state at each temperature. 22°C and 7°C hearts received a bolus of NE (12.5 ng/gm) or vehicle and were frozen 30 seconds after infusion. At 22°C, NE increased both GP (103.2±8.6 mmHg to 122.5±11.0 mmHg) and cAMP content (334.9±14.1 pmol/gm to 431.03±19.7 pmol/gm). At 7°C there was no increase in GP (71.7±12.7 mmHg to 72.6±14.6 mmHg) or cAMP content (272.9±35.4 pmol/gm to 287.7±38.9 pmol/gm). GP could be increased at 7°C one minute after the NE bolus, but there were no detectable changes in cAMP. These experiments show that hypothermic isolated hamster hearts are capable of maintaining function at 7°C and suggest a dissociation between increases in contractility and increases in cAMP with NE stimulation during severe hypothermia. (Supported by NIH HL 08682.)

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INSULATION OF SLEEPING BAGS AND UNDERMATS. Walter H.Cottle and Harvey A.Scott* (SPON: W.H.Cottle). Univ. of Alberta, Edmonton, AB Canada T6G 2H9.

In connection with studies of heat balance of subjects sleeping outdoors under winter conditions a simple heated manikin has been developed to assess insulation provided by various sleeping systems (sleeping bags and undermats under simulated winter conditions. A hollow human-like fiberglass form filled with water is maintained at 37-40C. Testing is carried out in a cold chamber with the device in the sleeping bag. The combination is positioned on the undermat laid out on a bed-like cart on which in turn a layer of crushed ice or snow can be provided. After equilibrium is reached the power necessary to maintain temperature is registered using a household-type power meter modified to provide an electrical output. Temperatures are sensed by thermocouples. Comparisons of various systems are made of the basis of heat loss through them and the temperature difference inside to out. A heat flow sensing sheet placed below the undermat detects the heat flow downward thus making evident the proportion of the heat loss which is downward to the snow versus that upward to the air. When human subjects are used as the heat source allowances are made for various factors including insensible water loss from skin. The effect of a vapour-proof liner on the apparent insulation has been evaluated.

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PLASMA GLUCOSE AND INSULIN CONCENTRATION IN EUTHERMIC AND HIBERNATING MARMOTS(Marmota flaviventris). G.L. Florant and W.A. Bauman*. Swarthmore College, Swarthmore,PA 19081 and Montefiore Hospital and Medical Center, Bronx, N.Y. 10467.

Pancreatic B cell function was investigated in euthermic and hibernating marmots by measuring plasma glucose(PG) and insulin (PI) concentration under normal conditions and following dextrose injection(500mg/Kg). A thermocouple re-entrant tube for recording body temperature and a permanent aortic catheter to collect blood were implanted in each animal. The PG assay was accurate to±5mg%. The PI concentration was determined by R.I.A. which was sensitive to 10pg/ml(2.5µU/ml of sample vol.).Euthermic control PG and PI levels were 140mg% and 18µU/ml respectively. After injection of dextrose,PG values rose to ➤700mg% within 5min; PI concentrations peaked at➤125µU/ml after 5-10 min(N=6); PG and PI returned to baseline levels after 120min. Throughout bouts of hibernation,PG and PI levels did not significantly change: entrance PG and PI values were 95mg% and 9 µU/ml; hibernation values were 103mg% and 13µU/ml;arousal levels were 103mg% and 14µU/ml. Injection of dextrose during hibernation elicited a rise in PG and PI which varied with body temperature.PG concentration rose quickly and persisted elevated longer. The rise in PI was delayed and PI levels remained elevated longer. These results lead us to conclude(1) the acute phase insulin response is blunted or absent at low body temperatures, and (2) that during all phases of hibernation, PG remains a potent stimulus for pancreatic B cell insulin release.

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THE MAINTENANCE OF MUSCLE DURING HIBERNATION IN THE BIG BROWN BAT, EPTESICUS FUSCUS. M.E. Yacoe* (SPON: W.R. Dawson). The University of Michigan, Ann Arbor, MI 48109

Successful hibernation in Eptesicus fuscus requires that sufficient muscle function be retained to allow flight upon arousal in spring. In this study, the extent of muscle maintenance is described. Total pectoralis (flight) muscle mass decreases during 4 months of hibernation in captivity, but the ratio of pectoralis mass to body mass remains constant due to an overall decrease in body mass. Likewise, the regression of total pectoralis protein on body mass does not differ seasonally. Mean cytochrome c content (nmoles/g wet wt) does not differ between hibernating (hib= 63.3±3.9, n=6) and active (act= 68.6±2.3, n=23) bats. Activities (µmoles/g wet wt·min @ 37°C) of the glycolytic enzymes, hexokinase (hib= 5.3±0.9, n=6; act= 7.6±0.6, n=8; $P<.05$) and phosphofructokinase (hib= 29.5±1.3, n=5; act= 41.9±1.2, n=5; $P<.001$), are both lower while those of the β-oxidative enzyme, 3-hydroxyacyl CoA dehydrogenase (hib= 546.2±74.3, n=10; act= 371.4±30.9, n=13; $P<.05$), and the TCA cycle enzyme, citrate synthase (hib= 472.2±34.3, n=11; act= 368.4±11.0, n=13; $P<.01$), are higher in hibernating animals. Cytochrome c values suggest that aerobic capacity is maintained through hibernation. The changes in enzyme activities suggest adaptations for increased fat metabolism and glucose sparing, which may be important in minimizing muscle protein loss during hibernation. (Supported by a Rackham Block Grant)

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IN VITRO THERMAL CONDUCTIVITY AND WATER CONTENT OF RABBIT KIDNEY CORTEX AND MEDULLA. K.R. Holmes, C. Pientka*, W. Ryan*, and M.M. Chen*. Depts. of Veterinary Biosci. and Bioeng. Faculty, Mech. and Indust. Eng. and Bioeng. Faculty. University of Illinois, Urbana, IL 61801.

In the measurement of tissue thermal properties, the kidney has typically been treated as a homogeneous tissue. It is also found that reported values for postmortem kidney tissue thermal conductivity (k; W/m K) vary widely. We have investigated the relationship between the water content and k in the morphologically distinct cortex (C) and medulla (M). We measured the mass fraction of water (ω) and the cooling coefficient ($k/(\rho c)^{1/3}$ of the C and M taken from seven anesthetized, heparinized rabbits (2.5-3.5 kg). In vitro (38.7 ±1.0 C), $k/(\rho c)^{1/3}$ was measured with our pulse-heated thermistor method (Chen and Holmes, J. Biomech. Eng., In press). k was determined using $\rho = 1.05$ kg/m^3 and $c = (\omega + 0.4(1-\omega))4.19(10^6)$ J/kg K (Cooper and Trezek, Aerosp. Med. 42:24, 1971). C and M were separated and ω determined after wet and dry tissue weighing. ω of the C (.777 ±.010) was less ($P < 0.001$) than that of the M (.834 ±.014) and the product ρc for the C ($3.81(10^6)$) was less ($P < 0.001$) than that of the M ($3.96(10^6)$). Measured values of k were related to ω as $k = -0.040 + 0.664\omega$; $r = 0.88$. Significantly ($P < 0.001$) lower k for the C (0.475 ±0.009) was observed compared to that for the M (0.516 ±0.014). These data agree with, but span the range of values typically reported for whole kidney k.

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INFRARED RADIATION AND THE CORNEA: LASER THERMOKERATOPLASTY AND FUNCTIONAL PROBES. Ronald D. Reed and G.W. Mikesell, Jr*, Dept. of Biology, USAF Academy, CO 80840 and USAF Medical Center, Wright-Patterson AFB, OH 45433.

Most corneal laser exposures to date have involved highly-absorbed wavelengths (e.g., 10.6 μm) which primarily cause epithelial damage. Especially for longer exposure durations, thermal damage of this type can be modeled as a function of corneal absorption characteristics for the laser wavelengths (Reed, Health Physics, 36: 73-75, 1979). Further computer modeling has permitted selection of wavelengths for thermally probing deeper corneal layers. One finding is the potential for noncontact thermokeratoplasty through laser-induced shrinkage of stromal collagen. This requires selection of wavelengths which will deposit sufficient energy to raise the stromal temperature above 55-63°C without significant damage to other ocular media. Our experiments to date have produced alterations of corneal curvature, but with excessive secondary effects. Other studies have explored more penetrating wavelengths (e.g., 1.4 μm) which have a major effect on integrity of the corneal endothelium. Still other wavelengths (e.g., 1.25 μm) may penetrate the anterior ocular media sufficiently to have a cataractogenic effect. As explored in preliminary experiments, these findings open the possibility of using lasers to mold corneal curvature or to probe function through selected heat deposition at different corneal depths. (Laboratory studies were performed at the Laser Effects Branch, USAF School of Aerospace Medicine, Brooks AFB, TX.)

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SIMULTANEOUS MEASUREMENT OF MULTIPLE CIRCADIAN PHYSIOLOGICAL PARAMETERS FROM INDIVIDUAL RATS. D.M. Edgar*, D.C. Holley, N.L. Kerst*, C.W. DeRoshia*, and C.M. Winget. Department of Biological Sciences, San Jose State University, San Jose, CA 95192 and NASA-Ames Research Center, Moffett Field, CA 94035.

An animal model has been developed which allows us to monitor multiple physiological parameters simultaneously from unrestrained, individual, male Sprague-Dawley rats (275-300 g). Deep body temperature (DBT) and heart rate (HR) were sampled via surgically implanted radio telemetry transmitters. Nalgene metabolic cages were modified with a fraction collector such that uncontaminated urine pools (urine volume, $\dot{UV}$) were collected at 3 hr intervals. Significant circadian rhythms were demonstrated in each parameter using periodogram, autocorrelation, and cosinor analyses. The table summarizes data collected from 3 rats during 10 days of controlled conditions (12L:12D, lights on 0600 hrs). Values were determined by summation dial analysis and are grand means ± SEM.

	DBT (°C)	HR (BPM)	$\dot{UV}$ (ml/3hr)	Na^+ (mEq/3hr)	K^+ (mEq/3hr)	Ca^{++} (uEq/3hr)
Rhythm Mean	38.04 ± 0.02	393.34 ± 1.48	1.24 ± 0.29	0.52 ± 0.01	0.77 ± 0.02	17.05 ± 0.83
Harmonic Amplitude	0.84 ± 0.06	38.14 ± 2.00	0.87 ± 0.36	0.24 ± 0.01	0.48 ± 0.01	5.85 ± 0.65
Acrophase (deg. ref. 0600 hrs)	270.35 ± 7.88	255.29 ± 7.56	257.86 ±14.90	283.50 ± 1.06	245.08 ± 2.24	116.15 ± 2.06

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DESYNCHRONIZATION OF CIRCADIAN HORMONAL AND PHYSIOLOGICAL RHYTHMS IN ABDOMINAL SURGERY PATIENTS. L.A. Farr, T.M. Gaspar, & D.F. Munn. (SPON: R.V. Andrews). College of Nursing, University of Nebraska Medical Center, Omaha, Nebraska 68105.

Urine, blood pressure, heart rate and temperature were sampled at two-hour intervals (0800 to 2000 hours) from twelve consenting surgical patients, daily during hospitalization and one day each week at home until individuals returned to normal activities. Urine samples were analyzed for cathecholamine metabolites, 17-ketosteriods, sodium and potassium. Data were analyzed by cosinor analysis (for rhythmicity) and Student's t-test. One patient retained circadian rhythmicity in five of the seven measured variables, two patients were rhythmic in either four or three variables, four patients were rhythmic in two variables and five patients in only one variable. Acrophase peaks of all but two individuals were phase-shifted from expected peak times. None of the subjects retained internal synchrony between acrophases and period lengths. The two individuals whose peaks were not phase-shifted returned to their normal activity schedules within seventeen days. The phase-shifted individuals took longer to resume normal activities. No other factor was unique to these two individuals. Results of this study suggest that maintenance of internal synchrony could facilitate patient's return to their typical schedules. These findings are limited, however, by the lack of measurements before entering the hospital and after return to normal schedules. Data of this type are being gathered at this time.

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EFFECTS OF 1,25 $(OH)_2$ VITAMIN D_3 ON THYROTROPIN SECRETION IN VITAMIN D DEFICIENT MALE RATS. M. Sar, W.L. Miller* and W.E. Stumpf*. Dept. Anatomy, Univ. of N.C., Chapel Hill, NC 27514 and Dept. Biochemistry, N.C. State Univ., Raleigh, NC 27650.

The demonstration of thyrotropes as 1,25 $(OH)_2$ vitamin D_3 target cells in the rat anterior pituitary (Sar, Stumpf and DeLuca, Cell Tiss. Res. 209, 161, 1980) led us to investigate the effects of 1,25 $(OH)_2$ vitamin D_3 on pituitary thyrotropin secretion. Two experiments were conducted. In the first experiment, 21 day-old, intact male rats (n=24) and in the second experiment 21 day-old, thyroidectomized rats (n=14) were used. The rats were fed on a vitamin D deficient diet supplemented with vitamins A, E and K. Five weeks later the animals were divided into two equal groups, control and experimental. Control rats received vehicle only, while rats in experimental groups each received daily injection s.c. 250 ng of 1,25 $(OH)_2$ vitamin D_3/100g body weight for 5 days. Blood was collected by decapitation 24 h after the last injection and serum was separated and assayed for TSH by double antibody RIA using NIAMD kits. 1,25 $(OH)_2$ vitamin D_3 increased serum TSH significantly ($p<.001$) in intact rats and in thyroidectomized rats, when compared with serum TSH levels of control rats. The present results in conjunction with autoradiographic localization data suggest that 1,25 $(OH)_2$ vitamin D_3 stimulates thyrotropin secretion by acting directly on thyrotropes in the anterior pituitary. (Supported by University Research Council Grant VC920 and PHS grant MSO9914).

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THE PROLACTIN SECRETING 235-1 CLONE FAILS TO EXPRESS DOPAMINE RECEPTORS OR DOPAMINE RESPONSIVENESS. M.J. Cronin and R.M MacLeod. Univ. Va. Sch. Med., Charlottesville, Virginia 22908

A new prolactin secreting 235-1 clone was derived from the 7315a anterior pituitary (AP) tumor. Studies using the dopamine (DA) antagonist ^{3}H-spiperone showed no measurable high affinity binding to homogenates of the clone (n=6). High affinity DA receptors on normal AP cells were not destroyed by mixing and homogenizing equal numbers of clone and AP cells (n=2). Low affinity binding that was not related to a DA receptor was present in the 235-1 cells. The use of a perfused cell column to study biological responsiveness revealed that neither DA (5-50 μM), bromocriptine (50nM) nor thyrotropin releasing hormone (TRH; 25 ng/ml) affected prolactin release from the clone but characteristically inhibited (DA & bromocriptine) and stimulated (TRH) prolactin release from AP (n=3). Dibutryl cAMP promptly stimulated prolactin release from both 235-1 and AP cells (n=3). The basal cAMP content of the clone was unchanged by DA (0.1-10 μM) but significantly increased by 13-16x (2.4 and 2.4 to 30.9 and 39.5 pmol/well) in the presence of PGE_1 (10 μM) during a 5 min exposure (n=2). DA did not alter the PGE_1 effect. In conclusion, although DA inhibits prolactin release from AP cells, DA does not modify prolactin release or cAMP content in the 235-1 clone. The lesion is certainly at the level of the DA receptor; whether other anomalies exist to further compromise the responsiveness, such as reduced TRH receptors, remains to be proven. (Supported by USPHS P60AM-22125-04 and CA-7535-17)

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EFFECTS OF CONTINUOUS INFUSION OF PORCINE FOLLICULAR FLUID(PFF) ON GONADOTROPIN LEVELS IN OVARIECTOMIZED RATS. Carl L. Thomas* and M.B. Nikitovitch-Winer, Department of Anatomy, University of Kentucky Medical Center, Lexington, KY 40356

The chronic effects of PFF (presumed to contain Inhibin) were examined by continuous infusion of PFF (1 ml/100 g BW/24 hrs.) for 10 days into unrestrained adult Sprague-Dawley rats ovariectomized either 1 hr. (acute ovx) or 3 months (chronic ovx) prior to infusion. Control animals in both groups received equivalent dosages of porcine serum (PS). Both PFF and PS were infused via indwelling cardiac catheters, which were also used to obtain blood samples on days 0-14. It was found that: In acute ovx rats, administration of PFF not only prevented the expected rise in FSH but also induced its decrease to hypophysectomy levels. PS had no effect in altering the rise in FSH. LH levels rose following ovx in both experimental and control rats. In the chronic ovx group, the elevated FSH levels were drastically reduced in PFF-infused rats (day 0: 1326±270 ng/ml; day 10: 289±64 ng/ml) while they remained high in PS-treated animals. LH levels remained high with either treatment throughout the experiment. When PFF infusion was terminated (day 10) FSH levels rose significantly within 24 hrs. These experiments demonstrate for the first time that PFF specifically and reversibly reduces plasma FSH levels and maintains its suppressive influence for prolonged periods of time. These newly demonstrated characteristics are propaedeutic to further progress in studies of Inhibin as a possible contraceptive agent. (Supported in part by BRSG Grant #RR05374).

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MULTIPLE SPECIES OF FSH EXIST WITHIN THE ANTERIOR PITUITARY (AP) OF THE MALE HAMSTER. Alfredo Ulloa-Aguirre* and S.C. Chappel. Dept. Ob.& Gyn., Univ. Penn., Phila, PA. 19104

FSH activity present within the AP of male hamsters was separated by two methods: Concanavalin A (Con A) chromatography and polyacrylamide gel isoelectric focusing (PAGIEF) to demonstrate species microheterogeneity. Following these separations AP FSH activity was measured by a specific radioreceptor assay (RRA) as well as the NIH FSH radioimmunoassay (RIA). When AP extracts were chromatographed across Con A, two peaks of FSH activity were observed by RRA and RIA. The RRA:RIA ratio of the Con A unbound species was 0.64 whereas the RRA:RIA ratio was 1.35 for the Con A bound species. When AP extracts were separated by PAGIEF, six species of FSH were detected by RIA. One of the six species was not recognized by RRA (pI=4.2). Of the five components recognized by RRA, two exhibited RRA:RIA ratios >1(pIs=6,5.6), one showed similar FSH activities (pI= 5.2) and the other two (pIs=5.0,4.6) exhibited RRA:RIA ratios <1. The results of the present study demonstrate that:1)multiple species of FSH exist within the male hamster AP which may be separated by Con A chromatography and PAGIEF;2)of the six species separated by PAGIEF, five appear to be intact hormone as evidenced by their ability to bind to a biological receptor 3)the RRA:RIA ratio of FSH activity of the species so separated was not always one, thus suggesting that the different physical properties of each (perhaps carbohydrate content) play a role in receptor binding. (Supported by NIH Grant #RO1-HD-14742-01)

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GONADOTROPIN RELEASE FROM SUPERFUSED, MICROCARRIER ATTACHED PITUITARY CELLS:COMPARATIVE EFFECTS OF PULSATILE & CONTINUOUS LHRH. James L. O'Conner*, Raymond R. Wolfe* and Carol A. Lapp* (SPON: V. B. Mahesh). Med. Col. of Georgia, Augusta, GA 30912

The purpose of these studies was to determine the comparative effects of pulsatile LHRH of increasing concentration (0,2,4,6, 8,10,12,14,16 ng/100 μl) as well as pulsatile and continuous LHRH of fixed concentration (4 ng/100 μl) on LH release from anterior pituitary cells. Tissues from 65 day female rats were trypsinized, attached to Cytodex I beads and loaded into a 3 ml syringe attached to a superfusion apparatus. LHRH was added to the superfusion buffer, thereby defining the temporal relationship between stimulation and response. Most reports have used pulses of several minutes duration; however, the present 100 μl pulses exposed the cells to smaller masses of LHRH than would have longer pulses at the same LHRH concentration. At a flow rate of .25 ml/min, pulsed LHRH cleared the system in the 8-28 min period subsequent to administration with maximum concentration reached at 16 min. The response pattern conformed to the same profile. Results suggest that (1) response does not require a large stimulating mass of LHRH; (2) both pulsatile and continuous LHRH of fixed concentration will desensitize if administered properly; (3) small increases in the concentration of LHRH pulses will extend pituitary responsiveness. The latter two results indicate that desensitization may occur in response to a repetitious concentration of LHRH rather than the pattern of LHRH administration. The manner in which LHRH stimulation is applied significantly affects the pattern of response. (Supported by NICHD grant HD-13100).

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DEVELOPMENT OF THE SELF-PRIMING EFFECT OF LHRH DURING THE SEXUAL MATURATION OF THE MALE RAT. S.J. Nazian* (SPON: R.P. Menninger). Department of Physiology, College of Medicine, University of South Florida, Tampa, FL 33612.

Pubertal (54 day old) male rats release more LH in response to LHRH if "primed" with small doses of LHRH than if pretreated with saline. Immature (30 day old) rats do not show this self-priming effect. To determine more precisely the age of onset of this response and to relate it to serum androgens, the following experiment was performed every 4 days from day 30 through day 54. Rats were anesthetized with ketamine HCl (10-20 mg/kg) and a blood sample obtained by heart puncture for RIA of testosterone (T) and androstenedione (A). Animals were then injected via the right jugular with 10 ng LHRH/100g BW or saline at time 0,30 and 60 min. At 90 min a blood sample was obtained, followed by an injection via the left jugular of 50 ng LHRH/100g BW. A final blood sample was obtained at 100 min. LH in the 90 and 100 min samples was determined by RIA. LHRH priming first resulted in a significant ($p < 0.01$) increase in LH increment at 46 days. Peripheral T and A were first significantly ($p < 0.05$) elevated and the ratio A/T first significantly ($p < 0.05$) decreased on day 42. These data indicate that the LHRH self-priming effect develops in the male rat between day 42 and 46 and appears to be preceded by changes in testicular steroid secretion.

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EPISODIC SECRETION OF TESTOSTERONE IN INDIVIDUAL MALE RATS. Gary B. Ellis* and Claude Desjardins. Department of Zoology, University of Texas, Austin, Texas, 78712.

Studies of diurnal variations in circulating T levels in *groups* of adult male rats have yielded inconsistent results. Reports describe a single daily elevation in plasma T, a bimodal pattern, and a trimodal pattern. Peak T levels are reported at a variety of times through the day and night. We reasoned that a consideration of the pattern of T secretion in *individual* animals would reveal the basis for the previous conflicting findings. Rats were fitted with an atrial cannula, and on 3 occasions (5, 10, and 15 days post-cannulation) blood was withdrawn every 5 min for 8 h (96 samples @ 0.2 ml). Withdrawn blood was replaced by a mixture containing 45% rat red blood cells and 2.5% human plasma proteins in Krebs-Ringer solution. Blood sampling was completed during the light hours of an LD 14:10 photoperiod. Episodes of T secretion spanned 3-6 h and were characterized by a slowly graded rise and fall of plasma levels. T peaked at levels 2- to 4-fold greater than circulating basal levels. Within a particular animal, on different days, T episodes varied in amplitude and timing. Thus, a particular secretory profile did not serve as a consistent hormonal "signature" for an individual rat. Because of the great plasticity in individual patterns of T secretion, grouped data are highly variable and potentially misleading. Moreover, consideration of individual hormonal profiles will lead to the description of testicular responses to discrete signals from the pituitary (i.e., LH pulses). [NIH HD-13470]

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INHIBITION OF ESTROGEN BIOSYNTHESIS VIA SUBSTRATE-INDUCED INACTIVATION WITH 10-ALLENYL-ESTR-4-EN-3,17-DIONE (RMI 18,882). J.O. Johnston*, C.L. Wright* and B.W. Metcalf* (SPON: D.M. Baldwin). Merrell Research Center, Merrell Dow Pharmaceuticals, Cincinnati, OH 45215.

Bioconversion of androgens to estrogens is catalyzed by aromatase. Selective inactivation of this enzyme may provide a therapeutic approach for regulation of estrogen-dependent processes. Aromatization is dependent upon cytochrome P-450 which requires NADPH for the sequential hydroxylation at C-19 position. The presence of an allene in this position as in RMI 18,882 (10-(1,2-propadienyl)-estr-4-en-3,17-dione) could cause the formation of a highly reactive allene oxide at the active site which would then alkylate the enzyme. The addition of RMI 18,882 to microsomal preparations containing aromatase from human placenta caused time-dependent loss of enzyme activity which followed pseudo-1st order kinetics, $K_i=1.4\times10^{-8}$. The enzyme $t_{\frac{1}{2}}$ at infinite conc. was 24 min. This inactivation was protected by the substrate, testosterone, indicating the inhibition was active-site directed. The time-dependent loss of enzyme activity didn't occur in the absence of NADPH generating system, suggesting the inhibitor required activation prior to enzyme alkylation. The compound did not dissociate from the active-site since enzyme activity was not restored after 24h dialysis. These data indicate RMI 18,882 acts as a substrate which induces active-site directed, irreversible inhibition of aromatase.

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ETHANOL AFFECTS ON THYMIC ESTROGEN RECEPTOR KINETICS. CJ Grossman and CL Mendenhall, Research Service, VA Medical Center, Cincinnati, Ohio.

The thymic (T) reticulo-epithelial cells contain estrogen receptors (ER) which we have previously characterized. These ER function as modulators of the T-cell immune response (IR), such that estradiol suppresses while castration stimulates. Male rats 100 g, were divided into groups for pair feeding: controls (C) vs ethanol (E) and castrate controls (CC) vs castrate ethanols (CE). E animals received 35% of caloric intake as E substituted isocalorically for carbohydrate (Lieber diet). On this regimen, the mean daily E consumed was 12.96 gm/kg/d. After 35 days of treatment, animals were decapitated and the thymus removed, weighed and homogenized in buffer (.05M Tris, 1mM EDTA) and cytosol isolated by high speed centrifugation. Thymic ER were measured by modified scatchard plot analysis. ER from C had a KA($\times10^9 M^{-1}$) of 1.09 ± .15 (mean ± SEM, n=4) which was not significantly different from E treatment (1.51 ± .18, n=4), but was significant ($P < .05$) with respect to the CC group (1.77 ± .22, n=5). The KA for ER from CC group was also significantly different ($P < .007$) from CE group (3.39 ± .41, n=4). By analysis of varients the KA of these groups was highly significant ($P < .0002$). It is concluded that while castration increases the KA of thymic ER, this effect is markedly potentiated by E.

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EFFECT OF SYNTHETIC ESTROGENS ON ARACHIDONATE TOXICITY IN MICE. A. Myers*, D. O'Day*, A. Papadopoulos*, E. Ramey, P.W. Ramwell and J.C. Penhos. Department of Physiology and Biophysics, Georgetown University, Washington, DC 20007.

We showed previously that estradiol (E_2) pretreatment is protective against mortality induced by IV sodium arachidonate (SA) in castrated but not intact male mice. E_2 had no effect in females in this thrombosis model. We have now tested two synthetic estrogens, diethylstilbestrol (DES) and ethinyl estradiol (EE_2). Intact adult male and female mice were pretreated subcutaneously with 30 ug/kg DES in oil, 0.5, 1.5 or 50 ug/kg EE_2 in oil, or an equal volume of vehicle daily for 7 days. Mice were then anesthetized and infused IV with 50 mg/kg SA and mortality was recorded. DES had no effect on mortality, with 71% mortality (15 of 21) in both pretreated and control males, and 48%(10 of 21) in pretreated vs. 38% (8 of 21) in control females. EE_2 had no effect in females, with 45%(9 of 20), 55%(46 of 84) and 48%(10 of 21) mortality for 0.5, 1.5 and 50 ug/kg pretreatments, respectively, compared to 43%(9 of 21), 49%(41 of 84) and 58%(11 of 19) for the respective controls. Males at these same EE_2 doses had mortality of 61%(11 of 18, n.s.), 58%(23 of 40, $p<0.05$) and 38%(8 of 21, $p<0.05$), respectively, vs. 85%(17 of 20), 78%(32 of 41) and 71%(15 of 21) in the corresponding controls. Thus, an estrogenic compound, EE_2, is significantly protective in intact male mice against SA toxicity. Females, which are less susceptible to SA induced mortality and have higher levels of endogenous estrogens, are not protected by exogenous estrogens.

VASCULAR SMOOTH MUSCLE II

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INTRACELLULAR ELECTRICAL ACTIVITY ASSOCIATED WITH MECHANICALLY EFFECTIVE NEURAL INPUT IN SUBMUCOSAL ARTERIOLES AND VENULES. Kathleen G. Morgan. Mayo Clinic, Rochester, MN 55905

Segments of the cat gastric submucosa were dissected from the mucosa and muscularis, pinned to the floor of a bath and superfused with an oxygenated, warmed (37°C) Krebs solution. The preparation contained an arterial and venous vascular tree extending from the 1st order vessels (which connect to the mesenterics) to the 3rd and 4th order branches (which enter the mucosa). Vessel diameter was measured through an inverted microscope and intracellular potential monitored with microelectrodes. Resting potentials in venules (-54±1.2mV, n=33) were significantly more positive than those in arterioles (-66±.6mV, n=79). All orders of arterioles and venules constricted during perivascular nerve stimulation at the mesenteric end of the first order vessels. In arterioles, single shocks consistently resulted in excitatory junction potentials (EJP's). Single EJP's occasionally triggered apparently regenerative responses (AP's) which were consistently associated with vessel constriction. However, constriction also occurred in association with large (7-28mV) EJP's in the absence of AP's, suggesting that AP's are sufficient but not necessary for contraction of these vessels. In venules, single EJP's were detectable in only 1 out of 33 vessels. Repetitive stimulation, however, resulted in graded depolarizations. Depolarizations as small as 2mV were associated with venular constriction. These results suggest that, in comparison to arterioles, venules have an increased mechanical sensitivity to depolarization and that this difference may be explained by the closer proximity of the venular resting potential to a mechanical threshold. Support: USPHS Grants HL 07111, HL 12186, and NS 14268.

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SPONTANEOUS ELECTRICAL ACTVITY IN SMALL PRESSURIZED MESENTERIC ARTERIES. Elane Zelcer* and Nick Sperelakis. University of Virginia, Charlottesville, Va 22908.

Some vascular smooth muscles (VSM) e.g. rat portal vein, exhibit spontaneous action potentials (APs), but such activity has not been reported in arterial VSM. Electrical activity was studied in guinea-pig small (100-200 μm) isolated mesenteric arteries pressurized to 40 mm Hg and held at 37°C. In most preparations, spontaneous APs were recorded, and had resting potentials of -35 to -55 mV, AP frequencies of 36-54/min, and amplitudes of 12-30 mV. Activity persisted in 10^{-6}M guanethidine or 10^{-6} g/ml tetrodotoxin (TTX), indicating myogenic origin. Sympathetic nerve stimulation (single 0.5 ms field stimuli) evoked APs between spontaneous APs and could drive the cells; this effect was blocked by TTX. During a single impalement, decreasing temperature to 35°C for 1-3 min, decreased spontaneous AP frequency. Spontaneous activity was never recorded in preparations equilibrated at 35°C. Addition of the vasodilator, adenosine, decreased AP amplitude and frequency reversibly. Although most arterial preparations are electrically inexcitable in vitro unless stimulated by the sympathetic nerves or unless inhibitors of K conductance are present, this arterial VSM shows spontaneous APs under physiological conditions of temperature and pressure. The spontaneous activity is similar to that recorded in vivo from guinea-pig and rat mesenteric arteries (Speden, 1964; Steedman, 1966). Such activity might be important in the physiological regulation of blood vessel tone. (Supported by NIH Grant #2P01 HL-19242).

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ALTERED ELECTRICAL PROPERTIES IN SMOOTH MUSCLE CELLS OF SMALL CEREBRAL ARTERIES FROM HYPERTENSIVE RATS. David R. Harder, Linda Brann* and William Halpern. Dept. of Physiology and Biophysics; University of Vermont, Burlington, VT. 05405

Some electrical properties of muscle cells from middle cerebral arteries of hypertensive (SHR) and normotensive (WKY) rats were measured. Under control conditions the muscle cells of arteries from SHR rats exhibited spontaneous electrical spike activity, and slow and fast oscillations in the resting membrane potential (E_m) when impaled with microelectrodes. In marked contrast the E_m of the muscle cells from WKY middle cerebral arteries was quiescent. The curves of E_m vs log $[K]_o$ were not different between arteries from SHR and WKY rats, and extrapolated to similar values of $[K]_i$. However, in the presence of ouabain the slope of the E_m vs log $[K]_o$ curve was greater in WKY rats and at all values of $[K]_o$ < 90 mM the degree of depolarization was greater in arteries from SHR rats. The rapid oscillations in E_m in arteries from SHR were voltage inactivated at ≈-30 mV leaving regularly occurring slow membrane oscillations which could be blocked by ouabain. These data suggest that smooth muscle cells of cerebral arteries from SHR have a greater electrogenic component to their E_m as well as altered permeabilities for K^+ and possibly Na^+ which both contribute to the spontaneous electrical activity not observed in cerebral arteries from WKY rats. These altered membrane properties in SHR rats may make these arteries more sensitive to neural and/or humoral stimuli. (Supported by NIH grants HL-27862 and HL-17335).

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EFFECT OF OUABAIN ON MEMBRANE POTENTIAL (Em) AND SODIUM (Na) KINETICS IN CAROTID ARTERIES OF AGED RATS. **Jane A. Madden,* William J. Willems and Steven R. Gambert*. The Medical College of Wisconsin at VAMC, Milwaukee, WI 53193**

Na-K ATPase activity declines with age in several rat tissues. Changes in ouabain-dependent Em and Na kinetics in rat carotid artery might reflect a corresponding decline in Na-K pump activity. Carotid vessels of 6 month (mature) and 20 mo old (senescent), male Sprague Dawley rats were mounted in an in vitro suffusion chamber and intracellular Em measured under control conditions and during ouabain suffusion with glass microelectrodes. Paired carotid arteries were incubated in ^{22}Na and radioactivity remaining in the tissue counted during washout with nonradioactive solution. This procedure was duplicated for tissues treated with ouabain during incubation and washout. Resultant data were processed by computer and efflux rate constants determined for both groups. The Em was not different in control arteries. However, the Em depolarization induced by ouabain was greater (P .05) in arteries from younger rats (26 mV vs 18 mV). Rate constants derived from Na washout curves in 6 mo ouabain treated carotids were significantly less than corresponding controls during several mid-curve time intervals. This result suggests impairment of Na efflux by ouabain. The rate constant in 20 mo ouabain treated arteries was not significantly different from controls. These data are consistent with the hypothesis that the Na-K pump is impaired in aged vessels, resulting in a lower electrogenic Em effect and decreased ouabain-dependent Na efflux.

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BLOOD PRESSURE AND SMALL VESSEL REACTIVITY IN MALE RABBITS OF DIFFERENT AGES. Thomas Lon Owen. Northern Arizona University, Flagstaff, Arizona 86011

A previous study in our laboratory indicated no significant differences in reactivity of vascular smooth muscle from female rabbits of different ages. To determine if male rabbits show the same pattern of vascular reactivity with age, direct blood pressure measurements were made on groups of male rabbits ranging from 3 months to over 24 months of age. The animals were sacrificed and strips of smooth muscle from the ear artery and skeletal muscle artery were removed and treated with norepinephrine, potassium, histamine and isoproterenol. Heart rate did not differ among different age groups but blood pressure showed a significant increase, then a leveling off with age. Vessel thickness increased with age, whereas vessel sensitivity to norepinephrine apparently decreased with age. The results suggest that male rabbits, unlike females, may show significant differences in vessel size and reactivity with age. It also appears that aging effects on blood pressure are not positively correlated with vascular sensitivity to norepinephrine. (Supported in part by USPHS. NIH Grant AGO #1112-03.)

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EFFECTS OF HISTAMINE ON CIRCULAR AND LONGITUDINAL MUSCLE LAYERS OF PERFUSED PORTAL VEIN. Bruce P. Brown*, Sinn Anuras, and Donald Heistad, Department of Internal Medicine, University of Iowa and VA Hospital, Iowa City, Iowa 52242.

We found previously, in vascular strips, that the circular muscle layer of the rabbit portal vein is more responsive to histamine than the longitudinal layer. The present study was performed to determine the effects of histamine in perfused portal vein. We perfused the portal vein of 8 rabbits at constant flow in vitro. Perfusion pressure was used as an index of responses of circular muscle. Tension in the long axis of the vein was used to reflect responses of longitudinal muscle. Peak perfusion pressure and tension were measured during infusions of 10^{-5}, 10^{-6}, 10^{-7}M acetylcholine (ACH) and histamine (H). ACH produced greater increases in tension than H ($p< .05$); for example, with 10^{-5}M infusions, increasgs in tension were: ACH $3.5x10^3 \pm 300$ dynes (mean ±SD), H $0.9x10^3 \pm 200$ dynes. In contrast, the increase in perfusion pressure was greater with infusions of 10^{-5}M H than with ACH ($p<.05$); H 2.2±.3mmHg vs. ACH .76±.3mmHg. Chlorpheniramine ($5x10^{-6}$M) produced specific, reversible blockade of the response to H in both layers of the perfused portal vein, while cimetidine (10^{-3}-10^{-4}M) did not reduce the response to H. We conclude: 1) In perfused portal vein of the rabbit, histamine (in contrast to ACH) affects circular muscle more than longitudinal muscle. 2) The effect of histamine on longitudinal and circular muscle is mediated by H_1 receptors. (Supported by Iowa Heart Grant and NIH Grant No. HL00795-02.)

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ENDOTHELIUM AND ARTERIAL EFFECTS OF ADENINE NUCLEOSIDES. J. G. De Mey and P. M. Vanhoutte. Division of Pharmacology, Faculty of Medicine, University of Antwerp, Wilrijk, Belgium.

To determine the role of the endothelium in the responses of isolated arteries to adenine nucleosides, rings of canine femoral arteries, with or without endothelium, were mounted for isometric tension recording. During norepinephrine (NE) induced contraction of control rings, adenosine (AD), AMP, ADP and ATP caused relaxation (order of potency : ATP = ADP > AMP = AD); theophylline inhibited the response to AD and AMP. Removal of the endothelium abolished the relaxations induced by ADP and ATP, but not those by AD and AMP. In control and endothelium free preparations, contracted with NE, the degradation resistant analogues $\beta\gamma$-CH3-ATP (APPCP) and $\alpha\beta$-CH3-ATP (APCPP) caused further increases in tension; in the control rings this effect was transient and followed by relaxation. The relaxations induced by ATP were not affected by indomethacin, mepacrine, eicosatetraynoic acid, tranylcypromine, APPCP or APCPP. These experiments indicate that : (1) inhibitory P_1 and excitatory P_2 receptors are present on arterial smooth muscle cells; and (2) the endothelial cells mediate the relaxant effect of ATP (and ADP) presumably through the involvement of endothelial ADP-ase rather than prostanoid formation.

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RELATION BETWEEN FRACTIONAL α_1 —ADRENERGIC RECEPTOR OCCUPATION AND CONTRACTILE RESPONSE IN VASCULAR SMOOTH MUSCLE. A. Sastre*, K. K. Griendling*, M. M. Rusher*, and W. R. Milnor, Johns Hopkins Univ. School of Medicine, Baltimore, Md. 21205

The relation between α_1-receptor occupation by an agonist and the contractile response of vascular smooth muscle was examined. The agonist used was L-phenylephrine (PE), in strips of canine ascending aorta. Isometric force generated per cross-sectional area (F/A) in vitro by PE (10^{-8} to 10^{-3} M) was the index of contractile response. Displacement of ^{3}H-prazosin bound to tissue homogenates by PE was used to determine the fractional receptor occupation. The concentration-response curves for PE were shallow, with a Hill coefficient of 0.64, and an ED50 value of 8.4×10^{-7}M. In contrast, PE bound to the receptor with a K_D of $\sim 9.1 \times 10^{-6}$M and a Hill coefficient near unity. The curve relating receptor occupation to response was consequently non-linear, and 50% of the maximum response appeared when 6% of the receptors were occupied. Maximal response occurred only with 100% occupation, implying that there were no "spare" receptors. Qualitatively similar results were obtained in strips of canine descending thoracic and abdominal aortas. (Supported in part by USPHS NIH Grants HL-12607 and HL-22675).

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REGIONAL DIFFERENCES IN α_1 —ADRENERGIC RECEPTOR NUMBERS AND ISOMETRIC FORCE IN CANINE AORTA. K.K. Griendling*, R.S. Green*, M.M. Rusher*, A. Sastre*, and W.R. Milnor. Johns Hopkins University School of Medicine, Baltimore, Md. 21205

Consecutive 2-cm segments of aorta, from aortic valve to mid-abdomen, were studied in vitro to determine the longitudinal distribution of α_1-receptors and isometric tension development. Maximum active isometric force per unit cross-sectional area (F/A) developed in response to L-phenylephrine (PE) was compared with the number of receptors in each segment. Binding of ^{3}H-prazosin by tissue homogenates was used to measure the number of receptors per gram of tissue (R_T). R_T decreased significantly with increasing distance from the aortic valve, falling from 456 fmol/gm tissue in the ascending aorta to 129 in the abdominal aorta (n=55, r = -.685, p < .001). The F/A was greater in the ascending aorta than in more distal regions, but there was no significant trend in the descending thoracic or abdominal aorta. Affinity of receptors for PE and prazosin was essentially the same in all regions (mean K_D for PE ~ 8 μM, for prazosin 90 pM). The binding characteristics of the receptors themselves were thus constant along the aorta, but the isometric force associated with occupation of a single receptor by PE increased with distance from the heart. The results suggest that the arterial tree exhibits quantitative, regional differences in the steps between receptor occupation and contractile response. (Supported in part by USPHS NIH Grants HL-12607 and HL-22675).

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POSTJUNCTIONAL ALPHA-2 ADRENERGIC RECEPTORS IN VASCULAR SMOOTH MUSCLE FROM SPONTANEOUSLY HYPERTENSIVE RATS (SHR). Joyce C. Johnson* and R. Clinton Webb. Univ. of Michigan Medical School, Ann Arbor, MI 48109

The selective alpha-2 adrenergic antagonist, yohimbine, was used to characterize postjunctional alpha-2 receptors in vascular smooth muscle from SHR and Wistar Kyoto normotensive rats (WKY). Tail arteries were cut helically into strips; the strips were mounted in organ chambers; and isometric contractions were recorded. Cumulative addition of clonidine ($4.3x10^{-10}$ to $4.3x10^{-5}$ M), an alpha-2 adrenergic agonist, produced contraction in arterial strips from both groups of rats. Arterial strips from SHR were more sensitive to clonidine than were those from WKY [SHR ED_{50} (N=8)=$5.7x10^{-8}$ M; WKY ED_{50} (N=8)=$24.5x10^{-8}$ M; $p < 0.05$]. Yohimbine ($8.6x10^{-8}$ to $8.6x10^{-7}$ M) was a competitive antagonist against clonidine. The competitive antagonistic properties of yohimbine (determined by Schild plot) were more pronounced in tail artery strips from SHR than in those from WKY [SHR -log K_B (N=4)=7.64; WKY -log K_B (N=4)=7.00; $p < 0.05$]. These results demonstrate that contraction induced by clonidine is mediated by alpha-2 adrenergic receptors in rat tail artery. The sensitivity of the receptors to clonidine is greater in tail arteries from SHR; and the affinity of the receptors for yohimbine is greater in SHR. (Supported by NIH grants HL-18575 and HL-00813 and grants from the Michigan Heart Association and the Michigan Memorial Phoenix Project)

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MECHANISMS OF ACTION OF DILTIAZEM ON MESENTERIC ARTERIAL MUSCLE. Eugene D. Jacobson, Joseph D. Fondacaro and Joseph DiSalvo. College of Medicine, University of Cincinnati, Cincinnati, OH 45267.

We examined effects of diltiazem (D), a calcium (Ca^{2+}) antagonist and mesenteric vasodilator agent, on helical mesenteric arterial strips (2x10 mm) contracted in a muscle bath preparation with KCl, which relies heavily on extracellular Ca^{2+}, and/or norepinephrine (NE), which mobilizes both extracellular and intracellular Ca^{2+}. With KCl (5-70 mM) graded doses of D (10^{-9}-$5x10^{-7}$M) produced mixed inhibition as shown by progressive increases in ED_{50} (20-40 mM) and decreased (20-60%) maximal tension attained (Tmax). With NE (10^{-8}-$3x10^{-5}$M) inhibition with low doses of D (below $5x10^{-8}$M) increased the ED_{50} for NE but did not alter Tmax (competitive inhibition), whereas higher doses ($5x10^{-8}$M) increased ED_{50} and decreased Tmax (mixed). These findings support the inference of a model involving three sites of Ca^{2+}-D interaction, namely (1) a voltage dependent, membrane Ca^{2+} channel where both D and KCl have pronounced effects, (2) a receptor mediated, voltage independent membrane channel at which NE has major effects and which is blocked by high concentrations of D, and (3) an intracellular site at which D and NE exhibit pronounced effects and KCl has minor effects.

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BIOCHEMICAL AND MECHANICAL CORRELATES IN SHR CEREBRAL AND MESENTERIC RESISTANCE BLOOD VESSELS. Joseph E. Brayden and William Halpern. University of Vermont, Burlington, VT 05405

The contractile protein composition of mesenteric (-mes) and posterior cerebral (-cer) resistance arteries (150μm, I.D.) of 25 week old normotensive Wistar Kyoto (WKY) and Spontaneously Hypertensive (SHR) rats was measured. Micro techniques for tissue homogenization and slab gel electrophoresis, and a highly focused laser beam densitometer were used to quantify actin (A) and myosin (M) extracted from about 100 μg of blood vessel. The following results were obtained:

	WKY-mes	SHR-mes	WKY-cer	SHR-cer
A/M (μg/μg)	2.0±0.3	2.1±0.2	2.1±0.2	3.0±0.3*

* SHR-cer significantly different (ANOVA, $p<0.01$) from all others. No differences among WKY-cer, SHR-mes, and WKY-mes values. Values are mean±S.D., n=3.

Estimates of cerebral vessel actin and myosin content (μg per μg tissue weight) indicate that the elevated SHR-cer A/M is due to a 44% decrease in myosin content and a 20% decrease in actin. This laboratory reported the same active smooth muscle stress in SHR-mes and WKY-mes (Warshaw, et al., Blood Vessels 17:257, 1980). For these vessels a change in A/M would not be predicted, and was not found. In contrast, recent findings in this laboratory (unpublished) suggest a 23% decreased active smooth muscle stress in SHR-cer vs WKY-cer. This finding may be explained in part by the lowered contractile protein content observed in SHR-cer. (Supported in part by NIH HL 26383)

PULMONARY CIRCULATION

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EFFECT OF LUNG INFLATION ON RESISTANCES OF DIFFERENT PARTS OF THE PULMONARY VASCULATURE. T.S. Hakim*, R.P. Michel* and H.K. Chang. Meakins-Christie Labs and Lyman Duff Lab, McGill Univ. Montreal, Canada, H3A 2B4.

Using the arterial and venous occlusion method at constant blood flow, we studied the effect of negative pressure lung inflation on the resistances of the arterial (R_a), venous (R_v) and middle (R_m) compartments in isolated left lower lobes of dogs, either in Zone III (zero venous pressure at the top of the lobe) or in Zone II (zero venous pressure at the bottom of the lobe) conditions. We observed a U-shaped relationship between the total vascular resistance (R_t) and the transpulmonary pressure (P_{tp}) with a minimum R_t at P_{tp} = 10 mm Hg (FRC). The U-shaped curve had a greater concavity when inflation was carried out in Zone II conditions. Below FRC (P_{tp} = 0), R_v rose by 20% in Zone III but by 92% in Zone II. Above FRC (P_{tp} = 20 mm Hg), R_m rose by 135% in Zone III but by 228% in Zone II. There were also increases in R_v and R_a above FRC, and in R_m and R_a below FRC; these increases were not significantly altered by the zone conditions. We conclude that the U-shaped curve which describes R_t vs P_{tp} is due to changes in R_a, R_v and R_m in the same condition. The rise in R_t below FRC reflects the influence of falling transmural pressures, whereas the rise of R_t above FRC reflects the influence of increasing lung volume. The concavity of the U-shaped curve depends to a large extent on the venous pressure relative to the height of the lobe (Supported by the MRC of Canada Grant MA-6474 and by USPGS Grant HL-24348).

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MICROPUNCTURE EVIDENCE FOR THE SITE OF VASCULAR COMPRESSION IN ISOLATED ZONE II DOG LUNG. J. Bhattacharya, S. Nanjo* and N.C. Staub. Cardiovascular Research Institute and Dept. of Physiol., University of California, San Francisco, CA 94143.

By lung micropuncture we have shown that in Zone III (venous pressure > alveolar pressure) the pressure drop downstream from 50 μm diameter venules is negligible (SCIENCE 210:327, 1980). In each of 5 blood perfused left lower lobes we micropunctured 4 subpleural 50 μm venules to measure pressure (servo-null technique) in both Zones III and II (venous pressure < alveolar pressure). We held arterial and alveolar pressures constant but varied venous pressure to steady levels above and below alveolar pressure. The table shows the summary pressure data in cmH2O (mean ± 1 S.D.).

Zone	Artery	Vein	50 μm Venule	Airway
III	17.7±0.6	10.3±.6	10.5±.2	7
II	17.5±0.3	2.9±.6	6.8±.5	7

The pressure drop between the 50 μm venules and the lobar venous outflow was 3% of total pressure drop in Zone III and increased significantly to 26% in Zone II. The principal site of vascular compression in Zone II is not in the alveolar wall capillaries but downstream in veins larger than 50 μm diameter (Supported in part by HL25548).

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THE IMPORTANCE OF ENDOTHELIUM IN THE ECONOMY OF NOREPINEPHRINE RELEASED FROM ADRENERGIC NERVE ENDINGS IN CANINE PULMONARY ARTERY. D.K. Rorie* and G.M. Tyce* (SPON: C.A. Owen, Jr.). Mayo Clinic and Mayo Foundation, Rochester, MN 55905.

The present experiments were done to determine whether endothelial cells, which are known to be metabolically very active in lung, are important in the removal of norepinephrine (NE) from junctional clefts in pulmonary artery. Pulmonary artery segments (3-4 mm diam) were cut into helical strips. Some of the strips were denuded of endothelium by gently stroking the intimal surface with a wooden applicator; control strips were left intact. After incubation in L-[^{3}H]NE ($6x10^{-7}$M) strips were mounted for superfusion and isometric tension recording. Superfusate was collected continuously before, during and after electrical stimulation (10 V, 2 msec, 2 Hz). Measurements were made of the amounts of [^{3}H]NE and its metabolites in superfusate and in tissue. Under basal, unstimulated, conditions somewhat more NE, more 3,4-dihydroxyphenylglycol (DOPEG) and less O-methylated metabolites (OMM) were released into superfusate from denuded veins than from control veins. Electrical stimulation elicited the overflow of large amounts of NE, DOPEG and OMM into superfusate in intact strips; in denuded strips there were striking decreases in the amounts of OMM produced. It is concluded that pulmonary endothelium participates in extraneuronal removal of NE released into junctional clefts by nerve stimulation; NE taken up into endothelium is primarily O-methylated. (Supported in part by HL 23217 and NS 9143.)

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HYPOXIC CONTRACTILE RESPONSES OF RAT MAIN PULMONARY ARTERY IN VITRO. Omar Hottenstein*, W. Mitzner, and J.T. Sylvester, The Johns Hopkins Medical Institutions, Baltimore, Md. 21205

Studies showing hypoxic vasoconstriction in isolated pulmonary vessels have required special, often non-physiological procedures. We have been able to demonstrate hypoxic contractile responses in vessels, not treated pharmacologically, in an aqueous media with glucose present. Main pulmonary arteries (MPA) from 7 male Sprague Dawley rats (2-15 mo.; 240-840 gm) were isolated and incubated in a modified Krebs-Henseleit solution (ph=7.536, PCO_2=30.5 torr, t=37°C). During alternating 41 min periods of high and low PO_2 (509 and 44 torr, respectively) isometric resting tensions and field stimulated active developed tension responses were recorded at 7 min intervals during all periods for 5 hours. Baseline tensions recorded after 30 min in each period were significantly elevated during hypoxia compared to high O_2 ($p<.05$). In the 2nd, 3rd, and 4th high O_2 periods the baseline tensions were reduced ($p<.01$), but the low O_2 baseline tensions were not changed. Thus, the difference in tension between low and high PO_2 increased progressively. Active responses in the first low O_2 trial were not significantly different from those in initial high O_2. Active tensions for the 2nd and 3rd low O_2 periods were significantly elevated after 12 min. when compared to a previous or subsequent high O_2 period ($p<.01$). We conclude that rat MPA studied in vitro repeatedly demonstrate increased baseline tensions and maintain greater sensitivity to electrical stimulations during hypoxic episodes.

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ANALYSIS OF CYCLIC HYPOXIC PULMONARY VASOCONSTRICTION. B.J.B. Grant and A.M. Schneider*. Departments of Medicine and of Applied Mechanics and Engineering Sciences, University of California San Diego, La Jolla, CA 92093 and Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109.

When the left lower lobe (LLL) of a dog is ventilated with nitrogen, LLL pulmonary blood flow ($\dot{Q}$) and alveolar CO_2 oscillate in a progressively damped fashion. This damped oscillatory response of blood flow can be abolished by maintaining LLL alveolar CO_2 constant (Benumof et al J. Appl. Physiol. 41:466-469, 1976). We set out to develop a mathematical model with realistic physiological parameters that behaves in a similar manner. Different models were tested. The simplest model that simulates the experimental results incorporates the additive effects of an exponential decrease of lobar $\dot{Q}$ in response to alveolar hypoxia (time constant 2 min) and a damped oscillatory response to alveolar hypocapnia. The hypocapnic response has two components: a vasodilator effect possibly related to decreases in hydrogen ion concentration and a vasoconstrictor effect possibly related to decreases in molecular CO_2. Both components (time constants of 3.5 min) interact by crosscoupled elements (time constants of 3.5 min). The model can be used to design experiments to test its validity. (Supported by Dorothy Temple Cross MRC Travelling Fellowship, Parker B. Francis Foundation, John F. Perkins, Jr. Memorial Fund, NIH Grant HL 17731, California Lung Association, University of Michigan Medical School Funds for Computing).

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COMPETITION BETWEEN ACUTE HYPOXIA AND CATECHOLAMINES FOR THE PULMONARY VASCULAR ALPHA CONSTRICTOR MECHANISM. R.J. Porcelli and M.V. Cutaia*. VAMC, Northport, N.Y. and SUNY at Stony Brook, N.Y. 11790.

The relation between the pulmonary vascular adrenergic system and acute hypoxia is a close one. Rises in pulmonary vascular resistance (RPV) in response to hypoxia and norepinephrine (NEPI) are enhanced by beta blockade and blunted by alpha blockade (JAP:34, 1973). Thus hypoxia and NEPI may share common mechanisms. This hypothesis was tested in the isoflow-perfused cat lung by comparing RPV changes when superimposing one stimulus on another. Acute alveolar hypoxia ($F_{I_{O_2}}$=0.08) itself raised RPV by 41±7% and reversed the response to NEPI (2.4ηM) to an 18±3%↑RPV($p<0.05$) compared to non-hypoxic NEPI infusion before and after hypoxia (33±5 and 29±7%, resp.). Greater NEPI concentrations (4.8 and 9.3ηM) infused during hypoxia produced larger vasodilations (-25±11 and -21±8%). However, the usual rise in RPV after 5HT infusion (2.4ηM) of 101±54% was not significantly altered during hypoxia (79±37%); thus, responses to 5HT and hypoxia were additive and no limit was demonstrated to rises in RPV with 2 non-competing agonists. These data indicate that hypoxia and NEPI share the alpha constrictor mechanism of the pulmonary circulation and that once the mechanism is utilized, the pulmonary vascular responses of NEPI reflect its β-activity. (Supported by the Veterans Administration, NIEHS-431-1373 and NHLBI-R01-HL-23210).

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REPETITIVE EXPOSURE PRODUCES AGENT-SPECIFIC ALTERATIONS IN PULMONARY VASCULAR RESPONSIVENESS, Cutaia, M.V.*, and R.J. Porcelli, VAMC, Northport, N.Y. and S.U.N.Y. at Stony Brook, N.Y. 11790.

Cumulative dose-response curves (DR) were constructed in the isolated blood-perfused cat lung by comparing changes in pulmonary vascular resistance (ΔRpv) to either: a) increasing concentrations of 5HT, Histamine (HIST), Norepinephrine (NEPI), Epinephrine (EPI), or b) decreasing levels of arterial PO_2 induced by FI_{O_2}=0.08. DR was performed hourly (X4), resulting in DR1→DR4, from which slopes and maximal responses (MR) were analyzed. Slope and MR to 5HT (.35 to 9.4ηM) were unaltered between DR1 & DR4 (181±41 vs. 145±37, %ΔRpv, resp.). In contrast, MR with HIST (.33-2.2ηM) and EPI (.26 to 6.9ηM) were each reduced by 80% during DR4 ($p<.05$). Although MR to NEPI (.36-9.3ηM) were similar between DR1 and DR4, the dose at which MR occurred fell from 2.3 to .71ηM. For hypoxia, the MR at DR3 (69±4%) exceeded MR at DR1 (33±3%) ($p<0.05$) while the doses at which MR occurred were similar. The tachyphylaxis shown to HIST and EPI suggests antagonism of their pressor action by increased H-2 or β activity. The reproducibility shown with 5HT may be due to the lack of specific antagonist receptors. The potentiation to NEPI and hypoxia with repeated DR suggests failure of these agents to enhance antagonistic receptor activity. (Supported by Veteran's Administration, NIEHS# 431-1373, and NHLBI-R01-HL-23210).

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EFFECTS OF CHRONIC HYPOXIA (CH) ON PULMONARY VASCULAR RESISTANCE CHANGES (%Δ Rpv) TO SELECTED BIOGENIC AMINES. Bergman, M.J.*, E.H. Bergofsky, and R.J. Porcelli, VAMC, Northport, N.Y. and S.U.N.Y. at Stony Brook, N.Y. 11790.

Changes in Rpv to Norepinephrine (NEPI), Histamine (HIST), 5HT and KCL were studied in control (C) and CH rats exposed to 10% O_2 for 2 (CH2) and 4 (CH4) weeks. CH had predictable effects on:

	HMCT(%):	Rt/Lft Heart Ratios:	Rpv(mmHg/ml/min)
C(n=17):	51±1.2	0.26±0.01	0.94±0.12
CH2(n=11):	70±1.4	0.36±0.01	1.45±0.13
CH4(n=10):	74±1.4	0.43±0.02	1.54±0.17

Excised lungs were perfused (constant flow) with Ringer's & pulmonary artery pressures were continuously measured. The lungs were ventilated & the left heart was opened so that left atrial pressure = 0. Cumulative doses of KCL in C (21 to 85 μM) gave linear increases in %ΔRpv (max. response, MR, = 29±9%). MR at CH2 (12±9%) and at CH4 (19±13%) were not significantly different from C. 5HT (2-20ηM) had similar results with regard to MR; C (56±25%), CH2 (66±16%) and CH4 (65±12%). In contrast, HIST (5-126μM) C responses (17±7%) were reversed at CH2 (-25±8%) and at CH4 (-23±9%), $p<.05$. NEPI (13-371ηM) at CH2 was similar (-12±10%) compared to C (19±8%), $p<.05$. CH4 (9±9%) was not significantly different from C. These data suggest that CH: 1) does not alter non-specific vascular contractility (KCL); 2) functionally changes H_1 to H_2 and α to β receptors, and; 3) does not alter 5HT responses, possibly due to the lack of 5HT-specific vasodilator receptors. (Supported in part by Veteran's Admin. & NHLBI-R01-HL-23210).

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THE EFFECTS OF FUROSEMIDE ON THE PULMONARY VASCULATURE. J. Ali*, C. Skoog*, H. Unruh*, and H.S. Goldberg, Departments of Surgery and Medicine, University of Manitoba, Canada.

Vascular pressure-flow (P-Q) relationships were determined in 6 isolated blood perfused canine left lower lobes. After stabilization for one hour in Zone II pulmonary blood flow was plotted following step decreases in pulmonary artery pressure starting at 35 torr. These measurements were repeated after doses of 3.5, 7.0 and 40 mgm of furosemide. The P-Q relationship was linear between maximum and 25% of maximum flows and was curvilinear at lower flows both with and without furosemide. The slopes of the linear portion of the curves as a group did not differ significantly from control although 5 out of 6 lobes showed increased conductance with furosemide. The mean intercept of the linear portion of the curve was 13.9 + 5.4 torr at control and significantly decreased ($p<.05$) with all doses of furosemide. The mean control measured pulmonary artery pressure at no flow was 9.3 + 3.3 torr and also fell significantly ($p<.01$) with all doses of furosemide. We conclude that furosemide decreases the critical closing pressure of pulmonary vessels. This may explain, in part, the demonstrated non-diuretic beneficial effects of furosemide in pulmonary edema. (Supported by the Manitoba Lung Association)

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INHIBITION OF OXIDANT AND LIPID INDUCED PULMONARY VASOCONSTRICTION BY ANTIOXIDANTS. G.H. Gurtner, P.L. Smith*, N. F. Adkinson, A. Knoblauch*, H. Makhzoumi*, and H. Sies. The Johns Hopkins Medical Institutions and the Baltimore City Hospitals, Baltimire, MD., 21205, Spital Limmital, Zurich, Switzerland, and the University of Dusseldorf G.F.R.

We have previously reported that lipid and hydrogen peroxides cause a marked pulmonary vasoconstriction in the isolated perfused rabbit lung (ARRD 134:246, 1981). We found that t-butyl hydroperoxide and hydrogen peroxide had similar effects at perfusate concentrations >2 μM. Unsaturated lipids, such as linoleic or the mixture of fatty acids used in intravenous hyperalimentation (Intralipid®), had a similar effect at higher concentrations. The pressor response was blocked by Indomethacin and could be correlated with thromboxane concentration in the effluent perfusate. Animals which had been pre-exposed to O_2 for 4 hours had a larger pressor response than control animals. Animals which were pretreated with the antioxidants butylated hydroxyanisole(BHA) I.P. or Vitamin E in the diet had markedly diminished pressor responses to peroxides or lipids. It seems possible that administration of peroxides or lipids which can undergo peroxidation activate the arachidonic acid pathway resulting in thromboxane production. The accentuated pressor response in the O_2 exposed animals might be explained by the endogenous formation of lipid peroxides or a decreased ability to detoxify peroxides. The lack of a pressor response in the antioxidant treated animals could be due to the ability of the antioxidant to directly scavenge arachidonic acid hydroperoxides and thus inhibit the system. (PHS Grant#HL10342)

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THE EFFECT OF ALTERED CAROTID SINUS PERFUSION PRESSURE ON BLOOD FLOW TO AN ATELECTATIC LUNG. W.B. Strawn, S.M. Hall*, J.L. Moffett*, and M.G. Levitzky. Department of Physiology, LSU Medical Center, New Orleans, La. 70112

The effect of altering carotid sinus perfusion pressure (CSPP) on the distribution of pulmonary blood flow during atelectasis was determined in eight anesthetized, chronically-instrumented dogs with bilateral isolated, perfused carotid sinuses. Unilateral atelectasis was produced by left airway occlusion. The dogs had electromagnetic flow probes implanted on their main (Q_T) and left (Q_L) pulmonary arteries, catheters in their left atria and pulmonary arteries, and had their left and right lungs separately ventilated through Carlens tubes inserted in tracheotomies. $PaCO_2$ and pH were kept within normal limits. After an initial period of bilateral ventilation with 100% O_2 and with CSPP = 100 mm Hg, the left airway was occluded and the fraction of cardiac output perfusing the left lung (Q_L/Q_T) fell from 0.38 to 0.24. PaO_2 fell from 339 to 74 mm Hg. When CSPP was reduced to 30 mm Hg, Q_L/Q_T fell further to 0.19 and PaO_2 rose to 97 mm Hg. When CSPP was returned to 100 mm Hg, Q_L/Q_T rose to 0.24 and PaO_2 fell to 80 mm Hg. These results suggest that stimulation of the baroreceptor reflex by decreasing carotid sinus perfusion pressure does not interfere with the local mechanism involved in the redistribution of blood flow away from a unilaterally atelectatic lung. (Supported by NHLBI Grants 22641 and 07098)

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LOBAR HEMODYNAMICS DURING ATELECTASIS IN THE INTACT DOG. C. A. Bradley*, M.E. Arnup* and N.R. Anthonisen. Section of Resp. Dis., Dept. of Med., University of Manitoba, Canada.

In 9 supine anesthetized dogs we measured pulmonary vascular pressures and blood flow distribution with radioactive microspheres (15μ) during left lower lobe (LLL) atelectasis. The dogs were ventilated with 88% O_2, 12% N_2 and lobar volume assessed by measuring LLL N_2 after occluding the LLL bronchus. In 3 dogs microspheres were injected at 100% and 70% FRC and in six at 100%, 50% and 25% FRC. After atelectasis the lungs were excised and measurements made of microsphere content, wet/dry wt. ratios, and lobar hemoglobin content, an indicator of blood volume. Pulmonary vascular pressures did not change with atelectasis. LLL blood flow averaged 24.6% of the cardiac output at 100% FRC, 22.9% at 70% FRC, 25.5% at 50% FRC, and 17.8% at 25% FRC. A significant decrease in blood flow was observed only at 25% FRC though other data indicates vascular resistance should have been increased at 50% FRC (15-20% TLC); it is possible resistance did not increase because of negative lobar pressures generated by lobar-chest wall interdependence. Lobar hemoglobin content was the same in atelectatic LLL as it was in control right lower lobe: vascular distortion secondary to atelectasis did not decrease lobar blood volume. Wet/dry wt. averaged 3.69 (SEM=0.12) in atelectatic LLL, significantly less than in control right lower lobe which averaged 4.10 (SEM=0.13). This result might be due to a selective increase in resistance upstream from fluid exchanging vessels.

PERIPHERAL CIRCULATION II

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EXERCISE HYPEREMIA DURING ISOPROTERENOL, CARBACHOL, AND ADENOSINE INFUSIONS. David E. Mohrman. Univ. Minnesota, Duluth, MN 55812

The purpose for this study was to determine how the local metabolic vasodilator mechanisms in skeletal muscle interact with other vasodilator influences and whether this interaction is the same with different vasodilator substances. Gastrocnemius-plantaris muscles of 18 dogs were isolated, denervated and perfused at constant pressure. Muscle blood flow ($\dot{Q}$) was measured electromagnetically and muscle O_2 consumption ($\dot{V}O_2$) was calculated from the O_2 content of arterial and venous blood samples. $\dot{Q}$ and $\dot{V}O_2$ were determined for a range of muscle activities from rest to 6 twitches/sec in the control state and during continuous intraarterial infusion of isoproterenol (ISO), carbachol (CARB), or adenosine (ADO). Infusion rates were initially adjusted to double resting $\dot{Q}$ and fixed thereafter so that arterial concentration remained constant despite exercise induced increases in $\dot{Q}$. During ISO infusion, $\dot{Q}$ was increased over control by the same increment at all $\dot{V}O_2$'s. The vasodilator effect of CARB disappeared at high $\dot{V}O_2$ whereas that of ADO was greatly augmented at high $\dot{V}O^2$. Thus the local metabolic vasodilator mechanisms interact quite differently with different non-metabolic vascular influences. Also the results with ADO infusion are opposite to those expected if ADO itself was the primary mediator of metabolic vasodilation in skeletal muscle. (Supported in part by USPHS. NIH Grant #HL 22975)

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POTENTIATION OF POST-EXERCISE HYPEREMIA BY DIPYRIDAMOLE IN THE CANINE GRACILIS MUSCLE IN SITU. Joyce M Kille* and Richard E. Klabunde. West Virginia Univ., Morgantown, WV 26506.

By examining the effect of dipyridamole (DIPY), the role of adenosine in post-exercise hyperemia was studied in a free-flowing, vascularly isolated canine gracilis muscle. Calculations were made for excess blood flow (EQ; ml/100g), excess oxygen consumption ($E\dot{V}O_2$; ml O_2/100g), and the tension-time integral (TT; kg·s/100g) following 1, 3, 5, and 10 sec of isometric tetanic contraction produced by nerve stimulation. Each muscle was stimulated in the absence and presence of an intra-arterial infusion of DIPY (1.0 μM in blood). This concentration blocks cellular uptake of adenosine. The data from 5 dogs, analyzed by linear regression, were:

	SLOPE	Y-INT	r	n	p
EQ vs TT	0.47	5.88	0.818	42	<0.001
$E\dot{V}O_2$ vs TT	0.05	1.18	0.779	42	<0.001
EQ vs $E\dot{V}O_2$	6.79	2.57	0.811	42	<0.001

DIPY enhanced EQ, particularly at the longer duration stimulations. In the presence of DIPY, the slope of the regression line for EQ vs TT increased by 50% and the slope of EQ vs $E\dot{V}O_2$ increased by 70%. The slope of $E\dot{V}O_2$ vs TT was not significantly altered by DIPY. Therefore, DIPY potentiated EQ following stimulation and this effect was not related to increased $E\dot{V}O_2$. If the action of 1.0 μM DIPY is to increase extracellular adenosine by inhibiting cellular uptake, then these data suggest that adenosine may contribute to post-exercise hyperemia. (Supported by NHLBI grant # HL 25412.)

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ADENOSINE RELEASE FROM SKELETAL MUSCLE DURING FREE FLOW EXERCISE. B.D. Fuchs*, M.W. Gorman and H.V. Sparks, Jr. Michigan State Univ., E. Lansing, MI 48824

The adenosine (ado) content of skeletal muscle does not significantly increase during free flow, 6 Hz exercise (Phair and Sparks, A.J.P. 237:1,1979). Since tissue measurements of ado may not be sensitive to changes in [ado] localized in a small perivascular compartment, we wished to test the ado hypothesis for exercise hyperemia using ado release (Rado = plasma flow times venous-arterial plasma [ado] difference), as an index of interstitial fluid [ado]. Isolated, blood perfused dog calf muscles were stimulated at 6 Hz under free flow conditions for 10 min. Plasma samples were collected before, during and after the exercise period for the analysis of plasma [ado] by HPLC. Degradation of ado in collected blood was stopped by EHNA (erythro 9-2 hydroxy-3-monyladenine hydrochloride) and dipyridamole. Exercise increased muscle blood flow from 9.1± 0.7 to 128±7 ml/min/100g, vascular conductance from .09±.01 to 1.33±.06 ml/min/100g/mm Hg, and $\dot{V}O_2$ from 0.26± .03 to 15.1±0.9 ml/min/100g. Mean venous PO_2 fell from 50 to 26 mm Hg. Associated with these changes, Rado increased from -0.09±.09 to 14.2±4.1 nmoles/min/100g. Together, tissue measurements of adenosine and Rado data suggest that ado released during exercise is not distributed in the entire interstitium. Furthermore, the cellular source of released ado remains to be determined. This means that measurements of tissue content of ado during exercise are not a sufficient test of the ado hypothesis. (Supported by USPHS NIH Grant #25779-02)

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DISSOCIATION OF pH AND CO_2 EFFECTS ON ADENOSINE METABOLISM BY CULTURED ARTERIAL SMOOTH MUSCLE. S.P. Bruttig, F.L. Belloni, R.A. Fenton*, R. Rubio and R.M. Berne. Univ. of Virginia, School of Medicine, Charlottesville, VA 22908

Cultured vascular smooth muscle (VSM) releases adenosine (ADO) (Bruttig et al., 1980; Microvasc. Res., 20:103), but this ADO release was not responsive to hypoxia, and the question of regulation of ADO release by VSM became paramount. The present study, with rat aortic VSM, determined the effect of pH on uptake and release of ADO and the effect of CO_2 on ADO release. Uptake of 8-^{14}C ADO by VSM cells was not affected by pH changes (6.8 - 7.4, phosphate buffer). However, ADO release (high pressure liquid chromatography) was depressed by lowering pH in this range. The effects of pH on ADO release at both 0% and 5% CO_2 were similar, but the absolute magnitude was significantly higher at 5% CO_2. Thus, at 0% CO_2, ADO release was depressed 50% by decreasing pH from 7.4 to 6.8, whereas it was enhanced > 100% at pH 6.8 when CO_2 was raised from 0% to 5%. In addition, ADO release correlated positively with CO_2 (0%-10%) at a constant phosphate buffer pH (7.4). Thus, the effects of CO_2 as an acid anhydride were overridden by an apparent direct effect of CO_2. The mechanism(s) by which either pH or CO_2 can alter ADO release from VSM remain unclear. However, these findings indicate a possible link between metabolism (CO_2 production) and ADO release by VSM. Therefore, CO_2-induced release of ADO by VSM may facilitate the vascular response to parenchymally-derived ADO. (Supported by NIH grants HL19242 & HL06308 and a VA Heart Assoc. grant).

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CORRELATION BETWEEN SKELETAL MUSCLE ACETATE CONTENT AND VASCULAR RESISTANCE. R.P. Steffen, J.E. McKenzie, A.T. Yachnis*, and F.J. Haddy. Uniformed Services Univ., Bethesda, MD 20014

We have reported that local infusion of acetate (AC) produces vasodilation in the dog forelimb (AJP 203:125, 1962) and that this dilation occurs mainly at the small vessel level (Physiologist 21:115, 1978). We have also shown that femoral venous AC concentration increases during treadmill exercise (Fed. Proc. 39:270, 1980) and that the increment produces dilation in the resting gracilis where AC output and vascular resistance correlate inversely during exercise (Physiologist 23: 156, 1980). In the present study, tissue AC content was measured in collateral free dog gracilis muscles at natural flow during twitch contractions (E) at three rates (6V, 0.3 msec, 0.5, 1 and 2 Hz, 10 min each). Contralateral muscles were used as controls (C).

		Mean Tissue Content			Mean Resistance		
Hz	n	C	E	P<	C	E	P<
0.5	6	702	774	.01	10.9	6.3	.01
1.0	6	442	726	.01	9.7	5.3	.01
2.0	6	461	903	.02	13.7	2.7	.01

With increasing stimulation, E-C tissue AC content (nmoles/g) and E-C vascular resistance (mmHg/ml/min/100g) were significantly correlated, r=.75, P<.001. These data and those reported previously suggest that AC may play a role in the mediation of exercise hyperemia.

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CHANGES IN THE RELEASE OF OSMOTICALLY-ACTIVE PARTICLES (Osm), INORGANIC PHOSPHATE (Pi), AND K^+ DURING ACTIVE HYPEREMIA IN SOLEUS (RED) AND GRACILIS (WHITE) MUSCLE OF CATS. Emma L. Bockman. Department of Physiology, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20014

The purpose of this study was to determine whether Osm, Pi, and K^+ are released during active hyperemia and whether the release differs between red and white muscles. Vascularly-isolated muscles were stimulated to contract isometrically at different frequencies for 15 min. Venous outflow was measured with a drop counter. Resting blood flow averaged 10.7±2.1 and 5.6±0.5 ml/min/100g for soleus (N=10) and gracilis (N=9) muscle, respectively. During contraction, blood flow increased to an average of 29±4 (range:18-59) and 21±3 (range:6.8-32) ml/min/100g in soleus and gracilis muscle, respectively. In soleus muscle, the change in blood flow during contraction did not correlate with the change in the release of Osm (r=0.59), Pi (r=-0.53) or K^+ (r=-0.30). In gracilis muscle, the change in blood flow did not correlate with the change in the release of Pi (r=0.34) but did correlate with the change in the release of Osm (r=0.72; P<0.05). In addition, the change in blood flow was significantly correlated with the change in the venous-arterial difference in K^+ (r=0.82; P<0.01) and the release of K^+ (r=0.95; P<0.001). These findings do not support a role for osmolarity, Pi, or K^+ in mediating active hyperemia in soleus muscle. However, the data are consistent with a role for K^+ in mediating active hyperemia in gracilis muscle. (Supported by USPHS HL-26345 and USUHS R07639)

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VASODILATING EFFECT OF SUBSTANCE P ON CONTRACTILE RESPONSES OF RAT AORTIC RINGS. D.C. Kikta, R.M. Threatte*, and M.J. Fregly. Dept. of Physiology, Univ. of Florida, Gainesville, FL 32610.

The effect of substance P (SP) on vascular responses of aortic rings from female rats was studied. Three different 4 mm segments of the thoracic aorta were tested: S-1, immediately inferior to left subclavian artery; S-2, immediately inferior to S-1; and S-3, the inferior end of which was 4 mm superior to the diaphragm. Addition of SP (6 µg/ml muscle chamber bath) to tissue, preconstricted with 10^{-8} M norepinephrine (NE), was associated with a marked relaxation of S-1 (18.9±4.3% of the contractile response), a significantly (p<.05) smaller relaxation of S-2 (4.2±0.8%), and no consistent effect on S-3 (0.8±2.5%). Following preconstriction with either 10^{-7} M phenylephrine or 5 X 10^{-6} M serotonin, SP induced relaxation of both S-1 and S-2; the relaxations of S-1 (14.2±2.8% and 13.1±3.2%, respectively) being significantly (p<.05 and p<.01, respectively) greater than those of S-2 (5.1±0.8% and 1.4±0.6%, respectively). Addition of SP to either S-1 or S-2, preconstricted with 20 mM KCl, was not associated with relaxation. Addition of eledoisin (EL, 6 µg/ml) to S-1, preconstricted with NE (10^{-8} M), induced relaxations (10.3±3.2%), which were not significantly different from those induced by SP (11.3±3.5%) in the same tissue. Maximal relaxations occurred within 30-50 sec of addition of either SP or EL. These data indicate that a particular area (S-1) of the thoracic aorta of the rat is more responsive to the vasodilating action of SP than other areas of the same artery. This particular area is also sensitive to EL. (Supported by Grant 693(2) from the Florida Heart Assn.).

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THE EFFECTS OF INTRAARTERIAL SUBSTANCE P INFUSION IN THE ISOLATED, INNERVATED OR DENERVATED CANINE FORELIMB PERFUSED AT NATURAL FLOW. D.E. Dobbins, A.J. Premen, C.Y. Soika* and J.M. Dabney. Dept. of Physiology, USUHS, Bethesda, MD 20014

Substance P is a naturally occurring, potent vasodilator peptide which has previously been reported to cause peripheral vasodilation by a direct action on vascular smooth muscle. In this study, substance P was infused at 300 ng/min into the brachial artery in completely isolated canine forelimbs perfused at natural flow, both prior to and after denervation of the forelimbs. In either the innervated or denervated forelimbs, substance P infusion resulted in a significant decrease in forelimb perfusion pressure and mean systemic arterial pressure which were simultaneous and identical in magnitude and time course. Skin and muscle small artery pressures were significantly decreased for the duration of the infusion period whereas skin small vein, skin large vein, muscle small vein and muscle large vein pressures were not significantly changed. Forelimb blood flow was likewise not significantly changed. Forelimb resistance was significantly decreased but the decrease tended to wane with time. When substance P was infused locally into the forelimb but the venous effluent from the forelimb was not returned to the animal, there were no changes in forelimb pressures or systemic pressure. These data suggest that this dose of substance P is not a direct peripheral vasodilator in the canine forelimb. Furthermore, these data indicate that this indirect action of substance P seen in this study is not mediated through the forelimb nerves.

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INTERACTION BETWEEN SYMPATHETIC TONE AND THE MYOGENIC RESPONSE. Robert A. Brace, Div. of Perinatal Biology, Dept. Physiology, School of Medicine, Loma Linda University, Loma Linda, CA 92350.

Sympathetic tone and the myogenic response both participate in regulating local blood flow rate but it is not known to what extent they interact. In order to explore potential interaction between sympathetic and myogenic tone, peak reactive hyperemic flows following 2 to 15 second brachial arterial occlusions were compared in the forelimb of the anesthetized sheep. The limb was partially isolated by including all tissue except the brachial artery, brachial and cephalic veins, and nerve trucks in a tourniquet. Brachial flow rate in the innervated limb averaged 22% of the denervated flow rate. The excess peak flow following an 8 second arterial occlusion averaged 14% (of the denervated flow) in the innervated limb and 41% in the denervated limb. Phenoxybenzamine or hexamethonium was infused intravenously in order to gradually eliminate sympathetic tone. The peak increase in blood flow rate following 2, 5, or 15 second arterial occlusions increased as sympathetic tone was decreased. Thus, the data suggest that there is a strong interaction between sympathetic tone and the myogenic response in the forelimb of the sheep.

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EFFECT OF REDUCED CEREBRAL O_2 CONSUMPTION ON THE CEREBROVASCULAR RESPONSE TO HYPOXIA. J.M. Donegan*, R.C. Koehler, M.D. Jones, Jr., M.C. Rogers and R.J. Traystman, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205

In order to test the response of the cerebral vasculature to hypoxia under conditions of reduced cerebral O_2 consumption ($CMRO_2$) cerebral hemodynamic measurements were made in 7 chronically implanted newborn lambs exposed to hypoxia before and during administration of sufficient sodium pentobarbital to produce EEG silence (~90 mg/kg). Arterial O_2 content was reduced from control (15.4 ± .9 vol % mean ± S.E.) to 10.7 ± .6 vol % (moderate hypoxia = MH) and 7.9 ± .6 vol % (severe hypoxia = SH). Cerebral blood flow (CBF) was measured with the radiolabelled microsphere technique and $CMRO_2$ was calculated using O_2 contents from arterial and sagittal sinus blood. In awake animals CBF increased from control (89 ± 11) to 118 ± 14 and 168 ± 14 (ml/100gm/min) with MH and SH respectively, whereas $CMRO_2$ remained unchanged from control (6.3 ± .8 ml O_2/100gm/min). Cerebral O_2 delivery (O.D.) was also unchanged from control (13.3 ± .8 ml O_2/100gm/min). Following pentobarbital, CBF, $CMRO_2$ and O.D. were reduced by 56%, 56% and 57%, respectively. MH and SH increased CBF from control (39 ± 4) to 44 ± 13 and 63 ± 4 ml/100gm/min. O.D. was unchanged from control (5.7 ± .6) by MH (5 ± 1.2) or SH (5.3 ± .5), as was $CMRO_2$ (2.8 ± .3). We conclude that while pentobarbital depresses CBF, $CMRO_2$ and O.D., the cerebral vasculature responds to maintain a constant O.D. during hypoxia, both before and after pentobarbital. SUPPORT: HL-10342

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EFFECT OF INDOMETHACIN ON HYPOXIC CEREBRAL VASODILATION IN NEWBORN LAMBS. J. Baskoff*, R.C. Koehler, M.D. Jones, Jr., M.C. Rogers and R.J. Traystman. Johns Hopkins Medical Institutions, Baltimore, Maryland 21205

We have previously demonstrated that oxygenase inhibitors blunt the increase in cerebral blood flow (CBF) with hypoxia (Fed Proc 39:498, 1980). Cyclo-oxygenase is the rate-limiting enzyme in the synthesis of prostaglandins which may play a regulatory role in the response of CBF to hypoxia. We studied five unanesthetized, chronically implanted newborn lambs (4-9 days old) to examine the cerebral hemodynamic response to hypoxia before and after indomethacin, a cyclo-oxygenase inhibitor. Catheters were implanted in the superior sagittal sinus and brachiocephalic artery under pentobarbital anesthesia. The lambs were studied at least 2 days postoperatively. Cerebral arteriovenous oxygen differences (A-V) were measured before and after indomethacin (10 mg/kg iv) during normoxia and hypoxic hypoxia (7-8% inspired oxygen concentration). Cerebral fractional O_2 extraction (E) is expressed by the ratio of A-V to arterial O_2 content. Our previous work has shown that E is well maintained during hypoxic hypoxia (Am J Physiol 240:H209, 1981). In this study, before indomethacin E = .46 ± .05 (± SEM) and rose significantly ($p<0.05$) to .72 ± .02 immediately after indomethacin infusion. During hypoxic hypoxia E was unchanged at .58 ± .02. These results indicate that cerebral oxygen delivery falls relative to O_2 consumption after indomethacin, but the response to hypoxic hypoxia was not further affected. SUPPORT: HL-10342

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BRAIN ECF pH AND BLOOD FLOW DURING ISOCAPNIC HYPOXIA. W. F. Nolan and D. G. Davies. Department of Physiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Cerebrovascular responses to isocapnic hypoxia (Pa_{O_2} = 33 ± 1 Torr) were examined in seven chloralose-urethane-anesthetized, paralyzed, artificially ventilated New Zealand white rabbits. Cerebral blood flow (Q) was measured using the radioactive microsphere technique. Vascular resistance (R) was calculated from Pa/Q. Brain ECF pH was measured continuously in the same animals using pH microelectrodes (1-2μ tip diameter) placed stereotaxically in the diencephalon. Total brain blood flow increased from 42.0 ± 3.4 to 69.2 ± 6.1 $ml \cdot 100g^{-1} \cdot min^{-1}$ ($p<0.01$) as R decreased from 2.03 ± 0.16 to 1.24 ± 0.09 $Torr/ml \cdot 100g^{-1} \cdot min^{-1}$ ($p<0.01$) following 5-7 min of isocapnic hypoxia. The vascular response of the diencephalon was similar; Q increased from 40.1 ± 2.7 to 69.7 ± 5.2 $ml \cdot 100g^{-1} \cdot min^{-1}$ ($p<0.01$) as R decreased from 2.10 ± 0.13 to 1.21 ± 0.07 $Torr/ml \cdot 100g^{-1} \cdot min^{-1}$ ($p<0.01$). Diencephalon ECF pH increased by 0.016 ± 0.006 pH units ($p<0.05$) during the first minute of hypoxia and remained significantly ($p<0.01$) elevated throughout the period of blood flow determination. We conclude that the early cerebral vasodilation during isocapnic hypoxia is not mediated by increased brain ECF acidity. (Supported by the Tarbox Research Institute and HL 25984.)

RENIN–ANGIOTENSIN SYSTEM

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DIFFERENTIAL RENIN RELEASE (RR) INDUCED BY PROSTAGLANDIN (PG) SYNTHESIS IN DOG ISOLATED SUPERFICIAL AND DEEP GLOMERULI. S. Schryver*, E. Sanders*, W.H. Beierwaltes and J.C. Romero. Dept. Physiology, Mayo Clinic, Rochester, MN 55905.

We have previously reported that arachidonic acid (AA)-stimulated RR operates via PGI_2 in rat isolated glomeruli. The cortical distribution of the renin-PG interaction has important implications in nephron heterogeneity, blood flow distribution, and in Na^+ handling. Superficial (SG) and deep glomeruli (DG) were isolated separately from dog renal cortex using a passive sieving technique. Glomeruli were superfused within glass chambers using Krebs-Ringer and either 1.6×10^{-3}M (n=6) or 3.2×10^{-4}M (n=5) AA. Effluent concentrations of PGI_2, PGE_2 and renin were determined by RIA. The 1.6×10^{-3}M AA produced similar increases of PGI_2 in SG (from 64 to 894 pg/ml, $p<0.01$) and in DG (52 to 809 pg/ml, $p<0.01$); and also in PGE_2 (62 to 545 pg/ml, $p<0.01$, and 42 to 545, $p<0.05$, respectively). However, RR was greater ($p<0.025$) in the SG (3.9 to 24.9 ng/ml/hr A-I, $p<0.01$) than in DG (1.1 to 6.4 ng, $p<0.005$). The 3.2×10^{-4}M AA induced smaller but similar responses of PGI_2 in SG (101 to 206 pg/ml, $p<0.025$) and in DG (104 to 197 pg/ml, $p<0.025$). The increases in PGE_2 were not significant. The RR occurred only in the SG and was half that seen with the higher concentration (3.4 to 11.9 ng, $p<0.05$). These results suggest that while PGI_2 and PGE_2 are released evenly among the glomeruli, PG-mediated RR occurs predominately within the glomeruli of the outer cortex. (Supported by grants from NIH [HL-16496], and Mayo Foundation.)

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ISOPROTERENOL STIMULATED RENIN RELEASE IS NOT ACUTELY DEPENDENT ON RENIN SYNTHESIS. Stephen A. Katz* and Richard L. Malvin. University of Michigan, Ann Arbor, Michigan 48109.

Rat renal cortical slices were incubated in a physiological salt solution supplemented with ^3H leucine and other, non-labeled amino acids. Control slices secreted 5.5%±.3% (mean ± SEM) of their renin content /hr. into the medium. When cycloheximide (CYCLO) was present (100 ug/ml) cortical slices secreted 4.8%±.5% of their renin content /hr. while protein synthesis was inhibited 97% as determined by washed TCA precipitable ^3H DPM's. When isoproterenol (ISP) was present (10^{-6}M), renin secretion increased 2-fold ($p<.01$). However, when both CYCLO and ISP were present in the medium, renin secretion again increased 2-fold ($p<.01$) while protein synthesis was inhibited 97%. It is concluded that: 1) a large storage pool of renin exists, since only 5.5% of the slice renin content is normally secreted each hour; 2) ISP-stimulated renin release is not acutely dependent on renin synthesis, since ISP significantly stimulated renin release despite near total inhibition of protein synthesis; 3) acute β-adrenergic stimulation of renin release is therefore elicited from a storage pool of previously synthesized renin. Supported by NIH grant HL18575 and the National Kidney Foundation.

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THE POSSIBLE ROLE OF DOPAMINE IN THE REGULATION OF RENIN RELEASE. Haruko Mizoguchi,* Victor J. Dzau*, Leland Siwek* and A. Clifford Barger, Harvard Medical School, Boston, MA 02115

A role for dopamine (DA) in the regulation of renin release was studied in trained conscious, uninephrectomized dogs. Catheters were implanted in the aorta, renal artery, vena cava and renal vein. An electromagnetic flow probe was placed around the renal artery. DA was infused into the renal artery in doses which caused no change in blood pressure or heart rate. The DA infusion in doses ranging from 0.14 to 3.0 $\mu g\ kg^{-1}min^{-1}$ resulted in significant and dose-related increases in plasma renin activity (PRA) and renin secretion rate. Within this dose range, DA induced renal vasodilatation and natriuresis. Intrarenal infusion of sulpiride (a dopamine antagonist) attenuated DA-induced increase in PRA and renin secretion rate. A similar response was observed with haloperidol. Infusion of propranolol, however, failed to alter the increase in PRA whereas phentolamine, significantly potentiated DA-induced renin release. The intrarenal administration of other vasodilators (acetylcholine and papaverine), in doses promoting renal vasodilatation without systemic hypotension, had no effect on PRA. In conclusion our studies demonstrate that DA is capable of stimulating renin release in conscious dogs by activating specific dopaminergic receptors. This dopaminergic mechanism appears to be independent of DA-induced renal vasodilatation. (Supported in part by NIH grant HL19467 and a gift from R. J. Reynolds Industries)

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INHIBITION OF RENIN SECRETION BY INFUSION OF BRADYKININ INTO THE LEFT CIRCUMFLEX CORONARY ARTERY. Avi Livnat and J.E.Zehr Dept. of Physiology, University of Ill., Urbana, IL 61801

Previously we reported a cardio-renal reflex which suppresses renin secretion (RS) following occlusion of the left circumflex artery (LC) in dogs. Since bradykinin (BK) has been shown to stimulate vagal non-medullated C-fibers emminating from the left ventricle and is secreted locally by the ischemic myocardium, we hypothesized that BK could be the local mediator which initiates the renin response to CAO. To verify this hypothesis we conducted 3 series of experiments to chloralose anesthetized dogs maintained on a salt-free diet for at least 3 days. An infusion needle was inserted into the LC for injection of BK or saline. Simultaneous measurement of renal blood flow and venous and arterial renin activities were used to calculate renin secretion. Each dog was subjected to an initial mild non-hypotensive hemorrhage. In Series I (n=7) BK (0.15 µg/kg) was injected into the LC. In Series II (time control, n=5) saline alone was injected into the LC and in the Series III (n=5) BK (0.15 µg/kg) was injected iv. The results of the first series indicated that RS was suppressed by 80%($P< 0.05$) during the 5th min after injection of BK into the LC. Injection of saline LC or BK iv did not suppress RS. This verified that the origin of the response to BK in the first group was in regions subserved by the LC. These results suggest that the suppression of RS following brief myocardial ischemia may be mediated by local release of BK.
(Supported by HL 15307 and the Illinois Heart Association)

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EFFECT OF PARATHYROID HORMONE ON PLASMA RENIN ACTIVITY AND PLASMA ALDOSTERONE CONCENTRATION IN DOGS. F. Blandino-Lopez*, E.G. Schneider, J.M. Kapsha* and S.D. Gleason*. Dept. Physiology, Univ. Tenn. Ctr. Hlth. Sci., Memphis, TN 38163.

Parathyroid hormone (PTH) can increase plasma renin activity (PRA) but its effects on plasma aldosterone concentration (PA) have not been studied. In this study the effects of PTH on PRA and PA were assessed in conscious dogs. On separate days each dog (n = 5) received a 1 hr infusion of either the vehicle or synthetic PTH (0.026 µg/min/kg) dissolved in isotonic saline and 0.3% bovine serum albumin. PRA values were significantly increased following PTH infusion when compared to vehicle infusion at 60 min (5.9 ± 1.4 vs 1.8 ± 0.6 ng/ml/hr; $p < 0.02$) and at 90 min (2.5 ± 0.5 vs 0.9 ± 0.3; $p < 0.03$). PRA levels were not different before the infusion and returned to control levels 3 hrs after the infusion. Plasma aldosterone concentration was not different at any time in dogs receiving either infusion. Urinary phosphate excretion was significantly increased by the PTH infusion while plasma phosphate levels were comparable following both infusions. Creatinine clearances and plasma sodium concentration were not different. Plasma potassium concentration declined significantly in the PTH-infused dogs although these values were not different from those obtained in vehicle infused dogs. These experiments demonstrate that PTH produced a marked increase in plasma renin activity without causing a concomitant increase in plasma aldosterone concentration in the dog. (Supported by NIH GR HL 16658)

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EFFECT ON PLASMA RENIN ACTIVITY OF RAISING BLOOD CONCENTRATION OF EPINEPHRINE TO THE HEAD. Michael D. Johnson. Department of Physiology, West Virginia University Medical Center, Morgantown West Virginia 26506.

Previous experiments demonstrated that physiologic increments of epinephrine (E) concentration elevate plasma renin activity (PRA), and that this effect apparently is mediated by an extrarenal event (Am. J. Physiol 236:H463-H470, 1979). The present experiments were designed to determine whether an elevation of circulating E conc. to the head could account for this elevation of PRA by E. Eight adult dogs were surgically prepared for blood sampling and blood pressure recording, and for E infusion into either the carotid and vertebral arteries, or a femoral vein (IV). Following a control period, E was infused for 45 min at a total rate of 25 $ng \cdot kg^{-1} \cdot min^{-1}$ either IV or into the head vasculature (3.5 $ng \cdot kg^{-1} \cdot min^{-1}$ into each vertebral artery and 9 $ng \cdot kg^{-1} \cdot min^{-1}$ into each carotid artery). PRA (in $ng \cdot ml^{-1} \cdot hr^{-1}$) rose from 1.8 ± 0.5 to 5.9 ± 1.2 during E infusion IV. PRA rose similarly, from 1.5 ± 0.4 (SE) to 4.1 ± 1.4 during E infusion to the head. Arterial blood E conc. rose similarly in response to both IV and head E infusions. Furthermore, the changes in hematocrit, heart rate and blood pressure were identical regardless of the route of infusion. The data indicate that 1) an increase in E conc. to the head blood supply is not responsible for the rise in PRA observed during IV E infusion, and 2) in contrast to most other vascular beds, the head apparently does not degrade circulating E. (Supported in part by USPHS grant HL 25555).

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THE EFFECT OF SODIUM CHLORIDE AND SODIUM BICARBONATE VOLUME EXPANSION ON PLASMA RENIN AND PROSTAGLANDIN E2 EXCRETION IN THE RABBIT. W.J. Welch* and C.E. Ott. Dept. of Physiology and Biophysics, University of Kentucky, Lexington, KY 40536.

Plasma renin activity (PRA) is reduced by volume expansion (VE) with sodium chloride (NaCl), but not with a similar VE with sodium bicarbonate (NaHCO3). Prostaglandins, especially PGE2, have been related to changes in renin release in several models and species. This study was designed to determine if selective NaCl or $NaHCO_3$ VE alters PGE2 excretion in the same manner as selective VE alters PRA. Anesthetized New Zealand rabbits were volume expanded with either .15 M NaCl (5% body weight) or .15 NaHCO3 (7.5% bw), with 30 minute clearance periods measured before and after VE. Glomerular filtration rate, PAH clearance, electrolyte excretion and arterial blood pressure were measured during each clearance period. The plasma volume increase in a group of eight NaCl VE animals and a group of seven NaHCO3 VE animals was not different (49±3.4% vs 55±8.4%). PRA in the NaCl group was significantly suppressed (11.4±2.0 to 5.2±1.3 ng/ml/hr, $p<.05$) following VE, but there was no significant PRA decrease in the $NaHCO_3$ group following VE (6.1±1.3 to 4.4±0.8 ng/ml/hr). Urinary PGE_2 excretion did not differ between groups both before VE (1.592±.677 vs .610±.150 ng PGE2) and after VE (18.5±7.2 vs 10.43±3.8 ng PGE2). Thus, in this model the decrease in PRA associated with NaCl volume expansion is not paralleled by decreases in PGE2 excretion. Unlike the selective VE effect on PRA, there appears to be no effect of selective VE on PGE2 excretion.

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ABSENCE OF A RENAL CONTRIBUTION TO BASAL BLOOD PRESSURE DIFFERENCES BETWEEN BORDERLINE HYPERTENSIVE (BHR) AND WISTAR-KYOTO RATS. Gary W. Randall* and Arthur M. Jungreis. Univ. of Tennessee, Knoxville, TN 37916

Systolic arterial blood pressures of BHR (155 mm Hg) and WKY (130 mm Hg) rats are invariant at 10 through 45 weeks of age [Lawler, et al., Fed. Proc. 40(#3), 528]. At 10 and 28 weeks, declining but significant differences in four renal hypertensive parameters persist: plasma renin (PRA), angiotensin I (AI), $[Na^+]$, and aldosterone (aldo). At 45 weeks, strain differences in these parameters are absent. Since only static measurements of these renal parameters were made, capacitance differences in these parameters between strains were sought. Unstimulated rates of aldo synthesis by adrenal cortex in vitro, quantities of circulating angiotensinogen, and the effects on PRA of AII and angiotensinogen were therefore determined at 45 weeks for both BHR and WKY rats. No strain specific differences in parameter capacity or regulation by AII or angiotensinogen were noted. We conclude that strain specific differences in renal hypertensive parameters to chronic systolic arterial pressure differences are compensatory rather than contributory at 10 & 28 weeks, becoming refractory to the systolic differences by 45 weeks of age. (Supported in part by USPHS. NIH Grants HL #19680 and AI #12779.)

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HEART WEIGHT AND ANGIOTENSIN II (AII) LEVELS IN NORMOTENSIVE SODIUM RESTRICTED RATS. R. D. Plotnik*, J. Mitchell* and D. F. Bohr. Univ. of Mich., Dept. of Physiology, Ann Arbor, Mi. 48109.

Cardiac hypertrophy has usually been regarded as a secondary response to an increased pressure load. Recent evidence (Circ. Res. 35:775, 1974) suggests that blood pressure may not be the only determinant of hypertrophy and that the renin-angiotensin system may play a permissive or contributory role. The present study evaluates the role of increased AII levels on heart size in normotensive animals. Male, age matched, WKY rats were placed on a low Na+ diet for five weeks in order to increase circulating AII levels. Similar control rats were placed on a regular Na+ diet. Blood pressures (BP), AII levels, body weights (BW) and heart weights (HW) were determined. The following table summarizes our results:

Group	Na diet (mEq/g)	Body wt. (kg)	BP (mmHg)	AII (pg/ml)	HW/BW (g/kg)
A (n=6)	.112	.279±.008	145±5.4	15.50±2.05	3.17±.06
B (n=6)	.010	.283±.007	142±3.7	24.66±2.49	3.28±.07
% change	-91.1	1.4	-1.9	59.1	3.5

HW/BW, blood pressure and body weight were not significantly different between the two groups, while AII levels were significantly higher ($p<.05$) in Group B than in Group A. These data suggest two possible conclusions: 1) salt restriction inhibits the hypertrophic action of AII, or; 2) this level of increased plasma AII, in the absence of increased blood pressure, does not contribute to cardiac hypertrophy. (Supported by NIH Grant #18575.)

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EVIDENCE FOR LIPOXYGENASE PATHWAYS IN RENAL ARTERIES AND ENDOTHELIAL CELLS: POSSIBLE RELATIONSHIP TO INDOMETHACIN-INDUCED ACUTE RENAL FAILURE. Naresh Chand* and Burton M. Altura. SUNY, Downstate Med. Ctr., Brooklyn, NY 11203.

The precise mechanism of indomethacin (INDO)-induced acute renal failure is not known. Isolated canine renal arteries (CRA) induced to contract with 5-HT or phenylephrine (PE) react with concentration-dependent relaxations to acetylcholine (ACH), bradykinin (BK) and arachidonic acid (AA), provided the endothelium (END) is left intact. Destruction of END, or incubation of CRA with nordihydroguaiaretic acid (NDGA), BW755C, or EYTA either inhibit or convert BK-and ACH-induced relaxant, into contractile, responses. INDO converts AA-induced relaxations into contractile responses, and enhances contractile responses to 5-HT, norepinephrine, PE and AA, as well as relaxations to PGI_2. CRA incubated with AA contract upon addition of INDO; these responses are inhibited by NDGA, EYTA, and BW755C. AA-dependent, indomethacin-induced renal arterial spasms are reversed by PGI_2 and compound FPL55712 (a leukotriene "SRS-A" receptor antagonist). These findings suggest that INDO inhibits the synthesis of PGI_2 in CRA thereby allowing AA to be metabolized via a lipoxygenase pathway(s) to the synthesis (and release) of hydroperoxyacid/leukotrienes; possibly explaining INDO-induced acute renal failure. In addition, ACH and BK induce renal arterial vasodilatation via release of inhibitory hydroperoxyacids/leukotrienes from renal END.

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EFFECT OF PROSTAGLANDIN SYNTHESIS INHIBITION ON THE DEVELOPMENT OF CONTRAST MEDIA INDUCED ACUTE RENAL FAILURE. Cobern Ott, Lakshmi Natarajan*, Shirley Whitescarver* and Nick Winer*. University of Kentucky, Lexington, KY 40536

A significant number of patients undergoing contrast media injections develop acute renal failure of varying severity. This study was undertaken to determine the role of prostaglandins in the development of this entity. Following control measurements (C), 23 rabbits were put on a low salt (LS) diet for 4 days. The measurements were repeated and the animals were divided into three groups. One group received 7 ml/kg of contrast medium (CM) or 24 mg/kg indomethacin (IN) in three equal doses or both contrast and indomethacin (CI). Plasma creatinine (PCr) concentrations were measured daily for the next 72 hours. Means ± SE for PCr (mg %) are shown below.

Group	C	LS	24 hr.	48 hr.	72 hr.
CM	.82	1.07	1.20	1.15	1.18
(n=8)	.09	.08	.11	.10	.11
IN	.85	1.09	1.92*	1.86*	1.62*
(n=7)	.09	.10	.26	.31	.25
CI	.96	1.13	3.24*	4.06*	2.84*
(n=8)	.09	.11	.57	1.07	.43

*Significant differences from LS

There was a small significant increase in PCr in the IN group but the increase in the CI group was significantly greater ($P<.05$). The results indicate that inhibition of prostaglandin synthesis may predispose the development of contrast media induced acute renal failure.

EXERCISE III

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THE EFFECT OF EXERCISE ON ISOENZYMES OF CARDIAC VENTRICULAR MYOSIN IN EUTHYROID AND THYROIDECTOMIZED RATS E. D. Pagani and R. J. Solaro. University of Cincinnati, College of Medicine, Cincinnati, Ohio 45267

We examined ventricular myosin isoenzymes in normal and thyroidectomized rats that had been swimming 75 min twice daily for 8 or 12 weeks. We prepared myofibrils from each heart for the measurement of myofibrillar actomyosin ATPase and myosin ATPase activities. A myosin enriched fraction was prepared from a portion of the ventricles by extraction in 100mM pyrophosphate and isoenzymes of myosin were separated by polyacrylamide gel electrophoresis using non-dissociating conditions as described by Hoh et al. (J. Mol. Cell. Card. 10:1053, 1977). There were three distinct myosin isoenzymes (V_1, V_2 and V_3) in ventricles of both sedentary and exercised euthyroid rats. Although V_1 was the predominant isoenzyme in sedentary and exercised euthyroid rat hearts, swimming resulted in an increase in the relative proportion of V_1 in the isoenzyme population. Associated with this shift we found a consistent increase in the Ca^{2+}-stimulated myosin ATPase activity with no change in the K^+-EDTA ATPase activity. While in some preparations made from the 12 week group there was an increase in the maximal myofibrillar ATPase activity, we did not observe this increase in rats that swam for 8 weeks. There was only one species of myosin isoenzyme, V_3, in ventricles of thyroidectomized rats, and this was not altered with 8 or 12 weeks of exercise. Moreover, the exercise did not induce a change in ATPase activities. We conclude from these studies that thyroid hormone may be involved in exercise induced changes in the properties of myosin. Supported by NIH-BRSG, HL 22619 (IIIB) and a Ryan Fellowship (EDP).

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LACK OF ADAPTATION OF LEFT VENTRICULAR GEOMETRY TO SEVERE PHYSICAL TRAINING IN ATHLETES. Mamoun Al-Nouri, Carl Foster, Michael Pollock(SPON) and Donald H. Schmidt. University of Wisconsin, Mount Sinai Medical Center, Milwaukee 53233.

This study reports the effects of severe physical training on the left ventricular(LV) dimensions in athletes. Subjects were 10 candidates for the 1980 US Olympic Speed Skating Team. The protocol included two-dimensional and M-mode echocardiograms and maximal oxygen uptake(VO_2) at the beginning(T_1) and upon completion of 3 months' severe training(T_2). Echo measurements included LV end diastolic diameter(EDD), posterior wall thickness(PWT), end diastolic thickness/radius ratio(t/r), t/r to systolic pressure ratio(t/r÷P), end diastolic volume index(EDVI) and LV ejection fraction(EF). Physiological parameters included VO_2, resting heart rate(HR) and P. The data

	EDD cm	PWT cm	t/r	t/r÷P	EDVI ml	EF%	VO_2	RHR	P
T_1	5.1 ±.4	1.02 ±.06	.39 ±.03	.0033 ±.0003	77 ±15	72 ±.5	64 ±3	54 ±9	121 ±8
T_2	4.9 ±.4	1.04 ±.08	.41 ±.02	.0036 ±.0005	76 ±12	69 ±.7	62 ±3	54 ±7	113 ±14
P	<.05	ns	ns	ns	ns	ns	ns	ns	ns

indicate that the severe training by these athletes, designed to improve speed skating performance, resulted in an almost total lack of adaptation as measured by LV geometry or VO_2. These findings imply that secondary adaptation to training in athletes is peripheral rather than central in character.

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EFFECT OF ENDURANCE TRAINING ON POSTURAL RESPONSES. P.S. Clifford*, T.J. Ebert, G.K. Smith*, J.A. Barney* and J.J. Smith. VA Med. Ctr., Wood, WI 53193 & Med. Coll. of Wisc., Milwaukee, WI 53226

Circulatory responses to postural stress are reportedly altered in endurance athletes. This question was further investigated by a comparison of the hemodynamic responses of 8 highly trained, male subjects, 20 to 29 yrs of age (TrS) and 8 untrained age-matched, male subjects (UnS) to graded, head-up tilt. Stroke volume and thoracic blood volume (TBV) changes were estimated with impedance cardiography and calf volume with strain gauge plethysmography. The carotid sinus - SA node reflex response was studied using Eckberg's neck suction technique.

The mean heart rates (HR) of the TrS were significantly lower than those of the UnS at rest and at all levels of tilt. When compared on the basis of equivalent % loss of TBV during tilt, there were lesser increases in HR and in diastolic and mean arterial pressures in the TrS than in the UnS. The bradycardic effect of increased carotid transmural pressure was greater in TrS than in UnS. The calf vascular distensibilities were similar in the two groups. These results confirm previous studies and indicate lesser hemodynamic responses of endurance athletes to head-up tilt. The mechanism of this insufficiency is not certain but the evidence suggests that [a] greater loss of TBV during tilt [b] inadequate responses of cardiopulmonary or arterial baroceptors and [c] the resting bradycardia of the endurance athlete may be important factors.

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EFFECT OF LESIONS IN THE LATERAL RETICULAR NUCLEUS ON THE EXERCISE PRESSOR REFLEX. G.A. Iwamoto*, M.P. Kaufman*, B.R. Botterman* and J.H. Mitchell. Univ. of Texas Health Science Center, Dallas, TX 75235

Electrical stimulation of ventral roots gives rise to a reflex cardiovascular response similar to that observed during static exercise. Although the afferent limb of the reflex is known to be comprised of small diameter afferent fibers from the contracting muscle, little is known of the central nervous system pathway(s) involved. The lateral reticular nucleus (LRN) of the brainstem is known to be an important site of integration for numerous types of visceral and somatic afferent information, many of which give rise to cardiovascular responses. However, the linkage between small diameter muscle afferents responsible for the exercise pressor reflex and the LRN has not been established. In anesthetized cats (n=5) stimulation of L7 and S1 ventral roots increased mean arterial pressure (MAP) (16.3+4mmHg) and heart rate (HR) (8+2.7bpm). Following bilateral lesion of the LRN, the increases in MAP and in HR were essentially abolished (MAP increased 0.94+0.7 mmHg and HR increased 0.4+0.4bpm). Unilateral LRN lesions and control lesions in pressor sites outside the LRN (n=3) did not affect the exercise pressor reflex. The LRN lesions also produced decreases both in resting MAP (-21.5+7mmHg) and HR (-27.2+8.4bpm). These data suggest that the LRN is important in the central pathway of the exercise pressor reflex and mediates a tonic pressor influence at rest.

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CARDIOVASCULAR RESPONSES TO STATIC EXERCISE IN CONSCIOUS DOGS-SIMILARITY TO THE RESPONSE IN HUMANS. J.C. Longhurst and G.A. Ordway. Univ. of Texas Health Sci. Ctr., Dallas, TX 75235

Upright hindlimb standing in dogs is known to increase blood pressure and heart rate. To examine this response more closely, 4 unsedated dogs were studied while standing upright on their hindlimbs and the cardiovascular (CV) alterations compared to the responses to passive 45° upright tilt in a sling. Standing upright on hindlimbs for 345+30 sec (mean+SE) significantly ($p<.05$) increased mean arterial pressure (MAP) 104+8.9 to 129+7.9mmHg, heart rate (HR) 140+20 to 164+17beats/min, dP/dt at 40mmHg developed pressure (dP/dt 40) in 2 dogs 2575+675 to 3113+762 mmHg/sec, cardiac output (CO) 5.3+.63 to 6.2+.47L/min, oxygen consumption ($\dot{V}O_2$) 18+2.3 to 22+2.2ml/min/kg while there were no changes in left ventricular end diastolic pressure (LVEDP) 2.6+.94 to 3.8+.75mmHg, systemic vascular resistance (SVR) 20+1.5 to 21+1.3PRU or stroke volume (SV) 40.2+6.5 to 38.9+4.1ml. Passive upright tilt for 510+164 sec did not alter MAP (110+11 to 105+7.4mmHg), HR (116+10 to 103+13beats/min), LVEDP (3.5+.61 to 2.1+1.0mmHg), dP/dt 40 in 2 dogs (2750+750 to 2388+488mmHg/sec), CO (4.8+.76 to 4.2+.84 L/min), $\dot{V}O_2$ (16+2.0 to 19+3.6ml/min/kg), SVR (24+2.0 to 28+5.0 PRU) or SV (42+5.2 to 40+3.3ml). These data indicate that the CV responses to hindlimb standing are opposite to the responses to upright tilt. Further, the hemodynamic response to hindlimb standing in dogs closely resembles the response to static exercise in humans, suggesting that this is an appropriate model for future studies.

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PULMONARY EFFECTS IN HEALTHY YOUNG MEN OF FOUR SEQUENTIAL EXPOSURES TO 0.4 PPM OZONE IN COMBINATION WITH VARYING LEVELS OF EXERCISE. Edward D. Haak, Jr.*, Milan J. Hazucha*, Ralph W. Stacy, Brock D. Ketcham*, Elston G. Seal*, Dennis E. House* & John R. Knelson*. U.S. EPA, Human Studies Division, Chapel Hill, NC 27514

In a series of 4 studies, 90 healthy non-smoking males, ages 19-30, were exposed to air or 0.4 ppm ozone for 4 hours at 72 ± 2°F and 40% RH on 4 successive days of a week. Compared to air exposure (Study I), subjects exposed to ozone with light intermittent exercise of 4 mph at 0% elevation (Study II) experienced significant decrease in FVC, FEV_1 and MMEF on the 1st and 2nd day of exposure. Since decrements on the 3rd and 4th day became smaller and nonsignificant, the group appears to have become adapted. This course of response is further supported by the symptomatic complaints which were highest on the initial exposure and then progressively diminished. Subjects exposed to ozone with heavy exercise of 4 mph at 10% elevation (Study III) had more marked reduction in spirometric variables. The trend of changes on successive exposures was the same as in Study II. Successive air exposures (Study IV) served as controls for the Study III. The results show that, 1) repeated exposures to ozone at the same exercise load diminish subject's response (adaptation), 2) low ozone loading did not appear to confer an adaptive protection against high ozone loads, and 3) a high percentage of normal young males are inherently sensitive to ozone. Supported by US EPA

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CHANGES IN ARTERIAL BLOOD GASES DURING EXERCISE. Benjamin M. Lewis. Hutzel Hospital Medical Unit, Wayne State University, Detroit, MI 48201

Arterial blood gas measurements were obtained at 30", 1'30" and 5'30" of a 6 min. step exercise test in 29 subjects who complained of dyspnea. PaO_2 was significantly (6torr) lower in the 30" sample in 9 subjects and significantly lower in the 1'30" sample in 15 subjects as compared with the 5'30" sample. Eleven subjects hyperventilated ($PaCO_2$ < 35 and pH > 7.45) at rest. Five of these had a lower PaO_2 in either the 30" or the 1'30" than the 5'30" sample. Twelve of the subjects who did not hyperventilate had the same findings. A steady state by respiratory measurements was present by 5'30" in 19 subjects and not present in 5, but the presence of a steady state did not affect differences between the two early samples and the final sample. In 14 subjects either the 30" or the 1'30" sample had a lower PaO_2 than the resting sample; 7 of these hyperventilated at rest.

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VENTILATORY ENDURANCE IN MEN AND WOMEN. Hsiun-ing Chen* and Bruce J. Martin. (SPON: J. E. Randall). Physiol. Sec. Med. Sci. Program, Indiana U., Bloomington, IN 47405

Men differ from women in various indices of exercise capacity such as grip strength and maximal oxygen uptake. However, it is unknown if males and females differ in their ability to sustain high ventilation, an ability that may influence exercise tolerance in both athletes and patients with lung disease. To investigate this question, 8 males and 8 females who were non-athletes and similar in age were studied. Both their 12-s maximal voluntary ventilation (MVV), and their long-term maximal ventilation were measured. The latter was quantified by two means: first, isocapnic hyperpnea began at a target of 30 l/min and was increased by 30 l/min each 4 minutes thereafter until a peak level was reached; second, 80% of the MVV was maintained until exhaustion. Men and women had similar short-term and long-term maximal ventilation:

	Males	Females	P
short-term maximal ventilation (MVV/VC)	36.5+2.3	36.0+2.4	NS
peak $\dot{V}_E$ as % of MVV	66+3	61+3	NS
endurance time at 80% MVV (min)	6+2	4+2	NS

It was concluded that after normalizing for body size, there were no differences in both short-term and long-term maximal breathing capacities between males and females. (Supported in part by NIH grant HL 26351)

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FAMILIAL ASPECTS OF HIGH VENTILATORY ENDURANCE IN ATHLETES. Bruce J. Martin and Hsiun-ing Chen*. Physiology Section, Med. Sci. Program, Indiana Univ., Bloomington, IN 47405

Endurance athletes possess superior ability to sustain high ventilation. While this capability may in some way aid exercise performance, its origin is unknown. Either training or genetics could explain the high ventilatory endurance of athletes. To investigate these possibilities, we compared the breathing endurance of 8 distance runners with that of 8 of their siblings who were untrained. Athletes and siblings were of similar age, and had similar 12-s maximal voluntary ventilation (MVV), after normalization for differences in vital capacity. However, we found on two separate tests that the athletes had a greater ability to sustain high $\dot{V}_E$ than did their brothers and sisters. In the first test, $\dot{V}_E$ was voluntarily incremented by 30 l/min each 4 min until the subject was unable to continue. Before exhaustion, the athletes reached a $\dot{V}_E$ that was a greater fraction of their MVV than did the siblings (75 vs. 62%; $P<0.01$). In the second test, 80% of the MVV was sustained until exhaustion. Endurance times for the athletes doubled those of the siblings (7 vs. 3 min; $P<0.05$). On both tests, the performance of the untrained siblings resembled that of previously studied groups of non-athletes. The failure of elevated ventilatory endurance to occur in family clusters suggests that it may primarily result from training, and not from genetic predisposition.

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VENTILATORY RESPONSE DURING MEDROXYPROGESTERONE ADMINISTRATION AND ITS EFFECT ON EXERCISE PERFORMANCE. H.W. Bonekat*, B.A. Staats. Mayo Foundation, Rochester, MN 55901.

Ventilatory response (VR) may be linked to maximal oxygen uptake ($\dot{V}O_2max$) (Martin, et al JAP 45:557, 1978). Progesterone increases VR. In order to study the interrelationship of VR and exercise performance, we administered medroxyprogesterone acetate (MPA) 20 mg t.i.d. X 5 doses to 10 normal males (age: 22-32 yrs., $\dot{V}O_2max$=34-64 ml/kg), in a double blind fashion using placebo control (C). Each subject performed a hypercapnic (HCVR) and hypoxic (HVR) ventilatory response, incremental and steady state ergometry. Cardiac output ($\dot{Q}$) determinations, by the CO_2 rebreathing technique, were made during the steady work state. The S value ($\Delta\dot{V}e/\Delta PACO_2$) of the HCVR was increased [mean (MPA) S=2.40 L/torr, (C) S=2.03, $p < .01$] but the A value (shape parameter) of the HVR was not. No change was observed in $\dot{V}O_2max$, heart rate max, anaerobic threshold (AT), or $\dot{Q}$. Ventilation ($\dot{V}e$) was increased below AT with MPA but not above AT. CO_2 production showed a slight tendency to be decreased with MPA at a given $\dot{V}O_2$ but not to the extent seen in females (Dombovy & Staats, Fed. Proc. 40:396, 1981). $\dot{V}e$ per unit CO_2 production ($\dot{V}e/V\dot{C}O_2$) was increased with MPA only during submaximal levels of $\dot{V}O_2$; this increase did not correlate with resting S.

Alteration of ventilatory response does not change $\dot{V}O_2max$. MPA stimulates Ve below AT. Cardiac output is unchanged by increased ventilatory responsiveness. (Supported in part by PHS grant HL 07222).

MYOCARDIAL METABOLISM

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SARCOLEMMAL UPTAKE OF LACTATE, PALMITATE, GLUCOSE, AMINO ACIDS AND NORADRENALINE IN THE ISOLATED PERFUSED RABBIT HEART. G.E.Mann* and D.L.Yudilevich* (SPON: W.N.Durán), Dept Physiol., Queen Elizabeth College, Univ. London, London W8, England.

Unidirectional uptake of substrates by the perfused rabbit heart was investigated using a paired-tracer dilution technique previously applied to the salivary gland (Bustamante, Mann & Yudilevich, J.Physiol. 313, 65-79, 1981). Following a bolus arterial injection of a labelled substrate and an extracellular tracer, D-mannitol, the coronary effluent was sampled sequentially. At tracer concentrations the maximal cellular uptakes (%) measured were: L-lactate, 50±4 (3); palmitate, 90; D-glucose, 10 & 13; L-alanine, 9±1 (4); L-phenylalanine, 41 ± 5 (4); taurine, 13 ± 5 (4).

Saturation of L-lactate and L-phenylalanine influx was observed as the perfusate concentrations were increased from 0.15 - 20 mmol/l. A Michaelis-Menten analysis indicated the following constants: L-lactate (K_m = 25.2±8.7 mM, V_{max} = 6.6 ± 1.7 µmol/min.g). As in our preparation capillary permeability is high (Mann, J.Physiol. paper in press), it is suggested that membrane carriers are located in the sarcolemma.

Noradrenaline (NA) uptake (31 ± 4, n = 4) was inhibited by 10 and 100 µmol/l NA and by 5 µmol/l imipramine but unaffected by 5 µmol/l propranolol. NA uptake may thus reflect neuronal reuptake rather than binding to the β-receptor, confirming similar findings in the dog heart (Cousineau, Rose & Goresky, Circ. Res. 47, 329-338, 1980).

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THE EFFECT OF CHRONIC THYROXINE TREATMENT ON MYOCARDIAL LACTATE OXIDATION. Marion Fintel*and Alastair H. Burns. Dept. of Physiology, LSUMC, New Orleans, LA 70112.

Hearts from control and chronically thyroxine treated Sprague Dawley rats were perfused in the working heart configuration with KRB buffer containing 0.4 mM palmitate bound to albumin, 5.5 mM glucose and 1 mM ^{14}C-lactate. The hearts from the treated rats had a significant increase in dry heart weight/body weight ratio, indicating that hypertrophy had occurred. The linear relationship of oxygen consumption to heart work (CO x Peak Systolic Pressure) was determined for both control and thyroxine treated hearts. No difference was found between the two groups. Myocardial lactate oxidation was measured and the percentage of oxygen utilized in the oxidation of lactate determined at various workloads. The percentage of oxygen consumption utilized in the oxidation of lactate averaged 16.2±0.7% for the hearts from control rats and 10.9±0.7% for the hearts from treated rats over the entire work range. Raising the preload of the heart from 10 cm to 20 cm increased the percent of oxygen utilized in the consumption of lactate from 14.7±1.9% to 17.0±1.8%in the control group and from 9.6±1.3% to 12.2±1.5% in the thyroxine treated group. This data suggests that thyroxine treatment accentuates the myocardial substrate preference for fatty acids.
(Supported in part by NIH HL22904.)

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LACTATE AND PALMITATE OXIDATION AND ATP AND CP LEVELS IN MYOCYTES FROM NORMAL AND CHRONICALLY STREPTOZOTOCIN-DIABETIC RATS. Victor Chen, Gregory J. Bagby, and John J. Spitzer Louisiana State Univ. Med. Ctr., New Orleans, LA 70112

The effect of chronic diabetes on the utilization of exogenous lactate and palmitate, and on ATP and CP levels in freshly isolated Ca^{2+}-tolerant, non-beating myocytes was investigated. The oxidation of lactate (1 mM) was 62% below normal, whereas the oxidation of palmitate (0.4 mM) was similar to the controls. Lactate oxidation by myocytes from normal rats was reduced by half in the presence of glucose or palmitate, while in diabetic rats, these added substrates reduced lactate oxidation by 25 and 56%, respectively. Palmitate oxidation in the myocytes from normal rats was diminished in the presence of glucose, but not of lactate. This competing effect of glucose on palmitate oxidation was not observed in the myocytes from the diabetic rats. O_2 consumption of cells from diabetic rats in the presence of either lactate or palmitate was lower than control. The alterations in substrate oxidation in diabetic rats were corrected by insulin treatment (5U/kg, twice daily). ATP and CP content in myocytes from diabetic rats were similar to those in normal rats and the values were comparable to the ones reported under in-vivo condition. There was no loss in energy-rich phosphates after 40 minutes of incubation in the presence of different substrates. (Supported by HL 23157, HL 22101, and HL 07098.)

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EFFECTS OF ESTRADIOL BENZOATE UPON IN VITRO MYOCARDIAL ANOXIC RESISTANCE AND IN VIVO CORONARY BLOOD FLOW IN THE FEMALE RAT. Loren G. Martin. The Oklahoma College of Osteopathic Medicine and Surgery, Tulsa, Oklahoma 74101

One month old castrate CD Strain female rats (Charles River) were given daily intraperitoneal injections of either 0.1 ml cottonseed oil (sham), 4.0 µg estradiol benzoate in 0.1 ml cottonseed oil, or 40.0 µg estradiol benzoate in cottonseed oil for a 16 week period. Coronary blood flow rates (in vivo) were compared among these various treatment groups by means of tracer microsphere methodology, and this parameter increased as a result of increasing levels of chronic exogenous estrogen administration. Other animals from these same treatment groups were sacrificed, and the in vitro anoxic resistance of an isolated right ventricular strip preparation was determined. Again, this measure of myocardial anaerobic competency was augmented as exogenously-administered estrogen levels were increased. These results seem to indicate that physiological levels of estrogen may afford the female myocardium, when compared to the male, some degree of protection against acute myocardial hypoxic insults, both at the intact circulatory level and at the isolated tissue level.

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FAILURE OF OXYGEN IN FLUROCARBON TO PREVENT INJURY AFTER 120 MINUTES HYPOTHERMIC POTASSIUM CARDIOPLEGIC ISCHEMIA OF PIG HEART. W.A. Dobbs and R.M. Engelman*, Univ. of Connecticut Health Center, Dept. of Surgery, Farmington, CT 06032

The hearts of 24 pigs were subjected to 120 minutes of hypothermic potassium cardioplegic arrest followed by 60 min of reperfusion. The vehicle for potassium cardioplegia(K+=35 mEq/L) was a crystalloid solution(KHES,n=12,(O_2) =0.4vol%)or an oxygenated flurocarbon(Fluosol-DA,n=12,(O_2)=6.0vol%). The response to ischemia and reperfusion was measured in terms of myocardial oxygen consumption(mvO_2), oxygen extraction(E_{O_2}) or tissue concentration of ATP and CP (μM/gwetwt). Mean values were:

		PREARREST	ARREST		REPERFUSION			
VEHICLE	TEST	CONTROL	1HR	2HR	15min	30min	45min	60min
KHES	MVO_2	2.97	____	____	2.39	2.45	2.29	2.02
	EO_2	.41	____	____	.30	.34	.27	.24
	ATP	4.10	3.67*	3.40*	3.15	3.12	3.08	2.95
	CP	6.54	2.33*	1.45*	6.40	6.94	7.41	7.81
FLUOSOL	MVO_2	2.78	____	____	2.36	2.70	2.51	2.97
	EO_2	.27	____	____	.25	.27	.24	.27
	ATP	4.39	4.68*	4.90*	3.51	3.29	3.40	3.23
	CP	6.92	6.34*	6.09*	7.53	8.05	8.64	8.52

*$p < .05$, FLUOSOL VS KHES

This pattern suggests that even though oxygen delivery during arrest prevented the changes in tissue ATP and CP, reperfusion injury was not prevented, since the concentrations of ATP and CP during reperfusion were not different.(Supported in part by NIH Grant 1RO1HL 22559).

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Cardiomegaly induced by a Transplantable Growth Hormone (GH) secreting tumor: A new model. Joseph C. Dunbar*, David G. Penney and Michael S. Baylerian*, Dept. of Physiol., Wayne State Univ. School of Medicine, Detroit, MI 48201.

Female Wister Furth rats were injected subcutaneously with 4-6 one mm piece of GH (Mt-T-W15) secreting tumor (T). The T is palpable after 4 wks reaching 80-100 gms after 9 wks. Increases in serum GH accompanies the T growth equaling 70X controls (C) at 9 wks. Cardiovascular (CV) studies were carried out at two stages; after 4 wks (small T = ST, ave. T wt. 4 g) rats were mildly anemic (hematocrit T, 31.6% vs C, 46.5%), and the LT rats showed more severe anemia (16.5%). Weight of the 2 ventricles (V) of the ST rats was not greater than C. However in the LT rats 2V wt. was 72% greater than C, with a somewhat greater increase in right V than in left V + interventricular septum (LV+S). Spleen: body wt. ratio in ST rats is 2-fold that of C. Open chest CV functions were studied under chloralose-urethane anesthesia. Cardiac index, stroke index, str. work, peak aortic flow, and the 1st derivation of aor. fl. were increased and peripheral resistance was decreased in ST rats and to a significantly greater level in LT rats. Differences in CV functions also persisted when the functions were normalized/g LV+S. Acute increases in preload produced greater increases in the above CV functions in the ST rats, but caused no change or decreased functions in the LT rats. We concluded that the cardiomegaly and resulting changes in CV function is due to increased GH. However the degree of participation of anemia in this model remains unclear.

CORONARY CIRCULATION II

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MYOCARDIAL ADENOSINE (Ado) RELEASE DURING TREADMILL EXERCISE IN THE CONSCIOUS DOG. Stephen Ely*, Alban Bacchus*, Robert Knabb*, Rafael Rubio, and Robert M. Berne. Dept. of Physiol., Univ. of Virginia School of Medicine, Charlottesville, VA 22908

Changes in interstitial fluid Ado should be reflected by Ado release into the pericardial space as well as coronary sinus blood. Therefore, [Ado] was determined in pericardial infusate (PI) samples by spectrophotometry and in arterial and coronary sinus plasma samples by HPLC during exercise (10 min, 4mph,10% grade) in dogs chronically instrumented for the determination of coronary blood flow (CBF) and myocardial O_2 consumption ($M\dot{V}O_2$). Exercise increased heart rate 77% from 127±16b/min, aortic pressure 16% from 105±10mmHg, CBF 31% from 96±5ml/min/100g, and $M\dot{V}O_2$ 81% from 11.6±1.0 ml O_2/min/100g. Coronary vascular resistance decreased 13% from 1.10±.13mmHg/ml/min/100g. [Ado] in PI increased 88% from 81pmol/ml. Myocardial Ado release ($\dot{R}$ Ado), calculated from the equation [(sinus Ado -art Ado)xCBF], indicated a net uptake of Ado at rest (14±10 nmol/min/100g), and a net release of Ado during exercise (82± 45 nmol/min/100g). Significant ($p<.05$) correlations were obtained for $M\dot{V}O_2$ vs. CBF (r=0.85), $\dot{R}$ Ado vs. CBF (r=0.69), $M\dot{V}O_2$ vs. $\dot{R}$ Ado (r=0.87), PI Ado vs. CBF (r=0.90), $M\dot{V}O_2$ vs. PI Ado (r=0.97), and PI Ado vs. R Ado (r=0.84). These data demonstrate that increases in myocardial oxygen demand during exercise in the conscious dog are associated with parallel increases in oxygen supply as well as cardiac Ado release, and therefore, support a role for Ado in the regulation of coronary blood flow. (Supported by NIH Grant HL10384).

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CHANGES IN MYOCARDIAL OXYGEN CONSUMPTION ($M\dot{V}O_2$) AND ADENOSINE PRODUCTION WITH ALTERATIONS OF HEART RATE. Robert M Knabb*, Stephen Ely*,Alban Bacchus*,Rafael Rubio,Robert M Berne. Dept of Physiol. Univ of Va. Sch of Med. Charlottesville VA 22908

For adenosine(ADO) to be a physiologically important mediator of coronary blood flow (CBF), conditions which alter the metabolic activity of the myocardium must be matched by appropriate changes in interstitial fluid (ISF) ADO concentration. Since it is not possible to directly sample ISF, we used two independent measures as indices of ISF ADO in open chest dogs. ADO was determined in pericardial infusate (PI) samples and in simultaneously obtained samples of arterial and coronary sinus plasma. $M\dot{V}O_2$ was altered by right vagal stimulation and atrial pacing. Myocardial adenosine release($\dot{R}$ ADO)(net production +) was calculated as (sinus ADO - arterial ADO) x CBF.

Results: mean ± S.E. (n = 5)

	VAGAL STIM	CONTROL	ATRIAL PACING
CBF (ml/min/100g)	28.65±2.92	44.98±6.46	51.24±5.07*
$M\dot{V}O_2$(ml/min/100g)	5.06±0.35	7.23±0.49*	8.56±0.48*
Heart rate (bpm)	85 ±3.5	140 ±6.5*	185 ±17.7*
PI ADO (pmol/ml)	45.92±5.79	78.64±10.18*	96.64±15.01*
$\dot{R}$ ADO(nmol/min/100g)	-3.76±0.96	-0.51±4.38	7.32±1.88*

* indicates significantly different from vagal stim $p < 0.05$

The results show a parallelism between $M\dot{V}O_2$, PI ADO, and $\dot{R}$ ADO, and suggest that increases in the oxygen demand of the myocardium associated with increases in heart rate are accompanied by increases in cardiac ADO release. The data support a role for ADO in mediating changes in CBF with metabolic activity.

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MODEL OF ADENOSINE TRANSPORT ACROSS MYOCARDIAL CAPILLARY WALL. John P. Manfredi* and Harvey V. Sparks, Jr. Michigan State Univ., East Lansing, MI 48824

To infer interstitial adenosine concentrations (ISF[ADO]) from measurements of ADO release (Rado), the importance of the capillary wall as a metabolic barrier must be determined. We estimated the relationship between myocardial Rado and ISF [ADO] by modelling ADO transport across the capillary wall. The model assumes that ADO crosses the capillary wall by diffusing along interendothelial clefts 100A wide, 1.2μ high, extending 0.4μ from ISF to capillary space. ADO's diffusion coefficient is assumed to equal that for sucrose in tissue water, $1.06 \times 10^{-6} cm^2/sec$. ADO is both taken up by endothelium with Km=3μM and Vmax=7.14pmol/min/cm^2 cell surface area, and deaminated by adenosine deaminase with Km=250μM and Vmax=12mol/min/ml cleft volume. The model predicts approximately 96% of ADO entering one end of the cleft will emerge at the opposite end, indicating uptake and/or deamination of approximately 4% during passage. If total surface area of pore openings is $26 cm^2/100g$, the model predicts this relation among Rado, ISF [ADO], and [ADO] in capillary plasma ([ADO]cap): Rado=67.3·ISF [ADO]+72.6·[ADO]cap, where Rado is in nmol/min/100g and ISF [ADO] and [ADO]cap are in μM. The model suggests that, despite uptake from and deamination within the clefts, Rado will have a sensitivity to ISF[ADO] of 67.3nmol/min/100g/μM. (Supported by USPHS. NIH Grant HL #25779-02)

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ADENOSINE POTENTIATES CORONARY FLOW AND INHIBITS OXYGEN CONSUMPTION DURING ISOPROTERENOL INFUSION IN ISOLATED PERFUSED GUINEA PIG HEARTS. D.F.Stowe and A.E. Beranek*Department of Physiology, The Medical College of Wisconsin, Milwaukee 53226.

Endogenous adenosine (ADO) levels rise with coronary flow (CF) during exercise or isoproterenol (ISO) infusion; exogenous ADO appears to reduce the positive inotropic response to ISO. Thus we tested if ADO: (a) potentiates the rise in CF and (b) inhibits the rise in myocardial O_2 consumption ($M\dot{V}O_2$) produced by ISO. We isolated and perfused 10 Langendorff hearts with Ringer's at 50 torr and 37°C and paced them at 4 Hz. Peak Peak isovolumic left ventricular pressure (P) and +dP/dt were used as indices of work and contractility. CF rose from 3.4 ± 0.2 (SEM) to 7.3 ± 0.8 ml/g/min with bolus ADO (400 nmol). ISO (11 ± 4 nM) alone increased steady state: CF to 4.8 ± 0.2 ml/g/min, $M\dot{V}O_2$ by 33 ± 7%, P by 52 ±15%, and +dP/dt by 81 ± 19%; during ADO (170 ± 40 nM) plus ISO, P fell to 24 ± 8% and +dP/dt fell to 53 ± 4%. Linear regressions showed (rise/run): slope of CF/ADO alone = 0.7 ± .04, CF/ADO with ISO = 1.4 ± .05 ml/g/min per 100 nM; slope of $M\dot{V}O_2$/ADO alone = 30 ± 9%, $M\dot{V}O_2$/ADO with ISO = 8 ± 11% per nM; slope of CF/$M\dot{V}O_2$ (baseline) = .05 ± .001, CF/$M\dot{V}O_2$ with ADO = .09 ± .004 ml/g/min per μl/g/min. All paired slopes were unequal ($P<.05$.). This study shows that exogenous ADO: (a) increases CF without a parallel rise in $M\dot{V}O_2$, (b) potentiates the rise in CF with ISO, and (c) inhibits the rise in $M\dot{V}O_2$ and work with ISO. Thus endogenous ADO may act to limit heart work while increasing CF with exercise.

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A NEW TECHNIQUE FOR THE ANALYSIS OF REGIONAL MYOCARDIAL BLOOD FLOW DATA OBTAINED WITH TRACER MICROSPHERES*. Michael D. Devous, Sr., University of Illinois, Urbana, Il 61801, and The University of Texas Health Science Center, Dallas, Tx 75235

Tracer microsphere methodology is extensively employed for the measurement of regional myocardial blood flow. However, the analysis of data obtained by the microsphere technique is widely variant in the literature and often neglects substantial flow information as a result of limited myocardial sampling. When extensive myocardial sampling is employed, typical graphical or tabular representation of the data obtained is unwieldy and difficult to comprehend. In this report, a method for complete sampling of the left ventricle is described. The data thus obtained is displayed in a pictorial fashion which allows the viewer an immediate comprehension of regional flow values over the entire subepicardium or subendocardium. Flow values are displayed on either a variable gray scale or color-coded scheme. The regional blood flow images are preserved in digital arrays and thus are available for computer processing. Such processing includes area analysis for regions at risk, quantitative evaluation of intervention effects, intercomparisons of histologic staining (e.g. infarct size) and regional blood flow, and analysis of time-dependent changes in myocardial blood flow. (*This work was supported by the American Heart Association, Illinois Affiliate.)

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FENTANYL EFFECTS ON MYOCARDIAL BLOOD FLOW IN A CONSTRICTED CORONARY BED. H. K. Jacobs, T. L. K. Rao*, and R. T. Stannard*. Loyola Medical School, Maywood, IL 60153

We have previously reported that high dose fentanyl reduces myocardial blood flow in both nonatropinized and atropinized dogs suggesting a vasoconstriction due to fentanyl. If vasoconstriction does occur, then a previously existing area of ischemia might be well served by fentanyl leading to a "reverse steal" phenomenon. This question was examined by measuring myocardial blood flows in seven enflurane anesthetized, atropinized, mongrel dogs using 15μ radiolabeled microspheres. Blood gases, pH and filling pressures were controlled within normal limits throughout the study. After taking control measurements, a portion of the left ventricle was rendered ischemic by placing a 25 gauge constriction around the LAD just below the first major diagonal branch. All parameters were measured following a 15 minute equilibration time. Fentanyl (50μg/kg) was administered and all parameters were remeasured at 20 minutes. After a one-hour pause, the LAD was ligated at the same site and data were again recorded before and at 20 minutes following fentanyl. Blood flows in the areas of the LV not supplied by the constricted/ligated artery showed a significant fall following fentanyl administration which was paralleled by decreases in cardiac work, MAP and MVO_2. Myocardial flow in the border zones or the infarct zones did not decrease with fentanyl. These data indicate that fentanyl does not cause any significant vasomotor changes and may be beneficial in terms of the oxygen supply/demand in ischemic areas.

MECHANICS OF BREATHING: AIRWAYS II

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EFFECTS OF VASOACTIVE INTESTINAL POLYPEPTIDE (VIP) AND ISOPROTERENOL (ISO) ON THE GUINEA PIG TRACHEAL POUCH RELAXATION INDUCED BY VAGAL AND SYMPATHETIC TRUNK STIMULATION. C.S. Venugopalan*, S.I. Said, and J.M. Drazen Dept. of Physiology, Harvard School of Public Health, Boston, MA 02115, V.A. Med. Cen., Dallas, TX 75216

VIP has been indentified as a possible neurotransmitter mediating non-adrenergic inhibitory activity. We reasoned that if VIP was the neurotransmitter of non-adrenergic inhibitory activity the incubation of VIP in the guinea pig tracheal pouch would not only result in relaxation of the pouch but that prolonged exposure to the neuro-effector would diminish the response to vagal stimulation. To test this hypothesis we compared: (1) the relaxant effects of VIP and ISO on the tone of the isolated guinea pig tracheal pouch *in vivo*; and (2) The effects of ISO and VIP incubation on the pouch relaxation induced by sympathetic and vagal trunk stimulation. ISO and VIP both produced dose dependent relaxation of the pouch. ISO was 40 times more potent than VIP on a molar basis. Incubation of the histamine toned tracheal pouch with ISO resulted in both pouch relaxation and loss of pouch responsiveness to sympathetic stimulation. Vagally mediated pouch relaxation was inhibited to a lesser extent. VIP produced relaxation of the histamine toned tracheal pouch and resulted in a greater loss of responsiveness to vagal than sympathetic stimulation. These data are consistent with the hypothesis that VIP is an inhibitory neurotransmitter and acts at a receptor which exhibits tachyphylaxis. (Supported by HL19732, HL00549 & HL14187)

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RESPIRATORY SYSTEM IMPEDANCES IN THE RAT. A.C. Jackson and J.W. Watson.* Primate Research Center, Univ. of Calif., Davis, Ca. 95616

Respiratory system impedances were measured by a modified forced oscillatory technique in 30 normal male CRD-free Sprague-Dawley rats at frequencies between 20 and 90 Hz. A resonance frequency was found (mean = 39 Hz) below which reactances were negative and above which reactances were positive. Resistances were generally found to be frequency dependent, increasing with increasing frequencies. Frequency dependent behavior in resistance has been ascribed to inhomogeneities in parallel airway pathways and to the effects of airway wall compliance. Optimization techniques were used to estimate the values of parameters in a variety of lumped-parameter mechanical networks incorporating parallel pathways and/or airway wall compliance. The model whose response compared the best with the data and that resulted in the most consistent parameter values was found to be one where the airways are separated into upper and lower components by a shunt pathway containing an airway wall compliance. The mean values for each of the parameters within the model were upper airway resistance (54 cm H_2O/l/sec), peripheral airway resistance (53 cm H_2O/l/sec), upper airway inertance (0.058 cm H_2O/l/sec^2), peripheral airway inertance (0.116×10^{-4} cm H_2O/l/sec^2), airway wall compliance (0.182×10^{-4} l/cm H_2O), and respiratory system compliance (1.267×10^{-4} l/cm H_2O). (Supported by NIH grant HL-25631 and EPA grant R-807661.)

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CORRELATION OF MAXIMUM EXPIRATORY FLOW AND AIRWAY AREA. W. Mazzei*, R. Castile*, J. Fredberg*, M.E. Wohl, G. Glass* and L. Brooks*. Harvard Medical School and Childrens Hospital Medical Center, Boston, MA 02115, and Cambridge Collaborative, Inc., Cambridge, MA 02142.

Among healthy adults of the same age and sex, a large variability in maximum expiratory flow (MEF) exists that cannot be accounted for by differences in height, weight, vital capacity (VC), or lung elastic recoil (J.A.P. 37:67, 1974). We investigated the correlation of MEF and airway area. Average tracheal area was measured during slow expiration from total lung capacity (TLC) to residual volume (RV) in 15 healthy adult males using an acoustic reflection technique (J.A.P. 48:749, 1980). Lung volumes and maximum expiratory flows were measured with a pressure compensated, volume displacement body plethysmograph and #4 Fleisch pneumotachomter. Mean intrathoracic tracheal grossectional areas were 4.2 ± 1.1, 3.6 ± 0.9, and 2.9 ± 0.9 cm^2 at TLC, 50% VC and RV respectively. There was a close correlation ($p<.01$) between MEF at 75% VC and intrathoracic tracheal area at RV. No correlation between tracheal areas and MEF at 50% or 25% VC was observed. This suggests that the size of the undistended trachea (tracheal area measured at RV) is related to the size of the flow-limiting segment during MEF at high lung volumes. Variation in tracheal size may account for part of the variability in MEF at high lung volumes. (Supported by NHLI NO1-HR 62901)

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AQUEOUS CANNABIS EXTRACT (THC-FREE) - A BRONCHODILATOR. Mohan Kumar*, G.N. Melville*, M. West*, M. Lee*, S.R. Wray* and L.H. Hamilton. Depts. of Physiology and Medicine, Univ. of West Indies, Kingston, Jamaica, W.I. and Wood V.A. Med. Ctr. Milwaukee, WI, 53193.

The intraperitoneal injection of 1 ml of a THC-free aqueous extract of marijuana plant (1.27 gm/100 ml) reduced specific airway resistance (sRaw) in apparently healthy rats and in rats with increased sRaw induced by chronic exposure to either marijuana or tobacco smoke. Mean sRaw was 1.87 ± 0.15 cm $H_2O.ml^{-1}s^{-1}$ before and 1.54 ± 0.12 cm $H_2O.ml^{-1}s^{-1}$ after marijuana extract in normal rats (18% decrease). In 20 animals with smoke-induced bronchitis the marijuana extract reduced sRaw from 7.38 ± 0.39 to 5.25 ± 0.24 cm $H_2O.ml^{-1}s^{-1}$ (29% decrease). The oral administration of 30 ml of a THC-free marijuana extract (200 mg active marijuana ingredient/100 ml of aqueous solution) resulted in a decrease in mean transit time (0.81 to 0.70 sec), an increase in $FEV_{1.0}$/FVC (68.4% to 72.4%) and an increase in peak flow (330 L/m to 347 L/m) 60 min after administration to asthmatic patients. Comparable spirometric changes were observed 30 min after Salbutamol, a beta adrenergic stimulant. No changes were seen in subjects who received a placebo instead of the extract. Thus, an aqueous-extract of marijuana plant (containing no water insoluble THC/cannabinoids) has been demonstrated to have bronchodilator effects in rats and humans with and without smoke-induced bronchitis. The effect was similar to that produced by the bronchodilator Salbutamol.

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THE INFLUENCE OF DRIVING PRESSURE DURING FORCED EXPIRATION OF RATS. J. L. Mauderly. Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185

Forced expiratory flow, volume and pressure relationships were studied over a range of driving pressures. Normal adult F-344 rats were anesthetized with halothane, intubated with orotracheal (1.7 mm I.D.) and esophageal catheters and placed in a flow plethysmograph. During hyperventilation-induced apnea, lungs were inflated to a transpulmonary pressure of 30 cm H_2O and deflated using negative expiratory airway pressures (Pex) of 0 (ambient), 5, 10, 15, 20, 30, 40, 50 and 60 cm H_2O. "Effort independence" of maximal flow was observed at all volumes after peak flow, which occurred at 80% of vital capacity (VC). A Pex of 50 cm H_2O was adequate to achieve mean peak flow. Isovolume pressure-flow curves demonstrated "negative effort dependence" (NED, reduced flow with increasing Pex) at 10, 15, 25 and 50% VC. The extent of NED differed among the rats, but was most marked at 50% VC. There was a linear relationship between the minimal Pex producing maximal flow and lung volume between 25 and 80% VC. Thus, in normal rats, the equal pressure point appears to travel upstream during forced expiration and then stop and reverse direction with increasing driving pressure. Preliminary data from elastase-treated rats did not demonstrate NED. (Research performed under U.S. Department of Energy Contract No. DE-AC05-76EV01013.)

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AIRWAY REACTIVITY IN THE PERIPHERY OF THE LUNG: MALE-FEMALE DIFFERENCES. A. Gertner*, H. Menkes, R. Traystman and B. Bromberger, The Johns Hopkins Medical Institutions, Baltimore, Md. 21205

The purpose of the present study was to determine whether sex differences exist in airways responses to inhaled histamine in the periphery of the lung. In 9 male and 9 female mongrel dogs we compared responses of collateral ventilatory channels to an aerosol of histamine delivered locally in the lungs. A fiberoptic bronchoscope was wedged in peripheral airways of anesthetized dogs. Increasing doses of histamine were directed through the bronchoscope. Measurements of collateral resistance (Rcoll) were used to monitor responses to histamine and lung inflation. Baseline measurements of Rcoll were similar for both sexes. The males responsed with greater increases in Rcoll than the females. Following doses of histamine ($1.5X10^{-6}$mg for males and $1.5X10^{-4}$mg for females) which produced similar increases in Rcoll, the effects of lung inflation and the time course of the responses were similar for the 2 sexes. It is, therefore, concluded that male dogs have greater reactivity to histamine in the lung periphery than female dogs. (Supported by ERC Grant #OH07090 NIOSH and SCOR Program Project HL14153-NHLBI)

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BREATHING He-O_2 CHANGES THE P-V CURVE OF THE DOG. N. Berend* and N.F. Voelkel. Pulmonary Physiology Unit, National Jewish Hospital, Denver. Colorado, 80206

In order to see if breathing a mixture of 80% helium, 20% oxygen (He-O_2) affects the P-V curve, eight anesthetized, paralyzed dogs were studied in a volume displacement plethysmograph. Static P-V curves on air after constant volume history were compared with P-V curves obtained after equilibration with He-O_2. The He-O_2 P-V curves shifted significantly upwards by an average of 6% total lung capacity. An exponential of the form $V = A - Be^{-KP}$ was fitted to the P-V data (V = volume at pressure P, A = maximum volume at infinite pressure, B = A minus intercept of the exponential on the volume axis and K = shape constant directly related to compliance). There was no change in K indicating that the shift was due to lung expansion rather than a change in compliance. Pretreatment of the animals with inhibitors of prostaglandin synthesis, indomethacin and meclofenamate (10 ug/kg), abolished the P-V shift with He-O_2. Infusion of prostaglandin E_1 at rates of 0.5, 1,2 and 4 ug/kg/min resulted in an upward shift of the P-V curve in a dose-dependent manner reaching a maximum after 2 ug/kg/min. No change in K resulted. Thirty minutes post infusion the P-V curves had returned nearly to baseline. We conclude that breathing a He-O_2 mixture causes the release of a bronchodilator prostaglandin which dilates the peripheral bronchial tree resulting in a parallel upward shift of the P-V curve. This needs to be taken into account in the analysis of flow augmentation with He-O_2.

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ELECTRICAL PROPERTIES OF THE CELLS OF THE FERRET PARATRACHEAL GANGLION. A.R. Cameron* and R.F. Coburn, Dept. of Physiology, Sch. Med. Univ. of Penna., Phila. Pa. 19104.

A preparation has been developed for electrophysiological study of the paratracheal ganglia of the ferret. Ganglia were observed with brightfield optics at 40X, lying on the dorsal surface of the trachealis muscle close to its insertion into the cartilage. Neutral red staining indicated the presence of 4-10 cells per ganglion. Nerve trunks joining ganglia were observed. Electronmicroscopy indicates the presence of large ganglion cells with many nerve endings on each cell. We have observed typical cholinergic endings. Electrophysiology was carried out at 35° using bevelled microelectrodes (35-45MΩ), without neutral red staining. Two cell types were observed. Type A (n=19) had a stable membrane potential of -37.2±1.6mV. Input resistance was 41.3±1.6MΩ with cathodal rectification in most cells. Membrane time constant was 3.7±0.45msec. Cathodal current injection caused spikes with a threshold at -22±1.5mV and a mean overshoot of 21.3±1.8mV. V_{max} of the action potential upsweep was 52±5V/sec. There was a profound after hyperpolarisation lasting several hundred msec. Cells usually fired singly to a cathodal current pulse no matter the pulse duration. Anode break excitation was occasionally seen. Type B cells (n=36) had a stable membrane potential of -52.7±2.2mV. Input resistance was 37.1±6.1MΩ and 80% of these cells exhibited anomalous rectification. Membrane time constant was 1.53±0.21msec. Cathodal current injection never gave spikes in these cells. Supported by NIH HL 19737.

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EFFECTS OF SURROUNDING STRUCTURES ON PRESSURE-DIAMETER BEHAVIOR OF EXCISED DOG BRONCHI. M. Nakamura*, D. Luchtel*, Y. Ikeda*, H. SASAKI*, T. Okubo*, T. Takishima*, and J. Hildebrandt, Tohoku Univ. Sendai, Univ. of Wash., & Virginia Mason Res.Ctr., Seattle, WA98101

The effects of adjacent large vessels and surrounding fibroelastic membrane on bronchial mechanics was studied in 5 excised dog lobes. The major bronchi were isolated from the rest of the lung by blocking 10-12 tributary bronchi with beads. After obtaining the intact P-V curves of these bronchial segments at three constant P_L (30,10,5 cm H_2O), the P-V curves to the same peak bronchial volume were measured after 4 dissections. (A) The blocked bronchi together with adjacent artery and vein were carefully dissected from the surrounding tissues, removing tributary bronchi and most parenchyma except a thin 1-2 mm layer. (B) All remaining parenchyma was carefully removed, still leaving large vessels. (C). The large vessels were separated, leaving the bronchial fibroelastic membrane. (D) Finally, this membrane was peeled from the bronchial segment. The peak distending pressure in (A) was almost equal to P_L at TLC, suggesting that in intact lungs near-homogeneity existed. In (B), a reduction of only about 10% recoil occurred from (A). The major reduction, a further 25%, occurred in (C) indicating that interdependence between bronchi and vessels contributes substantially to bronchial stiffness. A final reduction of 10-20% came in (D) without the outer membrane. Thus, bronchial P-V curves can differ by a factor of 2, depending on method of excision. Peribronchial pressure around relaxed intact airways may differ from P_{pl} by only a few cm H_2O (ie, Px≈0) at all volumes. (HL 14854).

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NONUMIFORMITY OF AIRWAY CLOSURE FROM APEX TO BASE IN EXCISED RAT LUNGS. J.J. Morgan*, C.E. Turick*, and D.G. Frazer. DHHS, CDC, NIOSH, ALOSH, DRDS and Dept. of Physiology, West Virginia University Medical Center, Morgantown, WV 26505

Male Long-Evans Hooded rats weighing between 200 and 300 gm were anesthetized with Sodium pentabarbital. The heart and lungs were removed en bloc and placed in a plethysmograph. Lungs were ventilated under 3 conditions: (a) in air, (b) inverted in saline, and (c) upright in saline. Differences in airway closure between the apex and base of the lungs were determined. The distribution of transpulmonary pressures over which the airways close during lung deflation was found in each condition using the method previously described by Frazer et al. (Resp. Physiol. 36:121-129, 1979). A distribution having a small standard deviation (SD) indicates a more uniform airway closure while a larger SD indicates a more nonuniform closure. Results showed that the SD was .6 for the inverted lung in saline, 1.0 for the lung in air, and 1.5 for the upright lung in saline. It can be concluded that airways of lungs inverted in saline close more uniformly than airways of lungs suspended in air or upright in saline. It also appears that airways in the base of a lung suspended in air normally close before airways in the apex. The liquid gradient along a lung suspended in saline causes the airways to close more uniformly when the lung is inverted and less uniformly when the lung is upright. (Supported in part by DOE contract #DE-AT-21-MC 11284).

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RESPONSE OF GUINEA PIGS TO INHALATION OF COTTON BRACT EXTRACTS. C.G. Hollinger*, R.E. Hyatt, J.R. Rodarte and M.S. Rohrbach*. Mayo Clinic and Foundation, Rochester, MN 55901.

The effects of cotton bracts extract on dynamic compliance (Cdyn), total pulmonary resistance (R_L), and respiratory rate (RR) were studied in spontaneously breathing anesthetized guinea pigs. Respiratory measurements were made using a water filled pleural cannula and an integrated flow plethysmograph. Cdyn and R_L were calculated at 2 and 5 minutes following challenge. One hundred breaths of extract were delivered by a DeVilbiss 645 nebulizer connected to the tracheostomy tube. In 6 guinea pigs exposed to Crude Bract Extract, Cdyn decreased (.74±.06 ml/cm H_2O to .36±.06 ml/cm H_2O), R_L increased (.10±.01 to .19±.03 cm H_2O/ml/sec) and RR increased (93±8 to 190±13 breaths/minute). All changes were significant. In 6 control animals there was no change in Cdyn, R_L or RR when challenged with concentrations of serotonin found in the extract. Two groups of 6 guinea pigs were challenged with either a high molecular weight (HMW) (The Physiologist, 1980, 23:45A) or a low molecular weight (Am. Rev. Resp. Dis., 1980, 121:252A) fraction which have in vitro activity. The HMW fraction increased RR (102±12 to 267±7 breaths/minute) with little change in Cdyn or R_L. The LMW produced little change in RR, R_L, or Cdyn. We conclude that the guinea pig is useful in studying the effects of cotton bracts extract. (Supported by USPHS NIH Grant HL 21894 and Parker B. Francis Foundation).

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COMPARISON OF THEORETICAL AND MEASURED IMPEDANCES (6-32 Hz) OF DOG CENTRAL AIRWAY MODELS. J.R. Krevans, Jr.* and A.C. Jackson. Primate Research Center, Univ. of Calif., Davis, CA 95616.

We developed computer models based on Crandall's equations (Theory of Vibrating Systems and Sound, 1926) to predict dog central airway resistances. A major concern was to investigate the relative importance of velocity profile distortion in the frequency dependent behavior of resistance. These equations were found to accurately predict resistance in long straight tubes (length/dia. >50). In shorter tubes these equations underestimated resistance, and the magnitude of this error was flow amplitude dependent. Similar results were obtained in a branching tube model. These errors are thought to be due to the effects of branching angles and entrance conditions. Resistances predicted from computer models based on published anatomical data of dog central airways were markedly lower than published data. Resistances of a dried central airway specimen were measured and found to be twice those predicted by these computer models, even with flow amplitudes as low as 10 ml/sec. We conclude that branching and entrance effects in the central airways are a major proportion of total resistance, and computer models not including these non-linear effects have limited usefulness in predicting airway impedances. Further, the magnitude of the increase in resistance with frequency due to velocity profile distortion, as described by Crandall, is small compared to the total measured resistance. (Supported by NIH grants HL-25631 and HL-26606.)

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MECHANISMS OF HISTAMINE INDUCED CONTRACTION OF CANINE AIRWAY SMOOTH MUSCLE. S. Shore*, C.G. Irvin*, T. Shenkier* and J.G. Martin*, (SPON: M. King). Meakins-Christie Labs, McGill Univ. Clinic, Royal Victoria Hospital, Montreal, Quebec, Canada.

To determine whether histamine has a local excitatory action on nerve endings in canine airways, we examined the effects of tetrodotoxin (TTX) (10^{-6}g/ml) and atropine (10^{-6}M) on the histamine dose-response curve of canine tracheal smooth muscle(TSM) in-vitro. The maximum tension produced by histamine (Tmax) in TTX pretreated specimens (6.82g/g tissue) was less than that obtained in control specimens (25.1g/g tissue) ($p<.001$, $n = 16$). TTX had no effect on the dose of histamine which produced 50% of Tmax (ED_{50}). Atropine decreased Tmax from 35.5 to 16.6g/g tissue ($p<.01$, $n = 7$) and increased ED_{50} from 1.74×10^{-5}M to 3.9×10^{-5}M ($p<.01$). Both ED_{50} and Tmax were log normally distributed and showed 10 and 35 fold variations respectively. To determine whether this variability of in-vitro histamine sensitivity could account for the observed variations in sensitivity to inhaled histamine in-vivo (Snapper et al.J. Appl. Physiol. 44: 738-742, 1978), we compared the dose of inhaled aerosolized histamine required to double pulmonary resistance ($ED_{200}R_L$) with the in-vitro histamine sensitivity in 14 dogs. The $ED_{200}R_L$ did not correlate with either Tmax or ED_{50}. We conclude that 1) histamine releases acetylcholine from parasympathetic nerve endings in canine TSM in-vitro 2) variations in histamine sensitivity of TSM in-vitro among dogs do not account for variations in histamine sensitivity observed in-vivo (Supported by MRC of Canada and the Cdn.Lung Assoc.).

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ROLE OF ENDOGENOUS HISTAMINE IN THE BRONCHIAL TONUS OF ASTHMATICS. V. POPA, Med. Coll. Ohio, Toledo, OH 43699

The purpose of this study was to determine whether endogenous histamine (H) affects the bronchial tonus of asthmatics. In 13 asthmatics we measured Gaw/V_L and FEF's before and after inhalation of saline (2 tests), 3.3, 5.5, 11.8, and 20.9 (2 tests) mg CP. In 9 subjects (NR) there was no significant change in Gaw/V_L (i.e. <+ 40%), FEV_1 (<+ 10%) and FEF's (<+ 20%). In 5 responders, (R) 3 types of changes were recorded: increase in Gaw/V_L after 20.9 mg CP (3R), increase in Gaw/V_L and FEF's after 11.8 and 20.9 mg CP (1R) and increase in FEF_{50} (1R) after 20.9 mg CP. In 5R and 4NR, Gaw/V_L and FEF's were measured before and after quantitative inhalation of H or acetylcholine (AC) until Gaw/V_L decreased by 40% (TD40). Then, H and AC tests were repeated after inhalation of saline, 20.9 mg CP and, for H tests only, 5.5 and 11.8 mg CP as well. TD40 of AC failed to change after CP. If no bronchodilatation occurred, DR for H(H+CP/H) was 1.7 - 3.7 in NR and 1.5 - 3.7 in R after 5.5 mg CP; and after 11.80 mg CP, 1.8 - 5.0 in NR 2.9 - 5.0 in R. After 20.9 mg CP, DR for H was 4.5 - 5.8 in Nr and 6.0 - 22.0 in R. The interindividual variation of TD40 for H was 240 x and that of DR for H was only 0.5 - 2.5 x. TD40 of H completely overlapped in 5R and 6NR. We conclude that in some asthmatics, peribronchial endogenous H modulates the resting bronchial tonus. DR for H needed for an H_1 blocker to dilate the bronchi is >6. The degree of bronchial hyperreactivity to H is independent of endogenous H and the binding affinity of H for H_1 receptors.

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HALOTHANE, ENFLURANE AND TRACHEAL SMOOTH MUSCLE TONE. E.M. Camporesi and J.V. Salzano. Dept. of Anesthesiology and Physiology, Duke University, Durham, N.C. 27710.

Tracheal smooth muscle tone was continuously assessed in an isolated segment of the upper cervical trachea of pentobarbital anesthetized dogs from the changes in pressure of a compliant cuff of an endotracheal tube inserted through the larynx. All animals had a low cervical tracheostomy and were breathing spontaneously through a non-rebreathing valve, or were ventilated with a constant VT after paralysis. A variable orifice vaporizer, interposed on the inspiratory limb of the breathing circuit, delivered variable concentrations of Halothane (H, 0 to 5%) or Enflurane (E, 0 to 3.5%) during one or two consecutive inspirations only. Spontaneous inhalation of H or E vapors was accompanied by dilation of the upper cervical tracheal segment, shortening of the duration of inspiration, a decrease of VT and shortening of expiratory time. The onset of tracheal dilation followed by 3 to 5 sec the beginning of inspiration. The amplitude of tracheal dilation was dose-related at low concentrations of H or E, but appeared to plateau at higher concentrations. The alterations of breathing pattern were similarly dose-related. During controlled ventilation tracheal dilation was also observed following H or E insufflation. Vagotomy, vagal cooling or atropine administration abolished the effect. The results are compatible with a H and E induced sensitization of vagal sensory receptors, on the one hand responsible for reflex modulation of airway tone, and on the other, contributing to the termination of inspiration. The data underline the coupling between breathing pattern and generation of airway tone. (Supported in part by NIH grant HL 23812.)

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EFFECTS OF CIMETIDINE ON FEMALE GUINEA PIG AIRWAYS IN VIVO AND IN VITRO DURING ONTOGENESIS. Charles Brink*, Pamela G. Duncan* and James S. Douglas. John B. Pierce Fndn. Laboratory New Haven, CT. 06519

Treatment of young or old female guinea pigs in vivo with cimetidine (30 mg/kg, i.p.) did not alter the histamine threshold doses. Propranolol (10 mg/kg, i.p.) reduced histamine threshold doses in young but not in old guinea pigs. Cimetidine was not effective in either age group after ß-blockade. Neither tracheal nor bronchial preparations from either age group when contracted with acetylcholine (50µM) were relaxed by dimaprit or 4-methyl histamine even after H_1 blockade with pyrilamine (20µM). Blockade of H_2 receptors with cimetidine (50µM) in bronchial tissues from young animals did not significantly affect tissue sensitivity or responsiveness to histamine. Bronchi from old guinea pigs became sensitized to histamine after cimetidine treatment. This effect was demonstrable after the bronchi were pretreated with indomethacin (17µM). The sensitizing effect of cimetidine is probably not related to the presence of H_2 relaxant receptors but to another unspecified effect of this drug. Our data also show that H_2 receptors have no physiological significance in modulating airway responsiveness to histamine aerosols in female guinea pigs. The absence of an effect of ß-blockade in old animals suggests that during ontogenesis the modulating actions of catecholamines upon airway responsiveness are significantly reduced.

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EFFECT OF ASCORBIC ACID ON AIRWAY RESISTANCE IN ASTHMATIC SUBJECTS. Vahid Mohsenin*, Arthur B. DuBois, and James S. Douglas. John B. Pierce Foundation Laboratory and Pulmonary Section, Yale University, New Haven, CT. 06519.

Previously, ascorbic acid was found to reverse the constriction of airways of healthy human subjects to methacholine. Indomethacin abolished this favorable effect. The object of this study was to investigate the effect of ascorbic acid on airways of asthmatic subjects. Seven subjects with asthma on no medication for 48 hr. underwent methacholine aerosol challenge, before and after 1 gm of ascorbic acid p.o. Changes in specific airway conductance (SGaw) were measured. Four of the subjects received 50 mg of indomethacin in conjunction with ascorbic acid on other occasions. The group mean ± SE for baseline SGaw was 0.125 ± .013 before and 0.133 ± 0.012 cm H_2O^{-1} Sec^{-1} after ascorbic acid, (P>0.5). However, the fall in SGaw (when expressed in % of baseline), three minutes after a methacholine induced bronchospasm was attenuated by ascorbic acid. The standard error of the difference (± 2.69) for paired values prior to (mean 74.80 ± 2.88 SE of group data) and after (82.20 ± 3.49) ascorbic acid was significant (p<0.02). Indomethacin abolished this effect (p>0.5). The results suggest a marginal pharmacological effect of ascorbic acid on methacholine induced bronchospasm, but the effect may be negligible therapeutically in asthmatics. Results in asthmatics are different from normal individuals. (Supported by NIH Grant #HL 23959-03).

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PROPRANOLOL-VAGAL-ALVEOLAR CO2 INTERACTIONS ON THE MECHANICS OF COLLATERAL VENTILATION DETERMINED WITH A WEDGED CATHETER. **L.E. Olson and N.E. Robinson. Michigan State University, E. Lansing, MI 48824**

The mechanical properties of a collaterally ventilating lung segment were studied in 18 anesthetized (chloralose-urethan) paralyzed (succinylcholine) mongrel dogs artificially ventilated with room air (FETCO2=5%). Nine dogs were pretreated with propranolol (Group II) and 9 dogs were not (Group I). With 0, 5 or 12% CO2 flowing into the segment, steady state resistance (cm H20/ml/sec) of segmental airways (Rss) and time (sec) for 90% pressure equilibration between the segment and airway opening after flow was discontinued (T90) were determined at FRC with the vagus nerve ipsilateral to the segment intact, sectioned or electrically stimulated. Vagal sectioning had no effect. Propranolol treatment had no effect on Rss or T90 with the vagus intact or sectioned. Segment hypo or hypercapnia did not prevent increases in Rss and T90 during electrical vagal stimulation.

	0% CO2	5% CO2	12% CO2
Rss Group I	1.34*	0.87	1.04
Group II	2.24	1.44	1.11
T90 Group I	11.19	8.63	9.98*
Group II	8.22	4.85	3.38

The data obtained during vagal stimulation (shown above) suggest that pulmonary beta two receptors are modified by changes in alveolar CO2 tensions. Additionally, because the differences in T90 cannot be explained by changes in Rss, beta blockade probably reduces segment compliance. **(USPHS HL-17768)**

CELL PHYSIOLOGY, BLOOD COMPONENTS AND NEOPLASIA

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CELLULAR CONTRACTION AND RELAXATION: ROLE OF FIBRONECTIN (Fn). Anwar A. Hakim. University of Illinois at the Medical Center. Chicago, Illinois 60612.

Human skin fibroblasts (HSF) synthesize and release two growth stimulating factors: a dialyzable activity which causes an increase in cellular proliferation (HFGPF)(Hakim, Experientia 34, 1515, 1978; J. Supramolecular Structure Suppl. 3,224, 1979), and a non-dialyzable activity that promotes cell attachment and adhesion. They have a finite life span, they proliferate in monolayers and they are contact inhibited. If cultured in media supplemented with 0.1M EDTA, trypsinized or incubated at 0 to 15°C, the HSF change from attached elliptical to round floating cell cultures. If treated with 0.1M EDTA, ATP, trypsinized or incubated at 0 to 15°C the attached HSF monolayers detach from plastic substratum and form floating round cells that progressively aggregate. In the presence of ATP spread on glass, but not on Fn-coated surface, contract and detach.Malignant melanoma cells HMMC) proliferate in multicell layers, they are not contact inhibited and they adhere together to form cell clumps. On Fn- but not on collagen-coated surface HMMC form monolayers. ATP at 10^{-3}M/liter disintegrates HMMC aggregates, whereas ADP reverses the ATP effects and render the cells more adhesive. HSF and HMMC were preincubated with ^{35}P-ATP for 15 min at 37°C, washed then seeded onto uncoated and Fn-coated surface. Cells seeded onto plastic surface did not attach. After 48hrs incubation and cells detached, the Fn-coated plates contained the ^{35}P-activity. Therefore, Fn is phosphorylated during ATP-induced cellular contraction.

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EFFECTS OF TRIMETOQUINOL AND RELATED BENZAZEPINE ANALOGS ON AGGREGATION, SEROTONIN UPTAKE AND SECRETION BY HUMAN PLATELETS. Huzoor-Akbar*, S. Navran*, J. Chang, D. Miller* and D.R. Feller*(SPON: H.P. Pieper). Col. of Pharmacy, Ohio State Univ., Columbus, OH 43210 and Ohio Univ. Col. of Osteopathic Medicine, Athens, OH 45701.

Blood platelets provide a readily obtainable cell system which is used for in vitro evaluation of (a) antiaggregatory agents, and (b) psychotropic agents. This report compares the effects of S(-)-trimetoquinol (I) with that of racemic 7,8-dihydroxybenzazepine (II) and 7,8-methylenedioxidebenzazepine (III) analogs of I on platelet aggregation, serotonin (5HT) uptake and secretion by platelets. Aggregation and 5HT secretion from platelets induced by arachidonic acid (AA) and U46619, a stable endoperoxide of PGH_2, was only inhibited by I. The inhibitory concentration-50's (IC50) for I against AA and U46619 were 47 μM and 11 μM, respectively. By contrast, the prostaglandin (PG) independent aggregation and 5HT secretion induced by phospholipase C was inhibited by all three agents and the rank order of inhibitory potency was III > II > I. In other experiments only II and III inhibited 5HT uptake by platelets in a concentration dependent manner. III was 5-fold more potent than II in inhibiting 5HT uptake into platelets. These findings show that (a) II and III are highly selective and more potent inhibitors of the PG-independent pathway of platelet aggregation than I and (b) the ability of II and III to block 5HT uptake by platelets may reflect a potential psychotropic action. (USPHS Grant HL 22533).

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A FACTOR IN NORMAL RABBIT SERUM WHICH SPECIFICALLY REACTS WITH STAPHYLOCOCCUS AUREUS. Linda Lizak Witt* and Paul Nathan. Shriners Burns Institute and the University of Cincinnati College of Medicine, Cincinnati, Ohio 45219.

Frozen and thawed normal rabbit sera (NRS) contain a factor(s) that reduces the Staphylococcus Aureus (St.a.) count detected in a bacterial suspension after a 2 hr incubation at 20°C. In 13 tests with NRS present at 25 to 50% of the reaction volume, 92.5 ± 1.5% (Mean ± SEM) of the St.a. were eliminated when the targets were 10^7 St.a./ml. In an additional 13 tests with NRS at 12.5% of the suspension volume, the cell count was reduced by an average ± SEM of 41 ± 7%. In 24 control tests, the suspension media alone affected only 10 ± 4.6% of the test bacteria. The serum activity has some degree of specificity; Pseudomonas aeruginosa and E. coli are not affected by NRS. Normal rat serum and chicken serum also possess an activity directed toward St.a. whereas normal dog serum and human serum are inactive. Heat inactivation of NRS (30 min at 56°C) in four tests showed a reduction of colony counts of 96 ± 0.92% of the St.a. The results show that a heat-stable normal serum product from rabbits (and possibly from rats and chickens) can specifically reduce St.a. colony counts recovered from cell suspensions and does not affect other bacterial species. The process initiating the development of the active serum factor is not known. Possibly bacteria resident in the digestive tract provoke the development of serum factors which may operate to control specific microbial infections.

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OSMOTIC PRESSURE OF HUMAN, SHEEP AND DOG ALBUMIN SOLUTIONS. N.C. Staub and M. Grady*, Cardiovascular Research Institute and Department of Physiology, University of California, San Francisco, CA 94143.

With the advent of selectively permeable membrane, strain gauge osmometers, several groups have reported deviations from the Landis and Pappenheimer colloid osmotic pressure (Π) equations (Handbook Physiol. Circulation II:961, 1963). We measured Π of commercially prepared human, sheep and dog albumin solutions up to 10 g/dl at 37°C and pH 7.4 using a YM-10 membrane (Amicon). We applied each sample three times in succession to achieve a plateau. The data were highly reproducible (c.v. < 4%) for all albumins in three runs over two weeks. Sheep and dog were identical, but human Π was 8% less at 10 g/dl. On polyacrylamide gel electrophoresis, all albumins showed some high molecular weight component but human albumin contained relatively more. The third order polynomial of best fit for the pooled data is:

$$\Pi(cmH_2O) = 3.7C + .25C^2 + .020C^3,$$

essentially identical to Landis and Pappenheimer's equation. The calculated molecular weight of albumin = 70 x 10^3 Daltons is 11% high because commercial, lyphilized albumins contain a high molecular weight contaminant, probably albumin dimer. [Supported in part by HL25816 (Program Project)].

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LOCALIZATION OF ERYTHROPOIETIN IN RAT LIVER. G.K. Naughton,* B.A. Naughton, P. Liu*, S.J. Piliero, and A.S. Gordon. N.Y.U. Dept. of Biology and College of Dentistry. New York,N.Y.10003

Immunological studies were performed utilizing a specific fluorescein labelled guinea pig-anti-rat erythropoietin (Ep) to localize the site of production and/or storage of this hormone in rat liver. Rat Ep was obtained by passing sera from hypoxic rats through an Amicon XM-100 filter, running the retenate on Con-A Sepharose, and separating the bound fraction on Sepharose G-200. The rat Ep was found to have a M.W. of 100-125,000. The degree of purity achieved was approximately 8-10,000 I.U. Ep/ml. Guinea pigs were inoculated with this purified fraction over an eight week period. Immune sera from these animals was precipitated with ammonium sulfate. IgG fractions were applied to a Cn-Br Sepharose column to which purified rat Ep was previously bound. Resulting Ab-Ag complexes were eluted and efficacy of the anti-Ep was tested using neutralization and immunoprecipitation tests. After further Ab purification,anti-Ep was coupled to fluorescein and applied to frozen sections of rat liver of: 1.normal, 2.hypoxic, and 3.hepatectomized (hepx) animals. Sinusoidal (Kupffer) cells showed varying degrees of fluorescence after hypoxia or following hepx whereas no fluorescence was noted in normal livers or in hepatic parenchymal cells of any of the groups studied. (Supported by NIH Grant # 2R01 HLB03357-23)

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VARIOUS FORMS OF MEGAKARYOCYTES IN THE SPLENIC RED PULP. S.H. Song. Biophysics Department, Health Sciences Centre, The University of Western Ontario, London, Canada. N6A 5C1.

Histological studies on the splenic megakaryocytes were performed after the red cell washout from the splenic red pulp in isolated, perfused spleens. Various stains were used including PAS, toluene blue and Gomori Trichrome stains.

Since it was reported that in the samples of splenic venous outflow, 5 different types of megakaryocytes can be found (Song, 1978), more vigorous search for mobile megakaryocytes is attempted from the histological sections of canine and feline spleens. Several types of megakaryocytes are identified especially in spleens of young animals, and previously bled animals. Projections - amoeboid-like pseudopoda or even horse-shoe type of cytoplasmic configurations are found in the red pulp near the marginal zone of the white pulp. These projections or villi forms are not associated with fenestrations which were found in the bone marrow sinuses. These projections are rather highly suggestive of active mobility than particulating into platelets. Therefore, in the splenic red pulp megakaryocytes can be mobile to seek the egress into pheripheral circulatory system by amoeboid movements. Also this mobility can suggest possible access for megakaryocytes to appear in the peripheral circulation as well as in pulmonary circulatory system.

Song (1978). Studies on splenic megakaryocytes: I. Recovery of megakaryocytes from the splenic venous outflow. Vox Sang.

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SISTER CHROMATID EXCHANGES (SCEs) IN MAMMARY CARCINOMAS OF DIFFERENT SIZES. Anna Goldfeder, Ranjit Banerjee,* and Jyotirmay Mitra.* New York University, Cancer & Radiobiological and Cytogenetic Research Laboratories, Dept. of Biology, New York, N.Y. 10003

We have previously shown (In Press, J.N.C.I. July 1981) that SCEs in dbrB tumors is significantly higher (P 0.001) than those in isogeneic bone marrow cells used for comparative purposes. In the present study we have compared dbrB tumors of two sizes (0.5 and 1.0 cu cm) to estimate a possible tumor size effect on the frequency of SCE by using BrdU tablet method. We have found that the SCE frequency of 1.0 cu cm tumor is approximately 15.0±0.27/cell which is slightly significant (P 0.05) as compared to 0.5 cu cm tumor having 14.53±0.36/cell. Further, when these data were analyzed as SCE/chromosome for more precision, it was found to be insignificant statistically. These findings indicate that the size of the tumor (0.5 to 1.0 cu cm) does not influence frequencies of SCE. Since the dbrB mammary tumor kills the host within two weeks, the use of larger than 1.0 cu cm tumor was not feasible for SCE analysis.

(Supported by Grants from American Cancer Society #PDT-107B and from NIH #12076).

MUSCLE PHYSIOLOGY II

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REDUCED CARDIAC FUNCTION IN ISOLATED, PERFUSED HEARTS FROM ALLOXAN-DIABETIC AND FASTED RATS. David W. Garber and James R. Neely. Department of Physiology, The M. S. Hershey Medical Center, Penn State University, Hershey, PA 17033

Hearts from diabetic rats showed reduced function when perfused by the working heart technique with Krebs-Henseleit buffer containing 11 mM glucose. The rats were injected with 60 mg alloxan per kg body weight and insulin maintained for 1 week. The animals were sacrificed 5 days after removal of insulin. At near-maximum work load, decreases occurred in peak systolic pressure (Control=189±2.01 mm Hg, Diabetic=164±1.54), heart rate (C=268±6 beats/min, D=220±14), and Ca^{++}-activated ventricular myosin ATPase (C=1.35±0.02 µm P_i/min/mg myosin, D=1.05±0.02). Pacing did not restore peak systolic pressure. When paced, maximum rate of intraventricular pressure development (dP/dt_{max}) was reduced (C=9.58±0.52 mm Hg/msec, D=6.95±0.28). Serum levels of T_3 (C=72.06±2.33 ng/dl, D=36.09±4.59), T_4 (C=3.86±0.36 µg/dl, D=1.29±0.23), and free T_4 (C=1.20±0.10 ng/dl, D=0.62±0.09) were significantly reduced. Hearts from non-diabetic animals which had been fasted for 5 days were also perfused. Although they showed a decrease in peak systolic pressure compared to controls (C=177±1.67, Fasted=163±2.11), heart rate was not decreased (C=265±17, F=278±17). A significant decrease occurred in Ca^{++}-activated myosin ATPase (C=1.59±0.06, F=1.43±0.03), dP/dt_{max} (C=9.38±0.32, F=7.85±0.34), serum T_3 (C=71.64±3.50, F=30.02±3.38), and serum T_4 (C=3.44±0.17, F=1.33±0.21). (Supported by grant #HL-20484.)

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ADENOSINE AND POSITIVE INOTROPIC RESPONSES ELICITED IN ATRIA. J.G. Dobson, Jr., Department of Physiology, University of Massachusetts Medical School, Worcester, MA 01605

Adenosine has been shown to attenuate the catecholamine-induced enhancement of cardiac contractility. This study was undertaken to investigate if adenosine is capable of inhibiting the positive inotropic responses produced by various contractile interventions. Isolated rat and guinea pig atria were bathed in physiological saline (PS), stimulated to contract isometrically at 2/sec and the rate of tension development (dF/dt, an index of contractility) recorded. In rat atria bathed in PS containing 2.5 mM Ca^{2+} 1 µM isoproterenol (ISO) increased dF/dt from 7.5±1.5 to 14.3±2.3 gm/sec and 10 µM adenosine (ADO) reduced the increase by 32%. ADO alone did not significantly influence dF/dt. In depolarized atria (23mM K^+) ISO restored tension development (i.e. dF/dt increased from 0 to 11.2±2.6 gm/sec) and ADO reduced this restoration by 64%. Theophylline (10^{-5}M) prevented the adenosine attenuation but atropine and indomethacin did not. Elevation of PS Ca^{2+} from 1 to 4mM in the absence of ISO produced a 4.3-fold increase in dF/dt that was not affected by ADO. In guinea pig atria increasing the frequency of contraction from 2 to 6/sec and paired-electrical stimulation enhanced dF/dt by 1.9 and 2.4-fold, respectively. However, ADO had no effect on the latter two inotropic responses. These results suggest that adenosine attenuates only those positive inotropic responses elicited by catecholamine stimulation. (Supported by grants 18280 and 22828 from the NHL&BL.)

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PROTECTIVE EFFECT OF CATION SUBSTITUTION ON CALCIUM PARADOX. Terrell L. Rich and Glenn A. Langer. Dept. of Physiology and Cardiovascular Research Laboratories, UCLA School of Medicine, Los Angeles, California 90024.

The isolated arterially perfused interventricular rabbit septum was used to investigate the protective effect on the calcium paradox of adding micromolar amounts of divalent cations during the Ca-free perfusion period. Flow rate, beating rate and septal temperature were kept constant. Muscle damage during 1.5 mM Ca reperfusion was assessed by quantitating creatine kinase (CK) release, ^{42}K loss, contracture development and recovery of active developed tension. The inclusion of 50 μM Ca^{2+} during 30 minutes "Ca-free" perfusion followed by Ca^{2+} reperfusion showed essentially complete protection, i.e., there was full mechanical recovery with no K^+ loss or additional CK release. Other cations substituted in 50 μM concentrations during the Ca-free period showed variable ability to protect. The order of effectiveness (Ca > Cd > Mn > Mg) was related to the crystal ionic radius, with those radii closest to that of Ca^{2+} (0.99A) exerting the greatest protective effect. It is proposed that hypothermia and the effective substituted cations exert a similar protective effect on the Ca-paradox by inducing a phase transition in the membrane lipids (from a more liquid to a less liquid state). It is striking that the cation sequence for effectiveness in Ca-paradox protection is the same sequence for potency of excitation-contraction uncoupling.

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COMPARISON OF THE Ca^{++} TRANSIENTS IN VENTRICULAR MUSCLE FROM CATS AND RABBITS. James P. Morgan* (SPON: John R. Blinks) Dept. of Pharmacology, Mayo Foundation, Rochester, MN 55905

Ca^{++} release from the sarcoplasmic reticulum (SR) may play a less important role in the activation of ventricular muscle from rabbits than in other mammals. To test this hypothesis, Ca^{++} transients were recorded in ventricular muscle from cats and rabbits microinjected with the bioluminescent protein aequorin. Light output (L) (i.e., Ca^{++}) and force of isometric contraction (T) were recorded at 4 sec intervals of stimulation. The effects of frequency of stimulation (F) and drugs known to affect the uptake and release of Ca^{++} from the SR were studied, i.e., isoproterenol (I), caffeine (C) and ryanodine (R). In the cat, increases in F increased (↑) peak L (PL) and peak T (PT) but decreased (↓) time to peak L (TPL), time to peak T (TPT), half-time of the decline of L ($T_{1/2}L$) and half-time of decline of T($T_{1/2}T$). In the rabbit, increases in F ↑ PL and PT but did not significantly affect TPL, TPT, $T_{1/2}L$ or $T_{1/2}T$. In both cats and rabbits, I ↑ PL and PT but ↓ TPL, TPT, $T_{1/2}L$ and $T_{1/2}T$; R ↓ PL and PT but ↑ TPL, TPT, $T_{1/2}L$ and $T_{1/2}T$. In cats, C ↑ PT, TPL, TPT, $T_{1/2}L$ and $T_{1/2}T$ but ↓ PL. In rabbits, the effects of C varied with the dose. In both cats and rabbits, L exhibited a single component under all conditions tested; distinct components related to Ca^{++} entry and release were not identified. These results indicate that although there are differences in the mechanisms that regulate excitation-contraction coupling in the cat and rabbit, similar processes control the activation and relaxation of ventricular muscle from both species. (Support: USPHS Grants HL 07111 and HL 12186)

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ISOVOLUMIC PRESSURE DEVELOPMENT BY THE LEFT VENTRICLE OF THE ISOLATED, GENETICALLY OBESE RAT HEART. Norman F. Paradise, Charles F. Pilati* and Judith A. Finkelstein*. Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272.

We sought to determine if left ventricular (LV) function of the heart from the adult, obese animal is impaired. Hearts from 38-52 week-old genetically obese (fa/fa), female Zucker rats (640 ± 18 g) and their lean (Fa/--) littermates (277 ± 7 g) were isolated under Nembutal anesthesia and supported metabolically by retrograde aortic perfusion (5 ml/min, 37°C) with physiologic solution containing suspended canine erythrocytes (hematocrit, 20%). The intraventricular septum was crushed to dissociate A-V conduction and the ventricles were paced at 180/min. A fluid-filled balloon was placed in the LV and pressure-volume (P-V) relationships were obtained. The fa/fa and Fa/-- end-diastolic P-V curves were similar, but the fa/fa systolic P-V relationship was shifted upward and to the left which indicated that the obese rat's heart had a greater pressure generating capability. This probably was related to the increased LV mass of the fa/fa heart (fa/fa LV mass of 0.96 ± 0.03 g versus Fa/-- mass of 0.68 ± 0.03 g) since, when normalized for LV wall thickness, fa/fa LV systolic pressures were not different from control. Thus, the intrinsic contractile function of the hypertrophied LV of the heart from the genetically obese, female rat does not seem to be depressed. (Supported in part by the Akron District Chapter, Inc., of the American Heart Association, by BRDG 1 S08-RR 09026 and by NIH RO1-NS 14344).

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EFFECTS OF PLASMA ON Cl-36 EFFLUX IN ISOLATED TOAD SKELETAL MUSCLE. D.D. Macchia. Indiana Univ. Sch. of Med., Northwest Ctr. for Med. Ed., Gary, Ind. 46408 and The Univ. of Chicago, Dept. of Med., Chicago, Ill 60637 (SPON: M.F. Asterita)

Toads were injected i.p. with a Cl-36 solution. The animals were allowed to sit for a time to permit in vivo equilibration of the isotope with muscle Cl-35. The muscles were then removed and the Cl-36 efflux rates determined for muscles washed out in either a Ringer's solution or plasma sample. Muscles "washed out" in toad Ringer's were observed to have a mean Cl-36 efflux rate (0.042 ± .005 min^{-1}, n= 4) approximately 50% faster than the mean efflux rate measured in muscles washed out in plasma (0.029 ± .002 min^{-1}, n=5). When toad skeletal muscles were loaded in Ringer's in vitro (3-3.5 hrs), prior to the in vitro washout, the efflux rates were observed to increase still further (0.065 ± .010 min^{-1}, n=4). In a separate series of experiments, muscles from toads were loaded in vitro in a radiolabelled Ringer's solution and the contralateral muscles loaded in vitro in a Cl-36 labelled plasma sample. Little difference in the Cl-36 efflux rate was observed between muscles loaded in plasma and those loaded in vivo (0.029). Further, the efflux rates in muscles loaded and washed in Ringer's were greater than the contralateral muscles loaded and washed in plasma. These observations would suggest that the primary cause of the observed differences between muscles studied in Ringer's vs plasma is a plasma fraction absent in Ringer's, which affects membrane permeability. (HL10503 & 20592)

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PLASMA EFFECTS ON ANION PERMEABILITY OF TOAD SKELETAL MUSCLE. P.L.Golnick*,M. Anderson* and D.D. Macchia. Indiana Univ. Sch. of Med., Northwest Ctr. for Med. Ed., Gary, Ind. 46408.

Toad semitendinosus muscles were removed and one group of muscles incubated in a ^{35}S-SO_4 labelled toad plasma sample and the contralateral muscles placed in a radiolabelled Ringer's solution. Tissues were allowed to incubate for time periods ranging from 45 to 170 mins and the "sulfate space", S_o, measured. The S_o (in g SO_4 Space H_2O/g Muscle H_2O) of muscles incubated in plasma for up to 170 mins remained remarkably constant, measuring 0.19 ± .01 and 0.20 ± .01 (n=6) at times= 45 and 170 mins, respectively. These space values are similar to those measured in vivo (0.20 ± .01, n=13). On the other hand, the S_o of the contralateral muscles incubated in Ringers solution were observed to increase (0.18 ± .04 at t=45 mins to 0.30 ± .01 at t=170 mins, n=3). When muscles were incubated in toad Ringer's containing toad blood albumin (16 mg/ml) the S_o was observed to be similar to those values measured in toad plasma. Further, the S_o was observed to remain relatively constant over the time interval examined (0.19 ± .01 and 0.20 ± .02 at times t=45 and 170 mins, respectively). Since little difference in extracellular space (as measured morphometrically) was observed between muscles incubated in plasma and Ringer's solution, the above results were interpreted as a change in membrane anion permeability in the absence of some plasma fraction (i.e., albumin) permitting cellular entry of the normally impermeant anion. (Supported in part by USPHS NIH Grant AM 27148)

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EFFECTS OF RUTHENIUM RED (RR) ON POTASSIUM CONTRACTURES IN SKELETAL MUSCLE. **K. W. Snowdowne* and J. N. Howell. Univ. of Pittsburgh, Pittsburgh, PA, 15261, and Ohio Univ., Athens, OH, 45701**

Several investigators have reported effects of the hexavalent cation, RR, on excitation-contraction coupling. Using highly purified RR, we have been unable to detect any effects on K^+ contractures. Single twitch fibers or bundles containing 2 or 3 fibers from leg muscles of R. temporaria were mounted in a Hodgkin-Horowicz type chamber and their length was adjusted so as to produce maximum tetanus tension. Fibers were then equilibrated with solutions containing $TRIS^+$ in place of Na^+. Contracture tension was expressed as % of 100mM K^+ reference contractures obtained before and after test contractures. 45 min. exposures of fibers to 15μM recrystallized RR (c=60,778) caused no shift in the contracture curve. Similar exposures to commercial samples of RR or to RR that had been allowed to stand for a year following recrystallization produced a rightward shift of the curve corresponding to an increase in mechanical threshold of 7.5mV. Previous work had shown that 15uM RR causes a marked shift in action potential threshold. Since the effects of other multivalent cations on mechanical threshold are thought to arise from a surface charge mechanism within the t-tubules, the failure of RR to share these effects suggests that RR fails to gain access to the t-system. This conclusion is consistent with electron microscopic observations. (Supported by NIH AM 15533 and 22052 and the Ohio University College of Osteopathic Medicine.)

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VERTEBRATE SMOOTH MUSCLE CONTRACTILE ELEMENTS ATTACH TO AN AXIAL CYTOSKELETON.Roland M. Bagby and Margaret D. Corey.* University of Tennessee, Knoxville, TN 37916.

Many studies of smooth muscles show attachment of thin filaments to membrane-associated dense bodies(MADB).Some studies also show thin filaments attached to cytoplasmic dense bodies (CDB).Cooke and Fay(J. Cell Biol. 52:105,1972) proposed a cytoskeletal network(CSN) of CDB and intermediate filaments(IF) which attach to MADB primarily at terminal portions of cells, based on an axial concentration of CDB and IF in stretched muscles.Small(J. Cell Sci. 24:327,1977) also proposed a CSN of MADB, CDB and IF.In both models, contractile elements(CE) pass through or around the CSN without attaching to it.

We have fixed guinea pig taenia coli at various points on their length-tension relationship in both relaxed(.01 mg/ml epinephrine) and contracted (.01 mg/ml acetylcholine) states and examined their ultrastructure.Relaxed muscles showed CDB becoming more axial as length increased beyond L_o, in accordance with the Cooke and Fay model, but contracted muscles showed a random distribution of CDB at the same lengths.This is consistent with obliquely oriented CE being attached peripherally by thin filaments to MADB and at their other ends to the more axial CDB.Thus, when CE contracts, the transverse vector of CE tension opposes the axial movement of CDB.The models of Cooke & Fay and Small are not consistent with our observations of CDB distribution in contracting cells.
(Supported in part by NIH Grant HL-18077-06).

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NON-LINEAR STIFFNESS OF ACTIVE SMOOTH MUSCLE SUBJECTED TO SMALL STRETCHES. Richard A. Meiss. Indiana University School of Medicine, Indianapolis, Indiana 46223

Electrically-stimulated mesotubarium and ovarian ligament muscles from non-pregnant rabbits were subjected to sinusiodal oscillatory length perturbations (40 to 100 Hz) of small and variable amplitudes (0 to 100 micrometers). Stiffness of active muscle was calculated by measuring the amplitude of the resulting force perturbation and dividing it by the length perturbation amplitude. For perturbation amplitudes up to approximately 15 micrometers peak-to-peak (approx. 0.15% of the muscle length) the measured stiffness was not dependent on the stretch amplitude; at larger amplitudes the computed stiffness was reduced. For a given muscle, the absolute stretch magnitude at which the computed stiffness became dependent on the stretch amplitude did not depend strongly on the muscle length at which the measurements were made. It is possible that the point at which the deviation began reflects some internal dimension of the contractile apparatus.
(Supported by USPHS NIH Grant HD 10898)

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REDUCED CONTRACTURE OF DEEP SECOND DEGREE BURN WOUNDS COVERED WITH A SYNTHETIC DRESSING. Chenghui Fang*, J.W. Alexander*, Edward C. Robb* and Paul Nathan. Peking Med. College, Dept of Surgery, Peking, China, Shriners Burns Inst., and the Univ. of Cincinnati College of Medicine, Cincinnati, Ohio 45219.

Minimizing the development of wound contractures following deep partial thickness burn injuries would improve the cosmetic appearance and function of the healed skin. This study was designed to evaluate the potential beneficial effects of a synthetic burn dressing (Hydron - formed on the wound from a mixture of polyethylene glycol-400 and poly-2-hydroxyethyl methacrylate) when used to prevent scar contracture. Deep partial thickness burns were inflicted on both sides of the back of anesthetized guinea pigs by preheated metal templates (75°C for 10 sec). Twenty-two wounds, after three weeks of Hydron treatment, had significantly less contracture (26.6 $\pm$ 2.2%, Mean $\pm$ SEM reduction in the original wound area) than did 12 wounds treated by exposure (70.9 $\pm$ 1.7% reduction in the original wound area). Silvadene (a topical antimicrobial) treatment of 12 wounds for three weeks resulted in wound contractures of 61.9 $\pm$ 2.47%. When 10 of the test burn wounds were covered with Hydron for 6 weeks, only 36.7 $\pm$ 5.8% contractures were observed. Continuous coverage of the wounds by the Hydron dressing provides an effective splint which holds the wounds expanded and prevents the massive contractures associated with healing burn wounds in guinea pigs.

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THE UTILITY OF PSEUDO-RANDOM NOISE IN DIFFUSION AUGMENTED BY HIGH FREQUENCY OSCILLATIONS. J.R. Clarke and L.D. Homer. Naval Medical Research Institute, Bethesda, Md. 20014.

The nature of the pressure pulsations required to enhance gaseous diffusion in airways has not been well explored, other than to note that optimal excitatory frequencies seem to vary inversely with gas density. We compared sinusoidal oscillations and pseudo-random noise as a means of augmenting diffusion in a two compartment mechanical model. The oscillator was a loud-speaker receiving inputs from either a signal generator (sinusoidal input) or a Nicolet Fast Fourier Transform Analyzer (pseudo-random noise from 0 to 100 Hz). One compartment containing the speaker was filled with 02, and was attached through a valve to the second compartment, a bottle containing air. A pressure transducer located in the speaker compartment allowed power spectral descriptions of the pressures generated by the sinusoidal and random excitation. The rate of nitrogen washout was monitored by a mass spectrometer sampling from the bottle. For sinusoidal excitation the mixing process was most rapid at 35 Hz, with the speaker output varying only slightly for changes in frequency around 35 Hz. Mixing could also be achieved by pseudo-random noise. Details on the relative efficiencies of these two methods of excitation will be presented. The use of pseudo-random noise eliminates the need to alter oscillatory frequencies for varying gas densities. (Supported by Naval Medical Research and Development Command, work unit no. MR0001.1305.1273).

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CARBON MONOXIDE TOXICITY. G. Gutierrez*, D.R. Dantzker and H.H. Rotman. Univ. of Michigan, Ann Arbor, MI 48109

Haldane's principle, $M=pO_2$ [HbCO]/pCO [HbO_2] has been widely used to predict the equilibium concentration of HbO_2 and HbCO when blood is exposed to pO_2 and pCO. The predictive validity of this equation has been questioned by several investigators, since the term M is not a constant, but depends upon the amount of free hemoglobin available in solution. It is the purpose of this paper to propose a set of formulas to describe the equilibrium relationship between pO_2, pCO, HbO_2 and HbCO independent of the hemoglobin saturation level and M. Using first order kinetics, it is possible to formulate a differential equation whose steady state solution fits different sections of the O_2-Hb dissociation curve. A similar method is used for the CO-Hb dissociation curve. These equations are solved simultaneously, noting that [Hb]total = [HbO_2] + [HbCO] + [Hb]free. This results in equilibrium expressions for HbO_2 and pCO when HbCO and pO_2 are known. The heme to heme interaction effect is taken into account by shifting the origin of the steady state solutions. HbO_2 dissociation curves are generated using these equations under different levels of HbCO. The predicted HbO_2 values fall with ±7% of previously published data. The mathematical predictions are also compared to experimental values obtained in vitro when fresh heparinized human blood is tonometered under varying ambient concentrations of O_2 and CO. Eighty five percent of the predicted values lie within ± 5% of the experimental data. This validates the model as a predictor of HbO_2, given HbCO and pO_2.

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MAXIMAL OXYGEN UPTAKE (DMO_2) IN THE REPTILIAN VERSUS MAMMALIAN LUNG: THE TURTLE IS NOT FASTER THAN THE RABBIT. Barry Burns. MIEMSS, U.Md.,Balto, Md. 21201

Pulmonary membrane diffusing capacity was measured by the dithionite (DTT) method (J.Appl.Physiol.46 (1):100, 1979) in the lungs of 5 turtles (P.scripta 1 kg) and in 5 common New Zealand white rabbits (3.5-4.5 Kg). Lungs were perfused through the pulmonary artery (P_{PA}=14-20 torr) with a DTT solution (80 mM) containing 4 gram% albumin (25°C). Rabbits initially anesthetized with pentobarbital (35 mg/Kg, I.V.); turtles with Ketamine (120 mg/Kg, I.M.). Lungs were removed from the rabbits. Turtle lungs were left in-situ, the turtle placed on its back and a 4 cm square hole cut in the ventral shield to cannulate the pulmonary artery.

Results: DMO_2 (ml/min/torr, STPD) in the rabbit averaged 16.8 (± 0.37 s.e.) at a mean lung volume of 122 (±10 ml at 4 cmH_2O PEEP). The measured DMO_2 in the turtle averaged 0.128 (± 0.009) at a mean lung volume of 33 (± 3.7). If the DMO_2 values are normalized for the lung volume, the DM/VL ratio for the rabbit (0.137) is 34 times larger than the corresponding DM/VL ratio for the turtle (0.004) at 25°C. A significant membrane diffusion limitation for gas exchange may be present in the turtle under normal circumstances; whereas, O_2 uptake in the rabbit is never limited by membrane diffusion resistance.

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ARTERIAL HYPOXEMIA AFTER OLEIC ACID: ROLE OF DIFFUSION LIMITATION FOR 02. P.T. Schumacker*, P. Breen*, G. Hedenstierna*, N.J.H. Davies*, J. Ali, L.D.H. Wood, and P.D. Wagner. Depts. of Med., U. Calif., San Diego and U. Manitoba, Canada

Oleic acid has been used previously as a model of diffuse, hemorrhagic pulmonary edema. To determine whether diffusion limitation contributes to hypoxemia in this model, we studied simultaneous O_2 and inert gas exchange in 7 anesthetized, paralyzed dogs challenged with oleic acid (0.03 ml/Kg). Distributions of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) were estimated with the multiple inert gas elimination method. Cardiac output ($\dot{Q}_T$) was increased by opening peripheral A-V fistulas to stress equilibration by diffusion. Measurements were made at 2 hrs. post-challenge with the fistulas open ($\dot{Q}_T$ = 4.0±1.1 L/m) closed ($\dot{Q}_T$ = 3.0±0.7 L/m) and again open ($\dot{Q}_T$ = 4.0±0.7 L/m). Inert gas shunt with the fistulas open (35.0±4.5%) fell to 31.0±4.2% ($p<.05$) with the fistulas closed, and returned to 36.9±6.8% ($p<.025$) when $\dot{Q}_T$ was again increased. Measured arterial P_{O2} did not differ statistically from that predicted from inert gas $\dot{V}_A/\dot{Q}$ distributions at high $\dot{Q}_T$, and predicted values were only 1.4±0.7 torr higher at normal $\dot{Q}_T$ ($p<.05$). Thus, observed hypoxemia can be largely attributed to $\dot{V}_A/\dot{Q}$ inequality or shunt, and diffusion limitation does not contribute significantly to the hypoxemia in this model. The increased shunt at high cardiac output is therefore likely due to a redistribution of blood flow or an increase in the amount of edema, and not due to development of diffusion limitation. (Supported by HL 17731 and MRC, Canada.)

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ROLE OF LIMITATION OF OXYGEN DIFFUSION IN CANINE UNILOBAR OLEIC ACID PULMONARY EDEMA. P. Breen*, P. Schumacker*, G. Hedenstierna*, J. Ali*, P.D. Wagner*, and L.D.H. Wood*. (SPON: H.S. Goldberg). U. of Man., Canada, and U. of Calif, San Diego.

In pulmonary edema, an increase in cardiac output (Qt) causes an increase in intrapulmonary shunt (Qs/Qt). Conceivably, the increase in Qt increases a diffusion barrier for oxygen (O_2) transfer by shortening pulmonary transit time. Then reduced inspired O_2 (FIO_2) would impair diffusion further. Because incomplete O_2 diffusion is signalled by a difference between O_2 and inert gas transfer, we compared lobar venous PO_2 with lobar multiple inert gas transfer in a canine model where all edema is confined to one lobe. All measurements were made 2 hours after injection of oleic acid, and repeated 30 minutes after changing Qt (opening and closing a-v fistulas) and changing FIO_2 (100% O_2 and room air). During room air and O_2 breathing, PO_2 predicted by inert gas transfer was similar to the measured PO_2, and an increase ($p<.01$) in Qt (3.0 to 5.5 lpm) at each FIO_2 increased Qs/Qt but caused no change in the ratio predicted/measured PO_2. We conclude that in canine oleic acid edema diffusion limitation for O_2 does not contribute to Qs/Qt or to the increase in Qs/Qt when Qt increases. Because the fraction of Qt perfusing the edematous lobe (microsphere technique) did not increase with Qt, it seems unlikely that Qs/Qt increased by redistribution of blood flow to edematous regions. We speculate that Qs/Qt increased with Qt because edema increased or because hematocrit increased in edematous regions. (Supported by MRC of Canada and PHS#HL 17731)

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A CRITICAL VALUE OF TOTAL O_2 TRANSPORT IN THE RAT. R.P. Adams, L.A. Dieleman* and S.M. Cain. Dept. of Physiol. and Biophysics, Univ. of Alabama in Birmingham, 35294.

Rat skeletal muscle O_2 uptake ($\dot{V}O_2$) has been reported to be supply dependent even at normal blood flow rates. To find the point at which whole animal $\dot{V}O_2$ became dependent upon total O_2 transport (TOT), intact anesthetized rats were ventilated under hypoxic, normoxic and hyperoxic conditions while either normovolemic or hypervolemic. In this manner, TOT (cardiac output X arterial O_2 content) was varied over a range of 4.3 to 50.6 ml/kg·min. $\dot{V}O_2$ was measured in a closed circuit, double servospirometer system. O_2 contents were measured in carotid artery and right heart blood. Mean systemic arterial pressure and heart rate were recorded. Arterial PCO_2, pH, and rectal temperature were kept within normal limits. Cardiac output was increased by hypervolemia (212 ± 27 vs. 161 ± 17 ml/kg·min, $P<0.01$) but above TOT of 23 ml/kg·min, decreased extraction maintained $\dot{V}O_2$ independently of TOT ($\dot{V}O_2$ = 15.0 ± 1.0 ml/kg·min). Above that TOT the slope of the line relating $\dot{V}O_2$ to TOT was not significantly different from zero. Below that value, $\dot{V}O_2$ became linearly dependent upon TOT. For TOT between 4.3 and 16.0 ml/kg·min, $\dot{V}O_2$ = 0.65 + 0.75 TOT (r = .96). These data indicated that $\dot{V}O_2$ in rats does not depend upon TOT until it drops below a critical value of approximately 23 ml/kg·min which is about twice the critical value in the dog. (Supported by grants HL-14693 and HL-26927 from NHLBI and Stichting "De Drie Lichten" Hilversum, The Netherlands).

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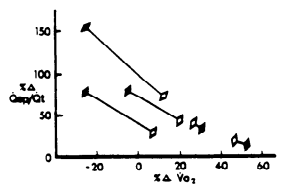
SHUNT CHANGES PRODUCED BY 100% OXYGEN IN CRITICALLY ILL PATIENTS. B. L. Beaver*, J. C. Cruz and T. E. Reilley*, Departments of Anesthesiology and Surgery, The Ohio State University, Columbus, Ohio 43210.

Shunt (venous admixture and $\dot{V}A/\dot{Q}c$ imbalance) measurements are carried out in critically ill patients while breathing therapeutic O_2 (30 to 100%). Theoretically, the shunt ($\dot{Q}sp/\dot{Q}t$) calculation is affected by changes in cardiac output ($\dot{Q}t$), O_2 uptake ($\dot{V}_{O2}$), mixed venous oxygen content ($C\bar{v}O_2$) and inspired O_2 (F_IO_2) per se (unpublished). Thermodilution $\dot{Q}t$ and arterial-mixed venous P_{O2} (PaO_2, $P\bar{v}O_2$) were measured in 5 surgical intensive care patients while breathing 40% O_2 and after 20 minutes of 100% O_2. Results are presented in the Table (mean ± s.e.). Although the table shows no difference in $C\bar{v}O_2$, $\dot{Q}t$ and $\dot{V}_{O2}$, these variables affect significantly the shunt calculation (Fig, closed symbols). Assuming no change in $C\bar{v}O_2$, the calculated shunt will be greater or lesser depending on the corresponding changes in $\dot{V}_{O2}$ (open symbols).

F_IO_2 (0.4 to 1.0)		Changes ( )	
PaO_2	torr	261	+26 **
$P\bar{v}O_2$	torr	5	± 2 **
$C\bar{v}O_2$	vol %*	1	± 0.5
$\dot{Q}t$	L/min	0.1	± 0.4
$\dot{V}_{O2}$	l/min*	0	± 0.04
$\dot{Q}sp/\dot{Q}t$	% *	6	± 2 **

*Calculated **p < 0.05



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EFFECT OF BREATH HOLDING TIME ON DlcoSB IN PATIENTS WITH AIRFLOW OBSTRUCTION. D.J. Cotton, J.T. Mink* and B.L. Graham*, Dept. of Medicine, University of Saskatchewan, Saskatoon, Sask., Canada, S7N OXO.

We measured the single breath diffusing capacity (DlcoSB) during quasi-static vital capacity single breath maneuvers in 15 normal subjects, 10 patients with radiographic emphysema and 11 asthmatic patients. We monitored CO and helium concentrations, airflow, and volume continuously. We measured DlcoSB using two methods: Method 1 utilized the entire alveolar sample and employed 3 equations to describe CO uptake during inhalation, breath holding and exhalation (IEEE Trans Biomed Eng 27:221, 1980); Method 2 (Quart J Exptl Physiol 46:131-143, 1961) utilized a small (100 cc) sample of alveolar gas obtained just after dead space clearance. In normal subjects DlcoSB did not change using either method when breath holding time decreased from 10 to 2 sec. In patients with emphysema DlcoSB decreased significantly ($p < .001$) with decreasing breath hold time (method 1: -35.9 ± 25.6%, mean ± 1SD) and decreased -90.7 ± 168% using method 2. In asthmatics, DlcoSB also decreased ($p < .05$ for both methods) with decreasing breath hold time (method 1, -10.5 ± 13.6%; method 2, -15.1 ± 13.9%). The reduced DlcoSB during short breath holding times could be due to failure of inhaled test gas to adequately mix with alveolar gas. (Supported by MRC Canada and Canadian Lung Association.)

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DIFFERENCES BETWEEN END-TIDAL AND ARTERIAL PCO_2 IN UNANESTHETIZED DOGS IN HYPERCAPNIA. Peter Scheid, Donald B. Jennings, Michael Meyer*, Trond Stokke* and Johannes Piiper. Dept. Physiol., Max-Planck-Inst. f. exp. Medizin, D-34 Göttingen, FRG

Gas-blood CO_2 equilibration in the alveolar lung during hypercapnia was studied in 6 unanesthetized dogs, that had been prepared for the experiments by a tracheostoma and an exteriorized carotid artery. PCO_2 in expired air was continuously monitored by a mass spectrometer, and arterial PCO_2 was measured by electrodes in samples withdrawn from the exteriorized carotid artery. Expired and arterial PCO_2 values were adjusted to alveolar conditions using the temperature measured in the right ventricle by a thermistor catheter.

When the dogs breathed 6 to 10% CO_2 (in air), arterial PCO_2 always exceed mixed expired PCO_2 and was within 1 Torr of mid-alveolar plateau PCO_2. The results are in agreement with earlier experiments in the anesthetized dog (Scheid et al., J. Appl. Physiol. 47: 1074-1078, 1979), but differ, for unknown reasons, from those obtained earlier by Jennings and Chen (J. Appl. Physiol. 38: 382-388, 1975) in a preparation similar to the present. It is concluded that passive CO_2 equilibration leads to equality between alveolar and capillary PCO_2.

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MODEL FOR THE LIMITING ROLE OF ALVEOLAR-CAPILLARY EQUILIBRATION FOR O_2 UPTAKE IN HIGH ALTITUDE HYPOXIA. J. Piiper. Dept. Physiol., Max Planck Institute for Experimental Medicine, D-3400 Göttingen, FRG

In deep hypoxic range (PO_2 from 40 to 10 Torr) the slope of the blood O_2 dissociation curve (O_2 content vs. PO_2), β, is approximately constant. For this condition the alveolar-capillary O_2 equilibration of a homogeneous lung model can be described by the simple relationship,

$$d = (PA-Pc')/(PA-P\bar{v}) = \exp[-D/(\dot{Q}\beta)].$$

(D, pulmonary diffusing capacity for O_2; $\dot{Q}$, pulmonary capillary blood flow; PA, Pc' and Pv, O_2 partial pressure in alveolar gas, end-capillary blood, and mixed venous blood, respectively.) With the data obtained by Cerretelli (J. Appl. Physiol. 40, 658, 1976) at an altitude of 5350 m and with the D values recently determined by a rebreathing technique using isotopic O_2 (Piiper et al., Bull. Europ. Physiopath. Resp. 15, 145, 1979) values for d could be calculated. For resting conditions d was 0.15, meaning moderate degree of diffusion limitation. The value obtained for maximum O_2 uptake exercise, d = 0.65, represents a high degree of diffusion limitation, implying that pulmonary O_2 uptake is more severely limited by alveolar-capillary diffusion than by the cardiac output.

PERIPHERAL CIRCULATION III

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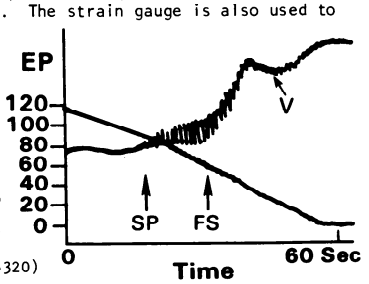
PLETHYSMOGRAPHIC MEASUREMENT OF ARTERIOLAR CRITICAL OPENING PRESSURE (COP) IN THE FINGERTIP. Richard A. Cohen* and Jay D. Coffman. Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118

A strain gauge placed on the fingertip within a pressure-tight chamber records volume (V) during a linear decrease in applied external pressure (EP). The first pulse denotes fingertip systolic pressure (SP). The filling of a low compliance (arterial) compartment is followed by a sharp increase in V as indicated at FS. In five subjects, FS (66±4.9 mmHg) coincided with the EP at which flow starts determined by venous occlusion (63±3.9) and iodine-131 washout (67±4.2). The difference, SP - FS, is the transmural pressure required to open arterioles and initiate flow, or COP. The strain gauge is also used to measure fingertip flow by venous occlusion (FBF, ml /min/100 ml). After environmental cooling (1h, 20° C), COP was 24±3.0 mmHg and FBF was 9±5 in eight subjects. Following digital nerve blockade, COP fell in each subject to 13±2.4, while FBF rose to 74±35. COP is a precise measurement of arteriolar tone; an important determinant of FBF. (NIH HL 26320)



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VASOPRESSIN PLAYS AN IMPORTANT ROLE IN BLOOD PRESSURE REGULATION IN CONSCIOUS DOGS. Ian A. Reid and Jeffrey Schwartz*. Dept. of Physiology, Univ. of Calif., San Francisco, CA 94143.

The role of vasopressin in blood pressure regulation during hemorrhage and water deprivation was studied in conscious dogs with the antagonist [1-(β-mercapto-β,β-cyclopentamethylene propionic acid)] arginine vasopressin.

Hemorrhage. Four dogs were subjected to a 15 ml/kg hemorrhage in the presence and absence of the antagonist. In the absence of vasopressin blockade, hemorrhage did not change mean arterial pressure (MAP) or heart rate (HR). In the presence of the antagonist (10 µg/kg i.v.) however, hemorrhage decreased MAP from 96±2 to 64±7 mm Hg ($P < 0.001$) and increased HR from 71±10 to 130±23 bpm ($P < 0.05$).

Water Deprivation. In six 48-h water-deprived dogs, vasopressin blockade did not decrease MAP. However, there were increases in HR from 87±8 to 138±17 bpm ($P < 0.001$), in cardiac output from 2.0±0.1 to 3.1±0.1 L/min ($P < 0.005$) and in plasma renin activity (PRA) from 12.4±2.2 to 25.9±3.4 ng/ml/3 h ($P < 0.001$), and a decrease in total peripheral resistance from 46.6±3.1 to 26.9±3.1 units ($P < 0.001$). When the same dogs were pretreated with the β-adrenoceptor antagonist propranolol, (0.5 mg/kg i.v.) the HR and PRA responses to the antagonist were attenuated and MAP decreased from 103±2 to 91±3 mm Hg ($P < 0.001$).

These experiments demonstrate that vasopressin plays an important role in blood pressure regulation in conscious dogs. (Supported by USPHS Grant AM06704).

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HEIERARCHY OF AUTONOMIC NERVOUS SYSTEM, ANGIOTENSIN, AND VASOPRESSIN IN THE MAINTENANCE OF BLOOD PRESSURE. Peter C. Houck, Mary J. Fiksen-Olsen*, Steven L. Britton, and J. Carlos Romero. Mayo School of Medicine, Rochester, MN 55905.

This study was designed to investigate the possible role of angiotensin and vasopressin in the maintenance of arterial blood pressure during acute blockade of the autonomic nervous system. Two groups of 5 dogs each were anesthetized with sodium pentobarbital and autonomic ganglia were blocked with hexamethonium (20 mg/kg). Thirty minutes later Group 1 received the vasopressin antagonist ($d(CH_2)_5Tyr(ME)$ AVP; 10 µg/kg) followed after a 30-minute interval by captopril (1 mg/kg). Group 2 dogs received the same drugs except the order of administration of vasopressin antagonist and captopril was reversed. Mean blood pressures ± 1 SE are shown in the table below.

Grp 1	Control	Hexamethonium	AVP-Antagonist	Captopril
	115 ± 4	84 ± 9	59 ± 11	43 ± 6
Grp 2	Control	Hexamethonium	Captopril	AVP-Antagonist
	120 ± 5	87 ± 6	76 ± 8	38 ± 5

Blood pressure fell similarly in both groups following hexamethonium. Either vasopressin antagonist (Grp 1) or captopril (Grp 2) produced a further decrease in blood pressure. Administration of the final drug resulted in yet another decrease in blood pressure. We conclude that vasopressin plays a role at least as important as angiotensin in the maintenance of blood pressure in the anesthetized, ganglionic blocked dog. (Supported in part by NIH grant HL-16496 and Mayo Foundation)

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THE EFFECTS OF BOTH ANGIOTENSIN AND ALPHA SYMPATHETIC BLOCKADE ON ARTERIAL PRESSURE AND BLOOD VOLUME DURING DECREASES IN PLASMA PROTEIN CONCENTRATION (PPC). R.D. Manning, Jr., and A.C. Guyton. Univ. Miss. Med. Ctr., Jackson, MS 39216

We had previously reported that a 35 percent reduction of PPC in unanesthetized dogs resulted in no change in blood volume. The objective of the present experiment was to determine the role of angiotensin II (AII) and the sympathetic nervous system in the maintenance of blood volume when PPC is decreased. Arterial pressure and fluid volume measurements were made on 12 splenectomized, unilaterally nephrectomized dogs during a 3 day control period and a 12 day experimental period during which angiotensin formation was blocked with SQ 14,225 and alpha sympathetic blockade was achieved with phenoxybenzamine. A group of 6 of these dogs (GR1) received daily plasmapheresis for 5 days during the experimental period to decrease PPC; the sham group (GR2) received no plasmapheresis. During the experimental period GR1 experienced a 36 percent decrease in PPC, no change in blood volume, a 45 percent decrease in mean arterial pressure and an 11 percent increase in sodium space. During the same period GR2 experienced a 15 percent decrease in PPC, no change in blood volume, a 32 percent decrease in mean arterial pressure, and a 6 percent increase in sodium space. These data indicate that neither AII or the sympathetic nervous system is responsible for the maintenance of blood volume in the face of chronic reductions in PPC. (Supported by NIH grant HL 11678)

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CONTRIBUTION OF ARTERIAL RESISTANCE AND OF DOWNSTREAM PRESSURE TO RENAL ARTERIAL AUTOREGULATION. Walter Ehrlich, Victoria Tsinberg*, W. Robert Taylor*, Wayne A. Mitzner, The Johns Hopkins Medical Institutions, Baltimore, MD. 21205

Renal arteries of anesthetized, intact dogs were perfused in situ under controlled inflow pressure (P). Blood flow ($\dot{Q}$) was measured by an extracorporeal $\dot{Q}$ transducer and P was measured by a P transducer on a side arm. Steady state (ss) $P/\dot{Q}$ relations were examined by changing ss P. Instantaneous (inst) $P/\dot{Q}$ relations for each established ss $P/\dot{Q}$ value were also ascertained by allowing P to fall so that zero $\dot{Q}$ was reached within 2 s. The ss P was then immediately reestablished. We found that the ss $P/\dot{Q}$ values from 40-100 mmHg P rise along one inst $P/\dot{Q}$ line. The almost flat part of the ss $P/\dot{Q}$ curve between 100-200 mmHg is caused by a rise in arterial resistance(Ra) - defined by the slope of the given inst $P/\dot{Q}$ line - and a rise in downstream pressure (Pd)- defined by the intercept of the given inst $P/\dot{Q}$ with the P axis. We conclude therefore that both, Ra and Pd contribute to renal arterial autoregulation. When P rises beyond the autoregulatory range Ra decreases again, whereas Pd continues to rise. (Supported by PHS Grant #HL10342)

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REGIONAL RENAL AND SPLANCHNIC BLOOD FLOWS DURING NICOTINE INFUSION: EFFECTS OF ADRENERGIC BLOCKERS. George J. Crystal, H. Fred Downey, and Fouad A. Bashour. Departments of Physiology and Internal Medicine and Cardiovascular Research Laboratory at Methodist Hospital, University of Texas Health Science Center at Dallas, Texas 75235

Renal (cortex and medulla) and splanchnic (duodenum, liver, pancreas, and spleen) blood flows were measured with 25-µ radioactive microspheres in anesthetized, open-chest dogs. The effects of nicotine (36 µg/kg/min) were evaluated alone and after either selective α-adrenergic blockade (phenoxybenzamine) or combined α- and β-adrenergic blockade (phenoxybenzamine and propranolol). Without blockade, nicotine increased arterial pressure (AP) 82%, but had heterogeneous directional effects on flows: pancreas (-64%), duodenum (-33%), kidney cortex (-31%), kidney medulla (-17%), liver (+5%), spleen (+70%). α-blockade prevented increase in AP during nicotine but changes in flows remained heterogeneous. After combined α- and β-blockade, nicotine increased AP 75% and decreased flow in all tissues. Results indicate 1) heterogeneous effects of nicotine in renal and splanchnic organs due to regional differences in activities of α- and β-adrenergic receptors, and 2) a potent non-adrenergic vasoconstrictor response to nicotine in these organs after adrenergic blockade. (Supported by Council for Tobacco Research - U.S.A., and the Cardiology Fund)

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DISTRIBUTION OF CARDIAC OUTPUT (CO) IN AWAKE AND ANESTHETIZED SWINE. W. J. TRANQUILLI,* M. MANOHAR, C. M. PARKS,* J. C. THURMON,* M. C. THEODORAKIS* AND G. J. BENSON.* Univ. Illinois, Col. Vet. Med., Urbana, Illinois 61801.

Organ blood flow ($\dot{Q}$) was studied in 9 pigs, using 15 µm tracer microspheres injected into the left atrium, during unanesthetized (control) state, during halothane (1.25%) + N_2O (50%) anesthesia, during halothane (H,2.25%) anesthesia, and during enflurane (E,4.0%) anesthesia. All anesthetic steps employed positive-pressure ventilation to maintain P_aCO_2 = 38 mmHg. Animals were allowed to recover towards the control state before changing anesthetic regimen. Forty-five min were allowed for equilibration with each anesthetic regimen before studies were begun. At control, the internal organs which constituted 8.25 ± 0.79% of the body mass received 45.46 ± 2.64% of the CO. Fraction of CO received by brain, heart, kidneys, liver (via hepatic artery) and gut was 1.13, 3.04, 12.95, 4.27 and 18.71% respectively. Arterial blood pressure and CO decreased significantly with each of the 3 anesthetic steps, the reduction being largest with H(47, 52%). With each anesthetic regimen, $\dot{Q}$ per unit weight of cardiac, renal, splanchnic, skeletal muscular, fatty and cutaneous tissues decreased significantly whereas brain and hepatic $\dot{Q}$ were unaltered from control values. Thus, the % CO received by the brain and liver had increased with H and E while it was unaltered for the other organs. In conclusion, we found that homeostasis was better maintained during H(1.25%) + N_2O (50%) anesthesia in comparison with H(2.25%) or E(4%).

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USE OF MICROSPHERES FOR MEASURING MUSCLE BLOOD FLOW IN EXERCISING RATS. M. H. Laughlin, R. B. Armstrong, J. A. White* and K. Rouk*. Dept. Physiol., Oral Roberts U., Tulsa, OK 74171

A catheter implantation procedure allowing use of radiolabeled microspheres (MS) for measuring muscle blood flow (BF) in rats during high-speed running was desired. Attempts to use existing procedures were unsuccessful, since reference catheters placed in any brachial, femoral, or caudal artery affected the rat's gait and a carotid catheter in the LV limited his ability to run. Silastic catheters placed in the renal artery and the ascending aorta minimized these exercise performance problems. However, it was necessary to establish that aortic MS infusions (MSI) result in good MS-blood mixing. The adequacy of mixing was tested with the following: 1) comparing radioactivity in reference withdrawal samples (R) taken from 2 locations in the aorta with LV and aortic MSI; 2) comparing BF to bilaterally paired tissues (kidney and 3 hindlimb muscles) in resting rats with LV and aortic MSI; and 3) comparing BF to bilaterally paired muscle samples (9 hindlimb muscles) in rats during running at various speeds. The % difference between proximal and distal R was the same for aortic and LV MSI. Also, BF to the paired tissue samples was the same in both resting and exercising rats with either LV or aortic MSI. These results demonstrate that aortic MSI result in MS-blood mixing that is at least as good as that obtained with LV MSI and can therefore be used to measure muscle BF during exercise in laboratory rats. (Supported by NIH AM25472 and AHA, Oklahoma Affiliate)

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A-V SHUNT AND CAPILLARY BLOOD FLOW DISTRIBUTION WITH NERVE STIMULATION.. C.H. Baker, D.L. Davis, and B.G. Lindsey. College of Medicine, Department of Physiology, University of South Florida, Tampa, FL 33612.

The distribution of blood flow between the parallel vascular circuits in the dog hindpaw has been assessed. Dogs were anesthetized and the right hindpaw was vascularly and neurally isolated. The venous cannula passed through a scintillation detector for obtaining isotope time-concentration curves. The skin flap served as a seal for a volume recorder. The animals were heparinized. The preparation was isovolumetric. The arterial tubing had side arms for measurement of perfusion pressure and injection of indicators-(I^{131}-albumin, Rb^{86} and SR^{85}-microspheres (15μm)). The animal received a continuous transfusion of homologous blood at the rate of the hindlimb venous outflow. Deep fibular nerve stimulation had its major effects on the A-V shunts. The nerve was stimulated at a frequency of 15 impulses per second at 80 volts and 0.3 msec duration under conditions of controlled perfusion pressure. Arterial flow decreased and resistance increased significantly ($P<0.01$). PS increased significantly while the mean transit times for I^{125}-albumin and labeled microspheres increased significantly. The recovery of the microspheres and vascular volume decreased significantly. The increased blood flow resistance caused by the nerve stimulation resulted in distribution of blood flow to the capillary circuit and a reduction in A-V shunt flow. (Supported by USPHS Grant HL 24151).

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THE RELATIONSHIP BETWEEN BLOOD FLOW AND ^{99m}Tc-LABELED METHYL DIPHOSPHONATE UPTAKE IN BONE SCANNING. Stanley A. Riggs, Jr.,* Michael B. Wood* and Patrick J. Kelly. Mayo Clinic, Rochester, MN 55905

With a canine tibia model, blood flow was increased or decreased in one hind leg of an unanesthetized animal. ^{85}Sr-labeled microspheres were used to measure blood flow; ^{99m}Tc-labeled methyl diphosphonate (MDP) scans of both the control and experimental hind legs were done at 3 h after injection. Five experiments without alteration of blood flow were done to validate the technique, 4 to produce a state of increased blood flow, and 4 to decrease blood flow to the hind leg. Histologic studies were done with microradiographic techniques. Blood flow was 2.48 ml/100 g per min for cortical bone and 12.5 ml/100 g per min for cancellous bone. When change in ^{99m}Tc uptake at 3 h is plotted against blood flow as determined by the microsphere technique, a parabola is described with a linear relationship (correlation coefficient 0.97) between change in ^{99m}Tc uptake and change in blood flow in both the control and decreased blood flow groups. The nonlinear component shows a disproportionately slower increase in ^{99m}Tc uptake with increased blood flow. Tests for nonlinearity show that the data describe a parabola with a coefficient of determination of 0.95. Thus blood flow is a major determining factor in the skeletal uptake of the ^{99m}Tc-MDP bone-scanning agent. Nonlinearity at high flows may be due to the increase in tracer extraction with high blood flows. (Supported in part by USPHS NIH Grant AM 15980)

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UPTAKE OF FATTY ACIDS, PROSTAGLANDINS, AMINO ACIDS AND SUGARS IN THE PERFUSED RAT LUNG IN A SINGLE CIRCULATION.
A. Syrota* Monique Girault* and D.L. Yudilevich* (SPON: J. Boyle III). SHFJ, Departement de Biologie, CEA, 91406 Orsay and INSERM U 13, Univ. Paris VII, Hôpital Claude Bernard, 75019 Paris.

Isolated lungs were ventilated and perfused (10 ml/min) with a Hanks culture medium containing Ficoll (70,000 MW: 70 g/l). A mixture of two or three labelled molecules (albumin, mannitol and test) was injected into the pulmonary artery, followed by venous sampling for 20 sec. From the tracer concentrations extraction (E), permeability-surface product (PS) and cellular uptake (U) were estimated.

E = 1 - test/albumin (intravascular label)

U = 1 - test/mannitol (extracellular label)

PS for mannitol was 2.8 ± 1.5 ml/min. per g. dry wt. (± SD, n = 243); however, E % was low: 8.8 ± 4.8.

Uptake was negligible for glucose, manoose, glycine, alanine, methionine, phenylalanine, lysine, glutamic acid, taurine, acetic acid, propionic acid and butyric acid. For fatty acids: palmitic, arachidonic, linoleic, linolenic and prostaglandin PGE_1, U ranged between 26-90%. Michaelis-Menten kinetic parameters for PGE_1 were measured and palmitate uptake was inhibited by albumin. These measurements reflect endothelial cell permeability. There is often a late uptake of methionine which can be inhibited by unlabelled substrate, suggesting facilitated transport by the epithelium.

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NIFEDIPINE REDUCES ACUTE HYPOXIC VASOCONSTRICTION IN AWAKE NEWBORN PIGLETS. Gregory J. Redding* and Pierre Escourrou* (Spon: Alan Hodson). Univ. of Washington, Seattle, WA 98195

Nifedipine (N), a calcium antagonist, reduces smooth muscle constriction in coronary arteries and airways. We measured pulmonary hemodynamics before and after N in room air (RA) and isocapnic hypoxia (H; FIO_2=10% $FICO_2$=4%) in unanesthetized piglets, 8±2 days of age, to see if N alters acute hypoxic pulmonary vasoconstriction (HPV) in newborn animals. Catheters were placed in 5 animals 24 hours before each study. Mean pulmonary and systemic artery pressures ($\bar{P}pa$ and $\bar{P}sa$), heart rate (HR), and cardiac output (CO) were measured before and during an infusion of 16 mcg/kg/min of N. Before N, H increased $\bar{P}pa$ by 70% and total pulmonary resistance (TPR) by 65%. N increased HR, $\bar{P}pa$, and CO but reduced $\bar{P}sa$ and TPR in RA (PaO_2=91±10 torr); and N reduced the rise in $\bar{P}pa$ and TPR despite an increase in CO during H(PaO_2=45±7 torr). We conclude that N reduces HPV but substantially increases CO in awake newborn piglets.

	Pre-N				Post-N		
	HR	$\bar{P}pa$	CO	TPR	HR	$\bar{P}pa$	CO	TPR
RA	163±9	13±1	.66±.06	20±3	260±33*	18±2*	.88±.15*	20±3
H	190±8	22±3	.67±.11	33±8	278±30	21±2	.94±.17	23±5
Δ	27±5	9±2	.02±.09	13±7	18±5	3±1*	.06±.13	3±3*

* $P<.05$ for pre-N vs. post-N comparisons on RA and for Δ. Values are expressed as mean ± standard error of the mean. Units: HR=beats/min; $\bar{P}pa$=torr; CO=L/min; TPR=torr/L/min. Supported by MCH Grant #000955

SHOCK I

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THROMBOXANE (Tx) AND PROSTACYCLIN (PGI_2) IN THE SYNERGISM OF GENTAMYCIN (GENT) AND INDOMETHACIN (INDO) DURING SEPTIC SHOCK. R.R. Butler*, W.C. Wise, P.V. Halushka, and J.A. Cook. Depts. of Physiology, Pharmacology, and Medicine, Medical University of South Carolina, Charleston, South Carolina 29425.

Fecal peritonitis is associated with increased TxA_2 and PGI_2. We sought to determine the role of these substances in mediating the beneficial effects of GENT (25mg/kg ip; 30 min pre-feces) and/or INDO (10 mg/kg ip; 30 min pre-feces). Shocked control rats received vehicle 30 min pre-ip feces. Plasma TxA_2 and PGI_2 were measured via RIA of their stable metabolites $iTxB_2$ and i6-keto-$PGF_{1\alpha}$ (6-KETO). Non-shocked rats have non-detectable levels (ND<200 pg/ml). Fibrin degradation products (FDP) were measured with a staphlococcal clumping assay.

Group	Survival Time Hours*	FDP(6 hr) μg/ml*	Tx(4 hr) pg/ml*	6-KETO(4 hr) pg/ml*
CONTROL	8.6±0.2(50)	18±8(4)	1681±248(12)	7450±933(12)
INDO	13.3±0.6(21)[a]	4±1(4)[a]	ND(10)[a]	ND(10)[a]
GENT	23.2±2.6(16)[a]	11±3(4)	1556±316(6)	3443±156(6)[a]
GENT+INDO	41.4±1.8(17)[a,b]	4±2(4)[a,b]	ND(10)[a,b]	ND(10)[a,b]

$P<0.01$ compared to [a]Control and [b]GENT; * = ± SEM(N)

GENT+INDO was the only treatment that gave long term survival (>48 hrs=35%;$P<0.01$). INDO alone decreased FDP, Tx, and 6-KETO and increased survival time. GENT alone did not alter FDP or Tx; however, we see decreased 6-KETO and increased survival time. GENT+INDO decreased FDP, Tx, 6-KETO, and enhanced survival. These results support the hypothesis that TxA_2 is involved in early sequelae and PGI_2 contributes to terminal pathophysiology of septic shock (Supported by NIH GM27673 and GM20387).

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PROSTAGLANDIN MODULATION OF ADRENERGIC VASCULAR CONTROL DURING HEMORRHAGIC SHOCK. Bond, Robert F., Carol H. Bond, Lorraine C. Peissner, and Eva S. Manning. Departments of Physiology, Kirksville College of Osteopathic Medicine, Kirksville, MO 63501 & Oral Roberts University, Tulsa, OK 74171.

This study was designed to evaluate 1) whether the initial compensatory skeletal muscle vascular constriction induced by hemorrhagic hypotension is primarily the result of increased adrenergic neural tone or circulating vasoconstrictor agents, and 2) whether the secondary skeletal muscle decompensatory vasodilation is caused by inhibitory action of prostaglandins on peripheral adrenergic nervous system. A constant flow vascularly isolated double canine gracilis muscle preparation in which one muscle served as innervated control for the contralateral muscle was used. Dogs were subjected to standard stepwise hemorrhagic shock protocol. In series 1, perfusion pressures to control muscles were compared to denervated muscles with the result that innervated muscle perfusion pressures increased initially from 105 to 175 mmHg, but subsequently fell significantly ($P<0.05$) to 147 mmHg. Only modest increases in perfusion pressures with no significant secondary fall was noted in denervated muscles. Series 2 compared innervated control perfusion pressures to pressures perfusing muscles pretreated with prostaglandin-synthesis inhibitor sodium meclofenamate (MCF). The MCF treated muscle perfusion pressures rose to 260 mmHg where they remained without the secondary fall noted in control muscles. These data support the two hypotheses tested. (Supported by AOA and NIH grant RR-09130.)

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ENDOTOXIN INDUCED INEFFECTIVENESS OF NOREPINEPHRINE.
R.M. Lust, H.F. Janssen, L.O. Lutherer, B.B. Boyer* and M.W. Cooper*. Depts. of Internal Medicine, Orthopedic Surgery and Physiology, Texas Tech Univ. H.S.C., Lubbock, Tx. 79430

Previous work in this lab has demonstrated significant depression of both contractility and contractile reserve following injection of 0.5 mg/kg endotoxin. Factors responsible for this depression are not known. To determine whether the depression is due to an inability to respond to catecholamines, responses to injected norepinephrine(NE) (0.6 ug/kg) were measured in 6 animals before and 2,10,30,60,90,120,150 and 180 minutes following the injection of endotoxin. Left ventricular and aortic pressures were monitored with a Millar catheter and an ultrasonic echocardiographic transducer was sewn to the pericardium for visualization and measurement of left ventricular function. Contractile strength was increased 270% in the control following NE injection. As early as 2 minutes after endotoxin the response to the same dose of NE was reduced to just 37%, and by 10 mins. was reduced further to 25%. There was some tendency towards recovery of responsiveness, but at 3 hrs. the response was still less than 50%. Thus, even at 3 hours after the initial insult, the animal remains at least 5 times less responsive to infused NE as compared to control. It is suggested that the cardiac depression and peripheral vascular changes associated with endotoxemia may be aggravated by an apparant ineffectiveness of catecholamines.

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PRESSOR ROLE OF CEREBELLUM AND RENIN-ANGIOTENSIN SYSTEM (RAS) DURING HEMORRHAGIC HYPOTENSION.
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Previous work in our lab demonstrated the importance of the cerebellum and the RAS in recovery of mean arterial pressure (MAP) following endotoxin administration. The current study investigated the role of the cerebellum and the RAS during hemorrhagic hypotension. Dogs were hemorrhaged (1 ml/kg/min) until MAP reached 50 mmHg and then observed for 180 min or until death. All cerebellectomized (CX) animals (n=8) died between 5 and 111 min following cessation of hemorrhage. All sham-operated (SO) animals (n=6) survived the full 180 min. MAP of SO animals returned to 109±6 by 45 min. In the CX group MAP was 74±4 at 45 min and declined thereafter. The MAP was 82±8 at 45 min in dogs (n=9) given captopril (CAP) (angiotensin I-converting enzyme inhibitor) beginning 15 min prior to hemorrhage. Four animals in this group died between 44 and 80 min with the MAP of the survivors reaching a maximum of 92±4 by 90 min. No significant differences among groups were noted for the percent estimated blood volume shed to reach 50 mmHg. However within the CAP group the percent was significantly less for surviving animals (34.3±2.1 vs 48.4±2.4). In preliminary studies ablation of the fastigial nuclei produced a response identical to cerebellectomy. This suggests that fastigial nucleus activation of the RAS is important for restoration of MAP following hemorrhagic hypotension. Other systems may partly offset angiotensin blockade if the cerebellum is intact.

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THE EFFECT OF SEVERE HEMORRHAGIC HYPOTENSION ON THE SKELETAL MUSCLE VASCULATURE OF THE CHICKEN.
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We have recently reported that hemorrhage to a mean arterial blood pressure (MABP) of 50 mm Hg in the chicken has no effect on total peripheral resistance or skeletal muscle vascular resistance (judged from changes in hindlimb perfusion pressure, Pp)(AJP 240: H9-H17, 1981). In the present study we report the effect of a more severe hypotension on skeletal muscle vascular resistance in the chicken.

Condition	MABP[1]	Pp	n
control	115 ±5	86 ±5	13
hem.	50 ±2	86 ±5	13
hem.	25 ±2	182 ±7	13
hem. + vagot[2]	25 ±2	184 ±10	7
hem. + Phen.[2]	25 ±2	92 ±10	6

[1] $\bar{X}$ ± SE
[2] blood flow = 7.1 ±0.5 ml/min; phentolamine 50 ug/min.

The sharp rise in Pp of the isolated constantly perfused hindlimb when the bird was hemorrhaged to a MABP of 25 mm Hg was unaffected by severance of the ischiadic nerve trunk or bilateral cervical vagotomy. However, infusion of an alpha-adrenergic antagonist into the arterial perfusion circuit during hemorrhage completely eliminated the response. The rise in Pp is of a magnitude similiar to that recently reported with this technique during asphyxia in the chicken. We conclude that the vasoconstrictor response to severe hemorrhagic hypotension (MABP = 25) in the chicken is likely due to cerebral ischemia, rather than a baroreflex.

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CARDIOVASCULAR AND METABOLIC RESPONSES DURING BURN SHOCK IN GUINEA PIGS TREATED WITH SEVERAL RESUSCITATION FLUIDS.
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Guinea pigs with indwelling arterial, venous catheters and thermistors were anesthetized with Ethrane and scalded through a template in 100°C water to produce a full skin thickness burn over 40% of the BSA. These animals were treated with 3 resuscitation fluids: normal daline (NS), lactated Ringer (RL) and hypertonic saline lactated (HSL). All showed a decrease in temperature and cardiac output in the first post burn (PB). NS and RL returned to preburn values at 8hrs and 24 hrs, respectively, while HSL values remained depressed. RL animals became acidotic at 4hrs while the pH of the groups was unchanged. As exoected, plasma lactate levels rose PB in all samples but were significantly higher in the HSL. An increase in plasma glucose levels was found at initially PB in all groups. It decreased moderately at 4hrs PB, and returned to preburn levels in NS and RL. However, the HSL PB became hypoglycemic by 8hrs (less than 50 mg/dl). FFA values fell initially but then recovered in all but the RL group by 8hrs PB. O_2 consumption decreased initially in all groups but only in the HSL was recovery to preburn level not found. The R.Q. for HSL was observed to be elevated throughout the duration of the PB experiment. Each resuscitation fluid was observed to have a different effect on metabolism and cardiovascular physiology. Supported by NIH Grant T2GM07029B.

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INCREASED SKELETAL MUSCLE GLUCOSE UPTAKE DURING THE HIGH CARDIAC INDEX(CI), HYPERMETABOLIC STATE OF SEPSIS IN THE DOG.
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Many reports in the clinical literature indicate an accelerated glucose turnover during high CI, hypermetabolic sepsis.Recent data from our laboratory indicate an increased skeletal muscle glucose uptake during endotoxin shock in the dog. The mechanism for this was shown to be related to local tissue hypoxia. The early septic state in which organ blood flow is not decreased and tissue hypoxia is not apparent is different than the low flow state of shock. Therefore, this study was undertaken to define the role of skeletal muscle glucose metabolism during high CI sepsis in the dog. Large dogs (20±2kg) of either sex were implanted with catheters for measuring cardiac output, blood pressure and intraperitoneal administration of live E. coli. Following control measurements, peritonitis was induced and the animals monitored daily until CI increased (>25%). The animals were then anesthetized and the constant flow perfused gracilis muscle was used as the test organ. Control animals received saline. Experimental muscle glucose uptake was .72±.1mg/min/100g whereas control muscle was .15±.04mg/min/100g. Lactate and pyruvate production by the septic muscles was significantly greater than control muscles. Oxygen uptake of either group did not change. These data provide evidence that skeletal muscle glucose uptake is markedly increased during high CI sepsis with no local hypoxia or changes in muscle O_2 metabolism.
(Supported in part by NIH grant GM26394)

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MICROVASCULAR FLUID AND PROTEIN FLUX IN PULMONARY AND SYSTEMIC CIRCULATIONS AFTER THERMAL INJURY.
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We studied the local and generalized microvascular response to thermal injury, monitoring transvascular fluid flux and protein permeability in burned and non-burned soft tissue and in the lung. Chronic lymph fistulas were produced in lung and soft tissue in 7 adult sheep. Lymph flux ($\dot{L}$) and the lymph-to-plasma protein concentration (L/P) ratio for four protein fractions separated by gel electrophoresis, were used to monitor fluid flux and protein permeability before and for 72 hours after a 25% full-thickness skin burn. There was a marked increase in both $\dot{L}$ and the L/P ratio for all proteins ranging from 35-108 Å radius in burn tissue for the entire 72 hour period, indicating a sustained increase in protein permeability. There was a transient increase in $\dot{L}$ and L/P for proteins 58Å and less in non-burn tissue, with the permeability change lasting about 12 hours. Fluid flux was significantly increased in the lung for 24-36 hours, but protein sieving was normal as demonstrated by a decrease in L/P ratio for all protein fractions, indicating the increase in $\dot{L}$ was not due to an increase in vascular permeability. (Supported by NIH grants GM27619, HL 18010 and the Firefighters Pacific Burn Institute)

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A SINGLE BREATH METHOD FOR MEASUREMENT OF THE PASSIVE MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM DURING ANESTHESIA. W.A. Zin*, L.D. Pengelly and J. Milic-Emili. Meakins-Christie Laboratories, McGill University, Montreal, Quebec.

In 6 anesthetized cats (Sodium Pentobarbital - 35 mg/kg) we measured airflow, changes in lung volume and tracheal pressure. The airways were occluded at end-inspiration (V_T). During the ensuing period of apnea (Hering-Breuer inflation reflex) the animal relaxed the respiratory muscles and the passive compliance of the respiratory system (C_{rs}) was computed by dividing V_T by the tracheal pressure. With the animal still relaxed the occlusion was rapidly released, and by plotting volume against flow during the expiration a straight line was obtained, the slope representing the time constant of the respiratory system: $\tau = C_{rs} \times R_{rs}$, where R_{rs} is the flow resistance of the passive respiratory system. From the measured values of τ and C_{rs}, R_{rs} was computed. With this information it was possible to quantitate the net pressure developed by either inspiratory or expiratory muscles during control (unoccluded) expiration. (Supported by MRC of Canada, Dr. Zin is supported by CNPq, Brazil).

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MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM IN ANESTHETIZED MAN. P. Behrakis*, A. Baydur*, B.D. Higgs* and J.Milic-Emili. Meakins-Christie Labs and Department of Anesthesia, Royal Victoria Hospital, Montreal.

After the first moments of a relaxed expiration, all the pressure due to the recoil of the respiratory system, $P_{rs}(st)$ is available to produce flow ($\dot{V}$). In the mid-range of lung volume(V), the static volume-pressure curve of the total respiratory system is nearly linear and $P_{rs}(st)$ can be expressed as $E_{rs}V$, where E_{rs} is total respiratory elastance. In spontaneously breathing humans, anesthetized with nitrous oxide (70% in O_2) we measured $\dot{V}$, changes in lung volume and tracheal pressure (P_T). After occlusion of the tracheal tube at end-inspiration (V_T), we measured P_T while the subjects relaxed the respiratory muscles. By dividing relaxed P_T by V_T, E_{rs} was obtained. With the subjects still relaxed, the tracheal occlusion was released to obtain the V-$\dot{V}$ relationship during the ensuing relaxed expiration. V was next multiplied by E_{rs} to obtain $P_{rs}(st)$. The $P_{rs}(st)$ vs. $\dot{V}$ relationships were curvilinear in all subjects and fitted the following equation: $P_{rs}(st) = k_1 \dot{V}$ and $k_2 \dot{V}^2$, where k_1 and k_2 are the constants of Rohrer's equation. In conclusion, in anesthetized humans the pressure-flow relationship of the respiratory system (including tracheal tube) is curvilinear and can be determined without recourse to paralysis of the respiratory muscles.

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DYNAMICS OF BREATHING IN INFANTS. J.P. Mortola, J.T. Fisher, B. Smith*, G. Fox* and S. Weeks*, Dept. of Physiology and Dept. of Anaesthesia, McGill Univ., Montreal, Canada H3G 1Y6.

Passive and active properties of the respiratory system have been measured in 10 infants at 10-90 minutes after birth and in 10 infants at a few days of life. Examination of the passive compliance (C) and of the expiratory flow-volume curves indicates that the end expiratory volume is maintained above functional residual capacity at both ages, but significantly more so at a few days (7.6 ml) than at 10-90 minutes (3.5 ml). The passive time constant is shorter at the early age due to the smaller C. The active time constant of the respiratory system is less than the passive value, due to a smaller active compliance, particularly at a few days. The active resistance is on the contrary similar to the passive resistance value, suggesting that losses due to the velocity of shortening of the inspiratory muscles are not relevant in infants. The active stiffening of the respiratory system provides more stability and a more ready volume response for any given change in pressure; its price however is a higher work of breathing. At the optimal breathing rates the active work is 127% (10-90 minutes) to 183% (a few days) higher than that computed from the passive values. The inspiratory flow wave tends to be squared at both ages minimizing the energy losses due to friction.

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EFFECT OF CHEST WALL DISTORTION ON ESOPHAGEAL PRESSURE. P.N. LeSouëf*†, JM Lopes*, N Muller, & AC Bryan. Respiratory Physiol Res.Inst. Hospital for Sick Children, Toronto, Canada.

In adults esophageal pressure (Pes) has been shown to approximate mean pleural pressure (Ppl). However, this relationship may not hold true in preterm infants with severe chest wall distortion (CWD) as this could lead to an uneven distribution of surface Ppl. We therefore studied eight preterm infants (mean birth weight 1270 gm(range 910-1560 g),mean gestational age 31 w (range 28-33w), mean age 21 d (range 8-45 d)). Anteroposterior diameter of the rib cage and abdomen were monitored with magnetometer pairs, Pes with an open-ended water-filled 6 Fr gauge catheter and tidal volume with a face mask and pneumotachograph. CWD was considered present when there was inward motion of the rib cage on inspiration. In each infant a period with little or no CWD and a period with marked CWD were then selected for comparison. In each period, Pes swings required to generate identical tidal volumes were then assessed. For equal tidal volume, Pes increased significantly during periods of marked distortion in each of five infants ($p<0.05$) and remained unchanged in three. The overall mean increase was 12% ($p<0.05$). A change in lung volume and hence compliance did not appear to account for the changes in pressure observed. We conclude that the presence of CWD can result in higher Pes swings for the same tidal volume. This finding offers a possible explanation for the wide variation in airway resistance and lung compliance reported in preterm infants, as these are based on measurement of Pes.(Supp Grant from U of W Australia)

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SHAPE AND REGIONAL VOLUME IN IMMERSED LUNG LOBES. G.T. Ford*, D. Gillett* and N.R. Anthonisen. Depts. of Medicine, Universities of Manitoba and Calgary, Canada.

We froze 10 isolated canine lower lobes by immersing them in chloroethene (specific gravity=1.4) at -20°C. In six instances the contralateral lower lobe was frozen over dry ice. The lobes were then sliced horizontally and the volume and weight of each slice measured, so that expansion (specific volume) and the amount of tissue (weight) could be assessed as a function of distance down the lung. Lobes frozen under chloroethene at low (35% TLC) and medium (60% TLC) volumes demonstrated a gradient of regional expansion which was about half that predicted on the basis of pleural surface pressure. Lobes frozen under chloroethene at high volumes (80% TLC) did not demonstrate a significant gradient of regional expansion. These results demonstrated tissue interdependence. When lobes frozen under chloroethene were compared with contralateral lobes frozen over dry ice, substantial differences in shape were evident. Chloroethene frozen lobes had greater vertical height and a smaller fraction of their weight was present in dependent regions: over the lower 40% of their vertical height lobes frozen in chloroethene had half as much tissue as did lobes frozen over dry ice. We demonstrated two mechanisms by which relative homogeneity of regional expansion was maintained in response to differences in pleural pressure: tissue interdependence and tissue movement from more compressed to less compressed regions.

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FUNCTIONAL RESIDUAL CAPACITY (FRC) IN AWAKE AND ANESTHETIZED RATS. W.J.E. Lamm*, J.R. Hildebrandt, J. Hildebrandt, and Y.-L. Lai. Virginia Mason Research Center, Seattle, WA 98101.

FRC, tidal volume (V_T), and frequency (f) were compared in 23 anesthetized rats with values later obtained when awake and unrestrained. A tracheal cannula with pneumatic airway occluder was implanted acutely, then FRC determined in a cone-shaped body plethysmograph. Four-six hrs after the anesthesia, repeat measurements were made. In the awake state, FRC = 1.02 ± 0.22 ml/100 g, V_T = 0.39 ± 0.06 ml/100g and f = 142 ± 22 breaths/min. FRC of the excised lung was measured by saline displacement and averaged 83 ± 14% (n=14) of the calculated box values, reflecting effects of gas absorption and cooling. During pentobarbital anesthesia (lying prone), FRC decreased ($P<0.01$) to 52.9%, V_T increased ($P<0.01$) to 147.4%, and f decreased ($P<0.01$) to 71% of awake values, leaving minute ventilation almost unchanged. Possible influences of abdominal or chest wall compression while lying prone were evaluated in a second group of 7 rats by adding spinal suspension to the above protocol for anesthetized animals. It appears that thoracic compression followed by a time-dependent volume history effect may account for the major FRC change. Some decrease in FRC may also be due to lower breathing frequency and loss of inspiratory muscle activity (expiratory braking and resting muscle tone in awake animals). Peak diaphragmatic EMG per unit V_T was shown to increase almost linearly with FRC, indicating the decreased diaphragmatic efficiency as lung volume is elevated. (Supported by NIH grants HL 20568, HL 27064, and HL 14854).

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EFFECTS OF ACCELERATION (+Gz) ON THE INTRAPLEURAL PRESSURE GRADIENT. H.I. Modell, Virginia Mason Research Center, Seattle, WA 98101

Although a number of investigators have examined the intrapleural pressure (Ppl) gradient in upright (+1Gz) man and animals, none have reported the influence of high +Gz stress on the gradient. We exposed 9 supine, anesthetized, adult dogs breathing spontaneously to +Gz levels ranging from 1 to +5Gz. Air-filled, right angled stainless steel cannulae having multiple side holes were placed in 2 to 4 sites from the 3rd to 9th intercostal (IC) space to monitor regional Ppl. To determine the influence of +Gz stress on the passive system, the animal was sacrificed with an IV injection of KCl, and the exposures were repeated immediately. In the live dog, the Ppl gradient at end-expiration increased with increasing +Gz stress. From +1 to +5Gz, Ppl changed by a mean of -1.32 cm H_2O/G at the 3-4th IC level. Ppl at the 7-8th IC space remained essentially constant. At the 9th IC space, Ppl became more positive by a mean of 1.94 cm H_2O/G. When active muscular tone was removed, the change in Ppl with +Gz at the 3-4th IC level was nearly twice that seen in the live animal. However at the 7-8th IC level, Ppl still remained constant with +Gz stress. The 7-8th IC level is the location of the last rib attachments to the sternum in the dog. The constant Ppl at this point may be associated with the structural transition from the relatively rigid container of the rib cage to the more distensible lower portion of the chest wall.
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ELASTIC AND RESISTANCE COMPONENTS OF THE RESPIRATORY SYSTEM IN OBESITY. Paul M. Suratt, Donald Kaiser, Henry Hsiao, and Dudley F. Rochester*. UVa Med Center Charlottesville, Va. and Biomed Engineering, U.N.C. Chapel Hill.

Although previous studies of respiratory mechanics in obesity have shown that the compliance of the total respiratory system (Crs) and chest wall (Ccw) are low, studies of mass loading the respiratory system suggest that, over the range of tidal breathing, resistance to gravity is a major component of work of breathing in obese subjects. We used the pulse flow method (JAP 1980: 49,1116) to measure Crs in 17 normal and 11 obese subjects with body mass indexes (BMI) ranging from 17 to 83 Kg/m^2. In 8 of these subjects (4 normal and 4 obese) Ccw and chest wall resistance (Rcw) were measured with the pulse flow method using the difference between esophageal and atmospheric pressure. Rcw was taken as the initial step rise in pressure divided by the pulse flow rate. Although BMI correlated with Crs when analysed alone ($r=0.44, p<.02$), when the effect of vital capacity and age were added in a multiple regression, the effect of BMI was no longer significant. BMI was highly correlated with Rcw ($r=0.92, p<.001$) but was not significantly correlated with Ccw. We conclude that elevated chest wall resistance is the major mechanical defect in obesity.

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BLOOD FLOW DISTRIBUTION DURING NEONATAL RESPIRATORY MUSCLE EXERCISE. E.F. Donovan*, U. of Cincinnati, Spon. L.I. Kleinman

Respiratory muscle exercise is accompanied by increased respiratory muscle blood flow (Q_{RM}). Cardiac output (Q_C) and organ blood flow were measured using the labelled microsphere technique in 14 unanesthetized newborn dogs ages 3-15d. Measurements made during respiratory muscle exercise induced by CO_2 rebreathing (RB) (steady state $FiCO_2$=0.031, FiO_2=0.33) were compared to measurements made breathing room air (RA). CO_2 rebreathing resulted in increased blood flow to the diaphragm (Qdia) (.35 v .67 $ml.min^{-1}.g^{-1}$) and intercostal muscles (Qint) (.31 v .51 $ml.min^{-1}.g^{-1}$). Brain, renal, skin, spleen and limb muscle blood flows were unchanged.

	Qc ($ml.min.^{-1}.kg^{-1}$)	$\frac{Qdia}{Qc}$ (%Qc)	$\frac{Qint}{Qc}$ (%Qc)	$\frac{Q_{GI}}{Qc}$ (%Qc)	$\frac{Q_{liver}}{Qc}$ (%Qc)
RA	269	.71	.31	18.7	.41
RB	280	1.41	.51	14.4	.31
P	NS	<.01	<.01	<.005	<.005

Although the fraction of Qc to the GI tract decreased, Q_{GI} during RB was similar to that during RA (1.51 v 1.41 $ml.min^{-1}.g^{-1}$). Increased Qc during RB was associated with an increase in Q_{GI} ($r=.92$, $p<.001$). Animals with no increase in Qc during RB (n=8) had a fall in Q_{GI} (1.17 v 1.71 $ml.min^{-1}.g^{-1}$, $p<.02$). Increased Q_{RM} during RB occurs primarily via a redistribution of Qc away from the GI tract and liver. Q_{GI} may be compromised in newborn animals with limited cardiac reserve during RB.

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HUMAN STERNOCLEIDOMASTOID EMGs: NORMATIVE DATA. John A. Bowden* and Patricia Lynne-Davies. Department of Medicine, Wayne State University School of Medicine, Detroit, MI 48201

We recorded surface EMGs from the right sternocleidomastoid muscle in 50 normal volunteers during 87 series, each consisting of 10 iso-volume breaths. Power density spectra were calculated after fast Fourier transform of the EMG signal, and the average centroid (fc) and median frequency (f med) between 10-250 Hz were computed for each series. Electrical activity was first reliably detected at a mean tidal volume (± SD) of 2.52 ± 0.71 L. Mean values for fc were 67 ± 9 Hz, and f med 58 ± 10 Hz. There were no detectable spectral differences based on sex, age or smoking history. A trend towards lower spectral values in more obese subjects did not achieve statistical significance, but signal-to-noise ratios less than 20:1 were associated with lower values ($p<0.02$). In 46 of the 87 series there was a pronounced low frequency power peak at 14 ± 2 Hz which, given the resolution of the analysis, we tentatively attribute to muscle tremor. We conclude from these data that frequency parameters of human surface EMGs have an acceptable reproducibility within and between subjects. (Supported by NHLBI Grant No. HL 26327).

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RIB CAGE AND ABDOMINAL MOTION DURING BREATHING AT HIGH LUNG VOLUMES. K.P. Strohl*, D. Wolfson*, A. DiMarco*, M.D. Altose. Dept. of Medicine, Cleveland Metropolitan General Hospital and Case Western Reserve University, Cleveland, OH 44109.

When lung volume is increased, inspiratory chest wall muscles are shortened. To investigate the effect of an increased lung volume on the mechanical function of inspiratory chest wall muscles, we studied the patterns of rib cage (RC) and abdominal (AB) motion in six normal subjects in a fixed seated posture during tidal breathing at functional residual capacity (FRC) and at a high lung volume (HLV) (61±3%, M±SE, inspiratory capacity) produced by 12 cmH_2O positive end expiratory pressure or by voluntary inspiratory muscle action. Subjects performed relaxation maneuvers before, during and after each trial and were coached to initiate breaths only from a "relaxed" RC-AB configuration. In all subjects tidal breaths from FRC were accompanied by outward RC and AB motion, but during equal sized breaths from HLV the AB moved inward while the RC moved outward. At HLV diaphragmatic electromyographic activity was 600±120% greater ($P<0.01$) and esophageal pressure swings were 480±58% greater ($P<0.01$) than during inspiration from FRC. Gastric pressure always increased 2.2±0.5 cmH_2O during inspirations from FRC, but invariably fell -1.4±0.4 cmH_2O during inspirations from HLV ($P<0.05$). We suggest that at HLV, breathing from a "relaxed" RC-AB configuration allows other chest wall muscles to overpower the diaphragm resulting in inward AB motion during inspiration.

Supported by NIH grant HL-25830.

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REGIONAL LENGTH CHANGES IN THE DIAPHRAGM OF ANESTHETIZED DOGS MEASURED WITH HALL EFFECT TRANSDUCERS. Arthur B. Otis and Cobern V. Peterson Department of Physiology, University of Florida, Gainesville, Florida, 32610

In order to make direct measurements of regional length changes of the diaphragm under in situ conditions, we have constructed a small length gage consisting of a miniature Hall generator and a small permanent magnet. Changes in distance between the two elements generate electrical signals which can be recorded. Three such gages are sutured to different regions of the abdominal surface of the diaphragm, which has been exposed by laparotomy. In some cases electrodes for electromyography (EMG) are inserted in the same regions. Connecting wires for EMG and gages are brought out through the abdominal incision, which is then closed. We have found that during spontaneous breathing in the supine position there is a linear relationship between costal length changes and volume changes as measured by integrated pneumotachogram. However, shortening of the crus always precedes that of the costal parts of the diaphragm, although no corresponding asynchrony occurs in electrical activity. During passive inflations the costal regions always shorten, but the behavior of the crus is less consistent. (Supported in part by NIH Grant 1 RO1 HL 2351502)

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RIB CAGE (RC) MECHANICS IN QUADRIPLEGIC PATIENTS. W.F. Urmey*, S.H. Loring, J. Mead, R. Brown*, A.S. Slutsky, M. Sarkarati*, A. Rossier*. West Roxbury V.A. Med. Cntr., West Roxbury, MA 02132, Harvard Sch. of Pub. Hlth. and Harvard Med. Sch., Boston, MA 02115.

Other investigators have shown that, contrary to Goldman and Mead's hypothesis, quadriplegics do not breathe along their respiratory system relaxation characteristics and that the RC paradoxes during spontaneous inhalation (SI). To test whether this distortion was due to inadequate abdominal support, we substantially increased intraabdominal pressure with a pneumatic cuff while measuring upper (URC) and lower (LRC) rib cage cross-sectional (C-S) changes during SI. Abdominal support diminished or reversed RC paradox, but the entire RC never moved along the relaxation characteristic. In several patients, the diaphragm drove the LRC, but not the URC, along its relaxation characteristic without being influenced by cuff inflation or postural change. Near the end of deep SI, accessory muscle recruitment invariably resulted in dominance of URC C-S increase. We also assessed passive RC distortability by comparing URC and LRC C-S changes during axial forcing of the RC at the costal margin and observed variable LRC/URC coupling. We conclude that the LRC/URC stability responsible for the single degree of freedom behavior of the normal RC during SI depends more on active muscle coordination than passive mechanical features. (Supported by V.A. funding, HL14580, HL22920)

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CONTRACTURE OF DIAPHRAGM WITH FATIGUE. Michael J. Miller*, Peter LaCouture*, and Jeffrey M. Drazen. Brigham and Women's Hospital, Boston, MA 02115

The mechanical response to a fatiguing stimulus was examined in isolated rat diaphragm. Diaphragm strips (mean length 18.2 mm) from six animals were placed in organ baths with oxygenated Tyrode's solution and studied isometrically. Repetitive submaximal stimulation via platinum electrodes (60 V, 250-800 msec duration every 10 seconds) produced marked fatigue (active tension < 25% initial values) within 45 minutes (mean 34, SEM=3.3). Passive tension rose dramatically with fatigue, from 202 mg (SEM=13) to 1461 mg (SEM=234). Total tension, therefore, rose from 538 mg (SEM=26) to 1509 mg (SEM=235), despite a decrease in active tension from 336 mg (SEM=20) to 48 mg (SEM=9). With stimulation discontinued, the muscle was allowed to shorten until the pre-fatigue level of passive tension was reached. This contracture averaged 3.0 mm (SEM=0.32) or 17% of total muscle length. Four additional strips were fatigued and not allowed to shorten after cessation of stimulation. Elevation of resting tension was found to be long lasting (> 1 hour after stimulation off) and not reversed by washing with fresh Tyrode's soltuion. Contracture of the diaphragm may contribute importantly to changes in lung volume during fatiguing inspiratory work. (Supported by NIH grants HL 00549 and 17382.)

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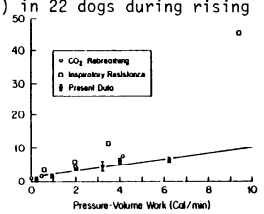
DIAPHRAGMATIC AND RESPIRATORY SYSTEM EFFICIENCIES. M. B. Reid* and R. L. Johnson, Jr. Univ of Texas, Southwestern Medical School, Dallas TX 75235

Previous studies have compared oxygen consumption of the combined respiratory muscles to pressure-volume (p-v) work on the lung (W_L)(see fig.). The resulting respiratory system efficiency was 15% during CO_2 rebreathing; it fell from 13% to 4% during increasing inspiratory resistance, which was attributed to a general loss of muscular efficiency as mean inspiratory pressure rose. However, present data compares diaphragmatic oxygen consumption and p-v work (Wd) in 22 dogs during rising inspiratory resistance, finding mechanical efficiency of the diaphragm to be 23% throughout. We further compared inspired volume (V_T) to diaphragmatic volume displacement and W_L to Wd in 10 dogs during inspiratory resistance: as resistance increased, the diaphragm assumed a greater role in volume displacement until, at high work loads, the diaphragm accounted for all of V_T and W_L while the rib cage muscles performed only isometric work to stabilize the thorax. We conclude that respiratory system efficiency is less than diaphragmatic, and declines during inspiratory resistance because the muscles of the rib cage require metabolic energy without performing p-v work at high inspiratory resistance.



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ELECTROMYOGRAPHIC ASSESSMENT OF THE RELATIVE CONTRIBUTIONS OF RESPIRATORY MUSCLES TO THE INSPIRATORY P-V RELATIONSHIP. F.J.R. Buick*, J.R.A. Rigg*, M.E. Easson* and L.D. Pengelly. Depts. of Medicine and Anaesthesia, McMaster University, Hamilton, Ontario, Canada, L8N 3Z5.

The EMG of contracting muscle is dependent on its rate and intensity of contraction, and the length of the muscle. The EMG assessment of respiratory muscle recruitment is, therefore, best performed using static pulmonary techniques. The integrated EMG (IEMG) of the diaphragm, parasternal muscles of the second intercostal space, and scalene and sternomastoid muscles were recorded while studying the static inspiratory muscle pressure-volume map of healthy subjects. Target mouth pressures were maintained for 5 seconds at different lung volumes. For the diaphragm and intercostal muscles, IEMG increased progressively with increasing mouth pressure at all lung volumes. In the scalene and sternomastoid muscles, little increase in IEMG was observed up to a certain pressure threshold, beyond which it increased markedly. The pressure threshold for these muscles was inversely proportional to lung volume. Thus, under static conditions, it is clear that the relationship between IEMG and inspiratory muscle activity depends both on the intensity of effort and the lung volume. (Supported by the Medical Research Council of Canada.)

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PENDELLUFT IN SUPINE AND PRONE ANESTHETIZED DOGS. R.D. Hubmayr*, B.J. Walters* and J.R. Rodarte. Mayo Clinic Fdn., Rochester, MN 55901.

We evaluated the interlobar redistribution of volume during inspiratory efforts against an occluded airway (Mueller Maneuver, MM) in 3 anesthetized dogs in the supine and prone positions. Regional lung volume (Vr) was determined from the positions of radiopaque metallic markers previously implanted in the parenchyma and recorded with a biplane video roentgenographic system. Vr's expressed as % TLC in both right upper (UL) and lower lobes (LL) at FRC (FRC%) and at peak negative oral pressure (MM%), developed as the animal tried to inspire against an occluded airway, were compared. During the MM pleural pressure (Ppl) measured with an esophageal balloon fell to approximately -20 cm H_2O in both positions. In supine dogs FRC% - MM% ranged from +0.4 to +3.3% TLC in the UL and -2.7 to -6% TLC in the LL, indicating movement of air from UL to LL. In the prone position the opposite was observed: FRC% - MM% ranged from -1.7 to -6.6% TLC in the UL and 0 to +6.6% TLC in the LL. The decrease in lobar volume was generally less than the corresponding increase in the other lobe. The relative contribution of cardiac and middle lobes, gas rarefication and an increase in lobar blood volume may account for this discrepancy. We conclude that during inspiratory efforts against an occluded airway in anesthetized dogs the applied Ppl changes nonuniformly and that thoracoabdominal coupling is profoundly influenced by position and possibly support of the animal. (Supported in part by NIH grants HL 21584, HL 07222 & HL 4664).

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DIAPHRAGMATIC LENGTH-TENSION CURVE OF NORMAL AND EMPHYSEMATOUS HAMSTERS. G.A. Farkas* and Ch. Roussos, Meakins-Christie Lab., McGill University, Montreal, Quebec, H3A-2B4.

In vitro Length-Tension (L-T) curve of the diaphragm (Di) was measured in two groups of inbred adult hamsters (> 40wks), randomly divided into 11 control (C) and 10 emphysematous (E) animals. Emphysema was induced by a single endotracheal instillation of elastase. Following a 24 week experimental period, FRC (mean ± SE) measured by means of a pressure plethysmograph was: C, 2.56 ± 0.08mls; E, 8.02 ± 0.31mls. Small costal Di bundles were then isolated. Optimal bundle length (L_O) was defined as the length at which maximal twitch tension occured. The L-T curve was measured by tetanically stimulating the Di at rest lengths varying between 0.45% and 1.25% L_O. Plotting the L-T curve as a percent of L_O and maximal tetanic tension (Pmax) revealed no difference between groups. In absolute terms, however, the L-T curve of E showed a significant parallel shift to the left. Pmax (mean SE) was similar for both groups: C, 2.06 ± 0.11Kg/cm^2; E, 1.93 ± 0.10Kg/cm^2, while L_O (mean ± SE) was significantly (< 0.05) shorter in the E group: C, 1.42 ± 0.05cm; E, 1.16 ± 0.04cm. Plotting FRC (mls/Kg) versus diaphragmatic L_O (cm) revealed a significant (< 1%) negative correlation (r= -0.60).

We conclude that the Di of emphysematous hamsters chronically adapt by decreasing diaphragmatic length in proportion to the degree of hyperinflation and thus continue to operate at an optimal length. (Supported by MRC)

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ROLE OF INTERCOSTAL MUSCLES IN THE RIB CAGE DISTORTIONS PRODUCED BY INSPIRATORY LOADS. Michael G. Sampson* and André De Troyer* (SPON: A. Grassino). Meakins Christie Labs., Royal Victoria Hospital, McGill University, Montreal, Canada.

We studied the patterns of rib cage (RC) deformation in six normal subjects breathing against different resistive and elastic inspiratory loads, and we examined, with concentric needle electrodes, the role played by the inspiratory intercostal muscles in the development of these patterns. Four of the subjects deformed their RC to a more elliptical shape during loaded inspirations; RC anteroposterior diameter became smaller and RC lateral diameter became larger. The RC deformation increased as the load increased, and it was independent of the type of load. Moreover, these deformations were invariably associated with a marked increase in the inspiratory activity of the intercostals situated in the lateral parts of the RC and a striking diminution of the activity in the parasternal area. On the other hand, two subjects breathed along their RC relaxation characteristic and they showed an increased inspiratory activity in all regions of the intercostal musculature. These findings indicate that 1) the pattern of RC deformation during loaded inspirations is closely related to the activity and coordination of the various inspiratory intercostal muscles and 2) the parasternal intercostals are not necessarily representative of all the inspiratory intercostals. They are also strong evidence against the concept that the parasternal intercostal electrical activity normally recorded during quiet breathing is an excitatory reflex activity. Supported, MRC Canada.

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THE ACTION OF THE ABDOMINAL MUSCLES ON THE RIB CAGE IN DOGS. A. De Troyer*, M. Sampson*, and S.Sigrist* (SPON: P.T.Macklem) Meakins Christie Labs., McGill University, Montreal, Canada.

The abdominal muscles are traditionally considered as pure expiratory muscles; however, there are at present no data regarding their mechanical effect on the rib cage. Using implanted electrodes, we separately stimulated the rectus abdominis (RA), the external oblique (EO), and the transversus (T) in anesthetized dogs in supine position, and we measured changes in rib cage dimensions by displacement transducers connected to screws fixed into the bony structures of the thorax. In all instances stimulation of the RA and of the T resulted in inward displacement of the rib cage, more markedly so with the RA than with the T. By contrast stimulation of the EO invariably displaced the rib cage outward. Opening of the abdomen enhanced the deflationary effect of the RA and of the T, and reversed the inflationary action of the EO into a deflating one. In no case, did the anteroposterior and lateral diameters of the lower rib cage move in opposite directions. We conclude that in supine dogs, 1) the RA, the EO, and the T have a direct deflationary action on the rib cage; 2) the increase in abdominal pressure per se has an inflationary action on the lower rib cage, and this effect overcomes the deflationary action of the EO; and 3) the abdominal muscles do not distort the rib cage when they contract bilaterally. (Supported by the MRC of Canada).

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ESTIMATION OF CHEST WALL VOLUME-MOTION COEFFICIENTS: A THIRD DEGREE OF FREEDOM. M.D. Goldman, H.R. Gribbin*, E.N. Bruce and E.M. Haacke*, Case Wes. Res. Univ., Cleveland, Oh. 44106

We used multilinear regression (MLR) techniques based on a 2 degree-of-freedom (d.f.) model of chest wall movement to estimate volume-motion coefficients (VMC) for rib cage (RA) and abdominal (AB) A.P. displacements measured by magnetometers. Estimates of VMC had large confidence intervals (C.I.) making it difficult to estimate volume changes or to quantify the separate RA and AB contributions to volume change. Nonetheless, tidal volume during quiet breathing could be well estimated using these VMC. We found values for VMC which had smaller C.I.'s and were closer to those expected from isovolume maneuvers, when the volume signal was delayed several tens of milliseconds relative to the RA and AB signals. Closer examination of the start of inspiration showed that the volume signal often lead both magnetometer signals. Because of this and the effect of delaying volume on the MLR estimation, we hypothesized that another d.f. of chest wall movement contributes to volume change even during quiet breathing. Further studies in which lateral rib cage displacement (RL) was recorded indeed demonstrated that in most cases RL was not linearly related to RA and often preceded it in inspiration. This suggests that time-shifting of volume in the MLR analysis allows us to account for part of the contribution of a 3rd d.f. of chest wall movement using RA and AB only. (Supported by HL-25830, HL-25233, V.A. and Parker-Francis Foundation)

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EFFECTS OF A 3RD DEGREE-OF-FREEDOM ON ESTIMATED VOLUME-MOTION COEFFICIENTS FOR A 2 DEGREE-OF-FREEDOM MODEL OF CHEST WALL MOVEMENTS. E.N. Bruce, E.M. Haacke*, H.R. Gribbin*, and M.D. Goldman. Case Wes. Res. Univ., Cleveland, Oh. 44106

Lung volume change during quiet and moderately stimulated breathing is accomplished through displacement of the chest wall (CW) along at least 3 independent pathways: the AP diameters of the rib cage (RA) and abdomen (AB), and the lateral diameter of the rib cage (RL). Often however, lung volume changes are estimated from measurements of RA and AB displacements, with RL displacements assumed to be so highly correlated with RA that the contribution of RL is "included" by measuring RA. We have tested this assumption using two models: one based on computer generation of simulated magnetometer data; the other on polynomial approximations to actual RA, AB, and RL data. In both cases multiple linear regression was used to estimate the volume-motion coefficients (VMC) for a 2 degree-of-freedom (d.f.) model (i.e. RA and AB) of CW motion from this data. The existence of a nonlinear relationship between RL and RA causes systematic errors in the estimation of VMC. If one allows a time shift of volume relative to RA and AB, then the best fit (minimum mean square error) occurs at that time shift which yields a close estimate of the correct VMC for AB and a coefficient for RA which includes that part of the RL volume contribution which is linearly related to RA. These coefficients would seem to be the most physiologically appropriate for the 2-d.f. model when only RA and AB measurements are made. (Supported by HL-25830, HL-25233, V.A. and Parker-Francis Fdn)

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DEGREES OF FREEDOM OF CHEST WALL MOTION IN MAN. J.C. Smith* and J. Mead. Dept. of Physiology, Harvard School of Public Health, Boston, MA 02115

Descriptions of chest wall volume displacements are currently based on a model of the chest wall consisting of two components, the rib cage (rc) and abdomen (ab), each representing a single degree of freedom (d.f.) of motion. We have identified two additional prominent d.f. and their associated chest wall volume displacements. The new d.f. are associated with changes in the attitude of the thoracic spine (ΔTsa) and lumbar spine (ΔLsa). The relationships between ΔTsa or ΔLsa and changes in cross-sectional area of rc(ΔArc) and ab (ΔAab) have been examined in several men. ΔArc and ΔAab were measured by inductive plethysmography. ΔTsa or ΔLsa were measured by magnetometry as changes in the distance (ΔD) between points parallel to the spinal axis on the anterior rc near the ziphi sternum and the anterior ab wall near the pubic symphysis. At any fixed lung volume (V_L) the relationship between ΔD due to ΔTsa or ΔLsa and the sum ΔArc + ΔAab is nearly single valued. The iso-V_L area changes are generally larger with ΔTsa and can be as large as those accompanying V_L changes of 25-30% VC. With the airway open, end-expiratory V_L changes little with ΔTsa or ΔLsa even though ΔArc and ΔAab are appreciable. The results suggest: 1.Respiratory system volume displacements are more completely described by treating the chest wall as a system with 4 d.f.; 2. The 4 d.f. functionally interact in a manner which tends to minimize changes in V_L during nonrespiratory changes in chest wall configuration. (Supported by HL14580 and HL07118)

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INDEPENDENCE OF DIAPHRAGM LENGTH AND CHEST WALL CONFIGURATION. S.H. Loring, J.C. Smith*, and J. Mead. Harvard School of Public Health, Boston, MA 02115.

Konno and Mead showed that when spinal attitude is fixed, chest wall volume changes may be conveniently divided into rib cage displacements (ΔRC) and abdominal wall displacements (ΔAbd). It has been thought that changes in diaphragm fiber length (ΔL-di) are closely coupled to ΔAbd ("the diaphragm-abdomen pathway") and relatively insensitive to ΔRC, and that lung volume changes (ΔVL) occuring without ΔAbd are nearly isometric for the diaphragm (1). To test this assumption, we studied 3 trained subjects during normal breaths (ΔRC: ΔAbd $\cong$ 3:1) and breaths taken without ΔAbd. We obtained an estimate of ΔL-di by magnetometers for transverse diameter, ultrasound for chest wall thickness and changes in height of the diaphragm apposed to the rib cage, and a diaphragmatic dome shape factor obtained from separate xray studies of Rochester et al. For a given ΔVL, ΔL-di was 80, 82, and 85% as great for the breath without ΔAbd as for the normal breath. These numbers are close to a theoretical prediction presented in an accompanying communication. Large isovolume maneuvers (ΔAbd and ΔRC without ΔVL) resulted in very small ΔL-di. We conclude that ΔL-di is closely coupled to ΔVL and relatively independent of chest wall configuration. (Supported by HL22920, HL14580, HL07118.)

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ANALYSIS OF VOLUME DISPLACEMENT AND LENGTH CHANGES OF THE DIAPHRAGM DURING BREATHING. Jere Mead. Department of Physiology, Harvard School of Public Health, Boston, MA, 02115.

Diaphragmatic volume displacements, ΔVdi, cause equal abdominal displacements. Since the rib-cage forms a variable part of the abdominal wall (the variable part being its area of apposition with the diaphragm) it shares in abdominal displacments. The fraction of total rib-cage displacements, ΔVrc, contributing to abdominal displacements is predicted from anatomic considerations and measurements. During quiet inspirations it is estimated that more than half of ΔVrc goes into abdominal expansion. This plus the outward displacement of the antero-lateral abdominal wall constitutes ΔVdi. In a typical inspiration in which the rib-cage accounts for 3/4 of the volume change, the diaphragm displaces nearly the same fraction. Associated changes in diaphragm length are estimated with a model. Diaphragm shortening during an inspiration in which only the rib-cage expands is estimated to be 20% less than during a normal inspirations. (Supported by HL14580.)

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CALIBRATION OF RESPIRATORY INDUCTIVE PLETHYSMOGRAPH. I.Chadha*, S. Birch*, G. Jenouri*, A. Schneider*, H. Watson*, M. Cohn* and M.A. Sackner. Mt. Sinai Med. Ctr., Miami Beach, FL 33140

The least squares method (LSQ) for calibration of the respiratory inductive plethysmograph (RIP) based upon differences in rib cage and abdominal contributions to tidal volume in 2 positions shows <10% deviation from spirometry (SP) in 89% of observations in 7 body postures (ARRD 123:181,1981). In this study, we compared LSQ to the isovolume angle calibration method (IV). Ten normal subjects were calibrated by LSQ, IV-Supine (SUP) and IV-Standing (STD) and validated with SP at tidal volumes (V_T) of 250 ml, 750 ml, 1250 ml with the isovolume angle measured in SUP and STD positions. The results were as follows:

METHOD	% Values RIP <10% from SP						% IV angles 45±3 degrees	
V_T	250 ml		750 ml		1250 ml			
	SUP	STD	SUP	STD	SUP	STD	SUP	STD
LSQ-SUP & STD	100	90	90	100	90	100	40	50
IV - SUP	80	70	90	70	90	80	100	40
IV - STD	50	80	20	100	50	100	30	100

Thus, in normal subjects, 1) LSQ gives a closer estimate of V_T as determined by spirometry than IV and less variability with change in body position, 2) IV estimates the fractional contributions of rib cage and abdomen more accurately than LSQ if body posture is not changed after calibration but may be less accurate when posture is changed. We conclude that LSQ which is easier to accomplish than an isovolume maneuver in untrained subjects is to be preferred when Respiratory Inductive Plethysmograph is used to monitor tidal breathing.

CONTROL OF BREATHING: INTEGRATED AND CO_2 RESPONSES

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LACK OF CEREBRAL BLOOD FLOW RESPONSE TO INSPIRED CO_2 IN PATIENTS WITH SLEEP APNEA. M.W. Eldridge* and J.A. Loeppky. Lovelace Medical Foundation, Albuquerque, NM 87108.

Poor ventilatory control in patients with sleep apnea (SA) is often attributed to a defect in central chemoreceptor function during sleep, however abnormalities in cerebrovascular responsiveness to blood gases may be a contributing factor. Common carotid artery blood velocities (v) were measured non-invasively during a 3-min rebreathing ventilatory response test to CO_2 in 7 normal (N) subjects while awake (mean age: 38 yr) and 5 patients noted to have severe SA (mean age: 55 yr) in prior sleep laboratory evaluations. Ventilatory response in N was 2.6 L/min/mmHg (range: 1.6 to 3.9) and 2.0 in SA (range: 0.1 to 3.5). End-tidal P_{CO_2} rose 22 mmHg in both groups. Carotid v and diameter were obtained continuously with a 5.0 MHz real-time, two-dimensional pulsed Doppler (Duplex Scanner-ATL) before, during and for 3 min after rebreathing. Resistivity index (RI) defined as (peak systolic v-mean diastolic v)/peak systolic v was maximally reduced in N after 90 sec on CO_2 by 27% (range: 16-40%) and returned to baseline within 60 sec after CO_2. Conversely, RI increased in linear fashion in SA by 12% (range: 7-22%) and remained elevated for 3 min after CO_2. These results indicate an abnormal autoregulatory cerebrovascular response to CO_2 in SA rather than chemoreceptor malfunction since ventilatory response may be adequate while awake. (Supported in part by Lovelace Medical Foundation Intramural Grant.)

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BRAIN BUFFER CAPACITY DURING PROLONGED HYPERCAPNIA. Y.-L. Lai, W.J.E. Lamm*, and J. Hildebrandt. Virginia Mason Research Center, Seattle, WA 98101.

Ventilatory adaptation to chronic CO_2 has been related to increases in arterial and CSF pH due to accumulation of HCO_3^-. CSF acid-base adjustment could involve changes in brain buffering capacity (β). We have therefore compared brain non-bicarbonate β before and after exposure to 7% CO_2. Rats were divided into 3 groups: air control, 3 days 7% CO_2, and 1 wk 7% CO_2. Rats were decapitated and the brains removed for immediate homogenization in 0°C saline. Each homogenate was then tonometered at 37°C with 2%, 5%, and 15% CO_2 in O_2 continuously for 3 hrs. At 30 min intervals, 0.5 ml samples were measured for pH, P_{CO_2}, and P_{O_2}. $[HCO_3^-]$ increased with time for the first 1½-2 hr of equilibration and then remained constant. Steady state values were plotted as $[HCO_3^-]$ vs pH. Slopes represent the non-bicarbonate β. Mean values were slightly but not significantly larger in the two chronic CO_2 groups. Average values (means ± SD) were 22.97 ± 2.66, 25.49 ± 0.48, and 26.02 ± 1.30 (meq/Kg pH unit) for control, 3 day and 1 wk groups, respectively. The in vitro CO_2 dissociation curves (CO_2 content versus P_{CO_2}) for the chronic CO_2 groups were shifted up compared to control, reflecting retained HCO_3^-. These results suggest that a slight increase in the noncarbonic β during chronic CO_2 exposure, possibly as a result of either the accumulation of additional buffers (NH_4^+, protein, etc), or increased blood in tissue, or a reduction in brain water content. (Supported by NIH grant HL 20568).

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RESPIRATORY SENSITIVITY TO HYPOXIA AFTER CAROTID BODY REMOVAL (CBR) IN AWAKE CATS. Fordyce, W.E., K.J. Franklin* and S.M. Tenney. Dept. of Physiol.,Dartmouth Med.Sch.,Hanover,NH 03755

3 groups of cats have been studied in order to deduce the role of the carotid body in ventilatory acclimation to hypoxia and to investigate the recovery of hypoxic sensitivity. Long term acclimation to CBR has been observed during 6 mo exposures to normoxia (N=6) and hypobaric hypoxia (HH; PIO2=83; N=5); tests were first made on the intact animal and then at 6 wk intervals following CBR. Also, intact cats were acclimated to HH (N=5) for 5 mo and then treated with CBR. Steady state breathing pattern (VT, TTOT) was measured in a plethysmograph while the animal was inhaling various CO2-free oxygen mixtures (PIO2=700,147,83,70 and 56 Torr). Neither long term CBR group recovered their normal hypoxic sensitivities. Although hypoxia produced hyperpnea, VT decreased with decreasing PIO2 and tachypnea (TTOT<1 sec) developed at PIO2=70-83 Torr in the normoxic cats and at PIO2 56 Torr in HH cats. Intact cats, before and after 5 mo exposure to HH, exhibited increases in VT with decreasing PIO2 and small changes in TTOT. At each O2 level, intact cats had larger VT and TTOT when compared to HH CBR cats; this latter group had larger VT and TTOT when compared to normoxic CBR cats. This suggests that the HH CBR cats obtained some degree of acclimation. 3 days after CBR, the formerly intact HH animals exhibited hypoventilation and ventilatory responses similar to normoxic CBR cats. (Supported by PHS grants T32 HL07449-01 and 5R01 HL02888-24.)

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EFFECTS OF CO_2 INHALATION AND VAGOTOMY ON ACTIVITY OF INTERNAL INTERCOSTAL (IIC) MOTOR UNITS IN CAT. Hideho Arita* and Beverly Bishop. Dept. Physiology, SUNY/Buffalo, NY 14214.

The purpose of this study was to define IIC activity in relation to CO_2 drive and vagal volume feedback. Single motor potentials were recorded with fine wire electrodes from the 8th IIC along with that of diaphragm and external intercostal muscle (EIC) in Dial-Urethane anesthetized, tracheotomized, spontaneously breathing cats during CO_2 inhalation (3%, 5%, 7%), and during airway occlusion, before and after vagotomy. Computer-based analyses on a spike-by-spike basis have revealed two types of IIC motor units. One type with small spikes and tonic expiratory activity was classified as tonic-E. The second type with large spikes and phasic expiratory activity was classified as late-E. Before vagotomy, both tonic-E and late-E were active during normocapnia. As CO_2 drive was enhanced, the discharge of late-E ceased and the inspiratory firing of tonic-E also ceased and its expiratory firing rate was slowed. In contrast, airway occlusion always augmented the firing frequency of both types of units. After vagotomy, the activity of both types of IIC units was markedly reduced or even silenced, while the inspiratory activity of EIC was augmented and prolonged. Airway occlusion either no longer activated IIC activity, or activated to a lesser degree. The results demonstrate that CO_2 drive depresses rather than augments IIC activity and that vagal feedback is essential for expiratory activity of IIC. (Supported in part by NHLBI Grant PO1-HL-14414. H. Arita is a Dr. Henry C. and Bertha H. Buswell Fellow.)

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EVIDENCE THAT VENOUS RETURN, PER SE, CONTRIBUTES TO THE EXERCISE HYPERPNEA. A. Huszczuk,* A. Oren,* L.E. Nery,* E.Shors, B. J. Whipp and K. Wasserman. Harbor-UCLA Med.Ctr.Torrance, CA 90509.

In order to regulate arterial PCO_2 during exercise, ventilation must be proportionally coupled to the CO_2 flux to the lung. To determine the role of the components of this CO_2 flux in the exercise hyperpnea, we previously removed CO_2 from the venous return ($\dot{Q}v$) in the exercising dog (Shors et al. Fed. Proc. 39:583, 1980). Ventilation ($\dot{V}_E$) decreased but hypocapnia ensued. In subsequent studies we also demonstrated that $\dot{V}_E$ changed as a linear function of right ventricular pressure, regardless of whether this pressure change was induced by Qv or by partially obstructing ventricular ejection (Huszczuk et al. Fed. Proc.40:568, 1981). And therefore, in the present study we determined during steady-state exercise the effect of reducing venous return and hence right ventricular pressure (utilizing partial cardiopulmonary by-pass) to or slightly below the control level. In 17 experiments (6 dogs) this invariably resulted in a decrease in the exercise hyperpnea; from 245% ± 71 S.D. to 175% ± 54 of the resting $\dot{V}_E$. This was associated with a slight, but insignificant, rise in $PaCO_2$. We therefore conclude that the rate of venous return plays an important role in the control of exercise hyperpnea, although the mediation is not exclusively this mechanism.

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HUMAN VOCAL CORD MOVEMENTS DURING HYPOXIA DIFFER FROM THOSE DURING HYPERCAPNIA. S. J. England* and D. Bartlett, Jr. Dartmouth Medical School, Hanover, NH 03755.

In awake human subjects, as in anesthetized cats, the vocal cords are abducted during inspiration but move toward the midline during expiration thus increasing airflow resistance. Expiratory glottic narrowing is reduced during hyperpnea induced by exercise or hypercapnia. Using a fiberoptic laryngoscope and video equipment, we have recorded and measured vocal cord movements during both eucapnic hypoxia and hypercapnia. When assessed at similar levels of minute ventilation, expiratory glottic narrowing was substantially greater with hypoxia than with hypercapnia in most experiments. A similar laryngeal response to hypoxia has been shown in anesthetized cats, but only following bilateral vagotomy. This expiratory laryngeal closure in vagotomized animals depends on stimulation of carotid body chemoreceptors. (Resp. Physiol. 42:189, 1980). The present findings in hypoxic humans, considered together with the earlier observations in cats, suggest that expiratory behavior of the larynx in both species is determined by a complex integration of afferent information from the lungs and from peripheral and central chemoreceptors. The net effect in hypoxic human subjects is narrowing of the glottis during expiration. (Supported in part by NIH Grant No. HL 19827 and grants from the Albert J. Ryan and Parker B. Francis Foundations.)

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PULMONARY MECHANICS DURING THE BIPHASIC VENTILATORY RESPONSE TO HYPOXEMIA IN THE NEWBORN MONKEY W.A. LaFramboise*, T.A. Standaert* R.D. Guthrie*, and D.E. Woodrum* (SPON:W.A.Hodson). Univ. of Washington, Seattle, Washington 98195

In a previous investigation (Physiol. 23(4),140), we determined that the hypoxic ventilatory response of the newborn monkey was biphasic despite a sustained elevation of airway inspiratory occlusion pressures ($P_{0.2}$). Dynamic pulmonary compliance and mean inspiratory pulmonary resistance were measured in 8 two day old Macaca nemestrina during normoxic and hypoxic conditions to determine whether a change in lung mechanics occurs during the biphasic response. Normoxic compliance was .71±.08ml/cm H_2O and resistance was .13±.02 cm H_2O·sec/ml at an end-expiratory lung volume (EELV) of 4.26±.47 ml (X±S.E.). Minute ventilation ($\dot{V}_E$), tidal volume (V_T), inspiratory flow (V_T/T_i) and $P_{0.2}$ significantly increased at 1 minute of hypoxemia while no significant change occurred in compliance and resistance. At 5 minutes of hypoxemia, $\dot{V}_E$ and V_T/Ti returned to control values and V_T dropped below normoxic values despite the fact that $P_{0.2}$ remained elevated. EELV increased to 6.21±.57ml and compliance fell to .58±.07ml/cm H_2O at this time - both significant at the $p<.02$ level when compared with normoxic values. Pulmonary resistance did not change significantly after 5 minutes of hypoxemia. These results indicate that the failure to sustain ventilation during acute hypoxemia in the newborn is accompanied by an increase in EELV and a resultant decrease in dynamic compliance. (Supported by NIH Grants HL 19187 and RR 00166).

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CONTROL OF RESPIRATION IN YOUNG ANESTHETIZED MYOPATHIC HAMSTERS. Evelyn H. Schlenker. Section on Physiology, University of South Dakota, Vermillion, South Dakota, 57069.

Tidal volume (VT), frequency (f), minute ventilation ($\dot{V}E$) were measured in 5 myopathic (MB) and in 5 random bred (RB) 30-day old hamsters before and after sodium pentobarbitol anesthesia. The values of VT, f, and $\dot{V}E$ were similar between the RB and MB hamsters. In unrestrained and unanesthetized MB and RB hamsters VT equalled .34 ± .07 and .36 ± .08 ml; and f equalled 104 ± 4 ± 22.3 and 108 ± 18.8 breaths/min, respectively ($\bar{x}$ ± SD). After anesthesia, however, f dropped to 69.6 ± 9.1 b/min in MB hamsters as compared to 103 ± 21 b/min in RB hamsters. VT dropped to .22 ± .05 ml in RB's and .18 ± .04 ml in MB's. Consequently, $\dot{V}E$ fell 40% in the RB hamsters and 68% in the MB hamsters. When RB and MB anesthetized hamsters were challenged to a rebreathing test using a hypercapnic-hypoxic stimulus, the product of the maximum pressure developed at the mouth times frequency for 2 seconds equalled 2060 ± 367 cm H_2O/ min in RB and 142.8 ± 91 cm H_2O/min respectively. These results indicate that anesthesia depresses respiration to a greater extent in MB hamsters as compared to RB hamsters. The factor affected most seems to be the frequency response in anesthetized MB hamsters. The response to chemical stimulation in anesthetized MB hamsters is also largely depressed. Analogous results have been noted in some patients with muscular dysfunction.

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Effects of Aerosolized Methacholine on Respiratory Drive. J.A. Salamone*, L.B. Eberlin*, E.C. Deal, Jr., S.G. Kelsen,and N.S. Cherniack, Case West. Res. Univ., Cleveland, Oh. 44106

In anesthetized dogs, methacholine-induced bronchoconstriction is accompanied by increased ventilation ($\dot{V}_E$), increased breathing frequency (F) and an increase in phrenic activity (Feb. Proc. 40:381, 1981). To further evaluate these changes in respiratory drive, thirteen vagotomized dogs, anesthetized with either pentobarbital or chloralose, were studied. In eight spontaneously breathing dogs, methacholine aerosols increased resistance (R_L) by a mean of 244% but did not significantly affect $\dot{V}_E$ or F. However, both the rate of rise and the peak phrenic neurogram increased to 134.1 ± 24.9 (mean ± S.D.) ($p<.05$) and 130.7 ± 11.5 ($p<.05$) % of control, respectively. To determine whether chest wall distortions during bronchoconstriction explained the increase in phrenic activity, five animals were given methacholine aerosols after they had been paralyzed, artificially ventilated with 100% O_2 and the chest had been opened widely. In these studies, although pCO_2 was unchanged, the peak phrenic increased to 116.1% ± 15.0% of control ($p<.05$) and the rate of rise increased to 132.3 ± 27.4% ($p<0.5$) as mean R_L increased 205%. Thus, only part of the respiratory stimulating effect of methacholine can be attributed to vagal afferents or chest wall mechanoreceptors. Preliminary studies suggest that the carotid sinus afferents are not responsible for the increases in phrenic, but that sympathetic afferents from the heart or lung may be responsible in some animals. (Supported by the V.A. and HL-25830)

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DEVELOPMENT OF EXPIRATORY MOTOR RESPONSES IN THE OPOSSUM. J.P. Farber and M.A. Maltby*. Department of Physiology, Univ. of Oklahoma Health Sciences Ctr., Oklahoma City, OK 73190

To evaluate developmental aspects of expiratory muscle utilization, studies were performed on unanesthetized suckling opossums. Ventilation was assessed using pressure plethysmography while electromyographic (EMG) activity of abdominal expiratory muscles was obtained using fine wire electrodes. In the youngest animals tested (12-15 days of age), coherent activation of expiratory muscles was not observed during positive pressure breathing (3-8 cmH_2O) or during inhalation of hypercapnic and asphyxiant test gases. Over the next 15-20 days, abdominal EMG activation became apparent with all of the above maneuvers; some animals also began to show abdominal muscle responses when inhaling room air. From about the 25-30th day of age, activation of abdominal muscles occurred during the first breath after the initiation of positive pressure while younger animals more typically activated after several breaths were taken. In animals prepared under light pentobarbital anesthesia with a suture around a vagus nerve, expiratory motor responses during inhalation of all test gases could be inhibited by unilateral vagotomy. In addition, unilateral vagotomy decreased expiratory muscle activation during positive pressure breathing and could also delay the initiation of the response. The results of vagotomy suggest that a component of expiratory motor activation during chemostimulation of breathing as well as pressure breathing depends upon maturation of vagal reflex loops. (Supported by NIH Grant #HL24865)

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PARASYMPATHETIC BRONCHOCONSTRICTOR FIBERS FIRE WITH AN INSPIRATORY RHYTHM TO EVOKE RHYTHMIC FLUCTUATIONS IN AIRWAY SMOOTH MUSCLE TONE. D.G. Baker and R.A. Mitchell. Cardiovascular Research Inst., Univ. Calif., San Francisco, CA 94143

In anesthetized paralyzed open chested cats, ventilated with low tidal volumes at high frequency, we recorded phrenic nerve activity, airway pressure, and either the tension in an upper trachea segment or the impulse activity in a pulmonary branch of the vagus nerve. Airway pressure and upper tracheal segment tension fluctuated with respiration, peak pressure and tension paralleling phrenic nerve activity. Increasing end tidal CO_2 or stimulating the carotid chemoreceptors with sodium cyanide increased both airway pressure and tracheal segment tension during the increased activity in the phrenic nerve. Lowering end tidal CO_2 or hyperinflating the lungs to achieve neural apnea caused a fall in airway pressure and tracheal segment tension and abolished the inspiratory fluctuations. During neural apnea the tracheal segment tension and airway pressure were the same as those following the transection of both vagus nerves or the administration of atropine (.5mg/kg). Numerous fibers in the pulmonary branch of the vagus nerve fired in synchrony with the phrenic nerve. Only these fibers had activity which paralleled changes in airway pressure and tracheal tension. We conclude that a major portion of the airway smooth muscle tone arises from parasympathetic fibers that fire during inspiration and which probably originate in the region of the ventral respiratory group in the medulla. (Supported by USPHS NIH Grant HL-24136.)

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CHANGES IN VENTRAL MEDULLARY ECF pH DURING ACUTE METABOLIC ACIDOSIS. D. G. Davies and W. F. Nolan. Department of Physiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Ventral medullary ECF pH was measured during 30 min of isocapnic metabolic acidosis caused by infusion of 0.2 N HCl in 5 chloralose-urethane-anesthetized, gallamine-paralyzed, artificially ventilated New Zealand white rabbits. Ventral medullary ECF pH was measured continuously with pH microelectrodes (1-2μ tip diameter) positioned 1-2 mm below the ventrolateral surface of the medulla. The following results were obtained:

min	pHa	Pa_{CO_2}	$[HCO_3^-]a$	ECF pH
0	7.390 ± 0.022	25.9 ± 0.8	15.6 ± 0.8	7.352 ± 0.112
30	7.246 ± 0.030*	25.8 ± 0.9	10.6 ± 0.9*	7.270 ± 0.105*

*p<0.005

We conclude that metabolic changes in blood acid-base balance are reflected rapidly in cerebral ECF. This response could account for the increase in ventilation observed during metabolic acidosis in peripheral chemodenervated animals. (HL 25984).

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O_2 AND CO_2 INDUCED CHANGES IN VENTILATORY GAIN DURING EXERCISE IN INTACT AND CAROTID BODY DENERVATED GOATS. G.S. Mitchell, C.A. Smith, L.C. Jameson* and J.A. Dempsey. University of Wisconsin, Madison, WI 53706.

Steady-state ventilatory responses to exercise were studied in 4 goats in normoxia (F_{IO_2}=0.21), hypoxia (F_{IO_2}=0.12), hyperoxia (F_{IO_2}=1.0), and hypercapnia (i.e., increased dead space ventilation in hyperoxia). Hypoxia (PaO_2 40-45 torr) had little effect on resting $\dot{V}_E$ or $PaCO_2$ but increased ventilatory gain during exercise ($\Delta\dot{V}_E/\Delta\dot{M}CO_2$) 20% ($p<0.05$). Hyperoxia affected neither $\dot{V}_E$ and $PaCO_2$ at rest nor $\Delta\dot{V}_E/\Delta\dot{M}CO_2$ in exercise. $PaCO_2$ increased 2.2 torr with increased dead space (420 ml BTPS) both at rest and exercise resulting in a 77% increase in $\Delta\dot{V}_E/\Delta\dot{M}CO_2$ ($p<0.02$). Measurements were repeated in 3 goats 2 months after surgical removal of the carotid bodies. Carotid body denervation 1) decreased $\dot{V}_E$ 26% ($p<0.01$) and increased $PaCO_2$ 8.3 torr ($p<0.02$) at rest with an apparent decrease in $\Delta\dot{V}_E/\Delta\dot{M}_{CO_2}$ of 14% in normoxia, 2) abolished the increase in $\Delta\dot{V}_E/\Delta\dot{M}CO_2$ in hypoxia, 3) caused hyperventilation at rest ($\Delta PaCO_2$=-4.5 torr, $p<0.01$) and in exercise ($\Delta PaCO_2$=-8.3, $p=0.05$) in hyperoxia, and 4) had no effect on the hypercapnic-exercise interaction. These results indicate that complex interactions occur between O_2 and CO_2 sensitive receptors and the factors involved in controlling ventilation during exercise. The carotid bodies are necessary for the hypoxic-exercise interaction, mask the hyperoxic hyperventilation, but do not appear to be involved in the hypercapnic-exercise interaction. (NHLBI and USAMR&DC).

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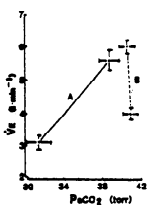
ISOCAPNIC HYPOPNEA RESULTING FROM PARTIAL CARDIOPULMONARY BY-PASS. A.Oren,* A. Huszczuk,* L.E. Nery,* E.C. Shors, B.J. Whipp, and K. Wasserman. Harbor-UCLA Med. Ctr.Torrance, CA 90509



CO_2 flux to the lungs can be altered by changing $C\bar{v}CO_2$ and/or the rate of venous return ($\dot{Q}v$). Reducing $C\bar{v}CO_2$ by means of extra-corporeal gas exchanger while maintaining $\dot{Q}v$, leads to hypocapnic hypoponea along the CO_2 response slope (line A in figure). Loading the right ventricle by increasing $\dot{Q}v$, or by partially obstructing its outflow, provides potent stimulation of minute ventilation ($\dot{V}_E$) (Huszczuk et al.Fed.Proc.40:568, 1981). Utilizing partial cardiopulmonary by-pass in anesthetized dogs we diverted ≃50% of $\dot{Q}v$ from the venae cavae to the abdominal aorta. Gas exchange variables and $\dot{V}_E$ were determined breath-by-breath and arterial PCO_2 was continuously displayed from an on-line PCO_2 electrode.The by-pass resulted in a decrease of $\dot{V}_E$ in all cases, which averaged 32.5% ± 1.7 SE. This hypopnea was isocapnic (line B in figure) despite the CO_2 output decrease (37.5% ± 2.0 SE) being significantly greater ($P<0.001$). This isocapnia must therefore have resulted from ventilatory control mechanisms which reflect both reduced $\dot{Q}v$ and a relatively increased dead space ventilation.

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VENTILATORY EFFECTS OF AIRFLOWS THROUGH THE UPPER AIRWAYS OF NEWBORN KITTENS AND PUPPIES. S.F. Al-Shway* and J.P. Mortola, Physiol. Dept., McGill Univ., Montreal, Quebec, Canada.

Ten kittens, 10 puppies, 6 cats and 4 dogs were anaesthetized with pentobarbital and tracheotomized; respiratory flow and tidal volume were recorded. Steady flows of room air of 20 or 50 ml $sec^{-1}kg^{-1}$ were delivered in the expiratory direction through a second cannula inserted just below the larynx, for a period corresponding to the duration of 3 breaths. Inhibition of the ventilatory pattern, with decrease in both breathing rate (F) and tidal volume, was observed in the newborn at both flows, and particularly more so at the higher flow. The decrease in F was due to a marked prolongation of the expiratory time; in 18 % of all the trials total apnea occurred for the period of the stimulus. No ventilatory effects were observed in adult dogs, while some inhibition was occasionally present in the cat. The ventilatory inhibition was reduced when humidified warm air was delivered, and was similarly observed when CO_2 enriched airflows were applied. After local anaesthesia of the laryngeal region or after bypassing the larynx the ventilatory inhibition disappeared. By closure of a nostril at any given airflow the upper airways pressure was substantially increased. This did not significantly alter the respiratory inhibition. We conclude that airflow through the upper airways can inhibit ventilation in newborn kittens and puppies presumably through the stimulation of temperature and airflow sensitive laryngeal receptors. (Supported by MRC Canada).

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THE EFFECT OF SO_2 ON THE RESPONSE OF RABBITS TO EXPIRATORY LOADING. P.W.Davenport and K.A.Rex*. Dept. of Physiology and Biophysics, Univ. of Texas Med. Branch, Galveston, Texas,77550

Eight rabbits were anesthetized, tracheostomized and placed supine.The diaphragm EMG was recorded from electrodes inserted into the diaphragm through an abdominal incision. The tracheal cannula was connected to a loading manifold which allowed the selective single breath loading of expiration. Two levels each of resistive, elastic and threshold loads and tracheal occlusion at end inspiration were presented 3 times each. We recorded airflow, volume, dia. EMG, integrated EMG, tracheal pressure and arterial blood pressure on a polygraph. The loading protocol was presented 4 times: control, after 15-20 min. exposure to 250-400 ppm SO_2, 1 hour after stopping exposure to SO_2, and after vagotomy. During control breathing, increasing load magnitude caused a progressive decrease in the expired volume and an increase in the expiratory duration (Te) as measured from the dia. EMG. The degree of prolongation of Te was related to the area under the expired volume trajectory. Exposure to SO_2 markedly reduced or abolished the prolongation of Te which returned after recovery. Vagotomy also abolished the prolongation of Te. These results suggest that the reported (Davies, et al., Respir. Physiol. 34: 83, 1978) selective block of pulmonary stretch receptors (PSR) in rabbits with SO_2 supports the hypothesis that PSRs are the afferents mediating the volume related prolongation of Te observed with expiratory loads.

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THE MODULATION OF FETAL BREATHING MOVEMENTS BY CSF $[HCO_3^-]$ IS NOT DEPENDENT UPON CHANGES IN ELECTROCORTICAL ACTIVITY (ECoG). A. Roger Hohimer, John M. Bissonnette and Bryan S. Richardson*. Oregon Health Sciences University, Portland, OR 97201.

Ventriculocisternal perfusions (JAP 50:880, 1981) were performed on 11 fetal lambs. Artificial CSF with $[HCO_3^-]$ between 6 and 40 mEq/l was perfused at 123 µl/min. Fetal tracheal pressures were recorded to determine the incidence and depth of FBM during a 3-hr period following an alteration of $[HCO_3^-]$ in CSF. Fetal blood gases and pH were measured and in 6 animals ECoG was recorded. The animals have been grouped according to the cisternal $[HCO_3^-]$ and the results given as means ± SEM.

	Cisternal $[HCO_3^-]$	FBM (%)	Depth (torr)	PaO_2 (torr)	PCO_2 (torr)	pH
Low (n=7)	17.3 ±0.8	45.7 ±6.8	8.9 ±1.6	20.0 ±1.4	48.8 ±1.4	7.389 ±0.006
Normal (n=4)	24.6 ±0.4	26.8 ±11.5	6.9 ±1.8	21.7 ±0.3	50.5 ±0.1	7.392 ±0.014
High (n=5)	30.7 ±0.4	0.6 ±0.2	3.0 ±0.2	19.6 ±1.4	50.5 ±1.1	7.391 ±0.012

Four low $[HCO_3^-]$ animals had differentiated ECoG; the incidence of high voltage (HV) activity was 47.8 ± 2.0%. FBM occurred during 77.8 ± 3.7% of low voltage and 30.9 ± 11.7% of HV. In 2 animals ECoG was not altered by high $[HCO_3^-]$ perfusions. We conclude that CSF $[H^+]$ is a critical stimulus to normal FBM and that elevated $[H^+]$ can cause FBM during HV ECoG.

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LONG-LASTING CENTRAL INHIBITION OF RESPIRATION: MEDIATION BY GABA AND ENDOGENOUS OPIATES. T.G. Waldrop*, D.E. Millhorn and F.L. Eldridge. Univ. of North Carolina, Chapel Hill, NC 27514

In addition to the direct effects during stimulation and the afterdischarge, stimulation of limb muscles or their afferents causes a post-stimulation inhibition of respiratory output (RO) which lasts for up to 1 hour. We have previously shown that this response is caused by a central neural mechanism involving the higher brain and cerebellum (Physiologist 23: 75, 1980). The purpose of the present study was to determine which neurotransmitters mediate this inhibitory effect. Anesthetized, paralyzed cats whose vagi and carotid sinus nerves had been cut were studied. Respiratory output was derived from peak integrated phrenic activity. Body temperature and $P_{ET}CO_2$ were kept constant by servocontrollers. Pretreatment with either an endogenous opiate antagonist (naloxone) or a GABA antagonist (bicuculline methiodide) prevented the post-stimulation inhibition. The response was not blocked by prior administration of either a serotonin antagonist (methysergide) or a dopamine and norepinephrine antagonist (α-methyltyrosine). These results suggest that both GABA and endogenous opiates, but not serotonin, dopamine or norepinephrine, are involved in the mechanism mediating the long-lasting inhibition of respiration caused by stimulation of limb muscles or their afferents. (Supported by USPHS Grants HL-17689, NS-11132 and the Parker B. Francis Foundation.

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CENTRAL NEURAL STIMULATION OF RESPIRATION BY SODIUM SALICYLATE. D.E. Millhorn, F.L. Eldridge and T.G. Waldrop*. University of North Carolina, Chapel Hill, NC 27514.

Therapeutic doses of sodium salicylate cause significant increases in respiratory output (RO); the mechanism remains unknown. It has been reported (JAP 41: 639, 1976; 46: 1029, 1979) that salicylate stimulates RO through its ability to uncouple oxidative phosphorylation and thereby increase metabolic CO_2 production ($\dot{V}CO_2$). We studied this possibility in anesthetized, paralyzed cats whose vagi and carotid sinus nerves had been cut. $P_{ET}CO_2$ and body temp were servocontrolled and kept constant. RO was quantified from peak integrated phrenic activity. Rate of CO_2 production was determined from the pumping rate of the CO_2-servocontrolled ventilator. In a separate animal salicylate did not affect carotid body output. Systemically administered salicylate (240 $mg/kg^{0.75}$ iv) led to less than a two-fold increase in $\dot{V}CO_2$ and a four-fold increase in RO. The time courses for $\dot{V}CO_2$ and RO were unrelated; the increase in $\dot{V}CO_2$ was complete in 10-15 min whereas RO continued to increase for at least 60 min. The increase in RO was not prevented by cervical (C_7-T_1) chordotomy. When salicylate was given into the third ventricle (12 $mg/kg^{0.75}$), RO still increased but without an increase in $\dot{V}CO_2$. We conclude that salicylate does not stimulate respiration through peripheral mechanisms but through central mechanisms. Supported by USPHS grants HL-17689, NS-11132, FR-05406 and the Parker B. Francis Foundation.

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MECHANISM OF HYPERPNEA INDUCED BY AMINOPHYLLINE. F.L. Eldridge, D.E. Millhorn and T.G. Waldrop*. University of North Carolina, Chapel Hill, N.C. 27514

Aminophylline causes an hyperpnea that has been thought to be mediated by its direct action on central respiratory neurons. We have reexamined this question in 40 anesthetized, paralyzed cats (vagi and carotid sinus nerves cut) whose end-tidal P_{CO2} and body temperature were kept constant by means of servocontrollers. Respiratory output (RO) was quantified from peak integrated phrenic nerve activity. Systemically administered aminophylline (8 mg/kg iv) caused RO to double within 10 min and to remain elevated for > 35 min. Neural output of the carotid body did not change. Slope of phrenic response to hypercapnia increased after aminophylline. Spinal cord transections at C_7-T_1, T_{4-5} and L_{1-2} had no effect on the response. Pretreatment with a serotonin antagonist (methysergide) had no effect, but two dopamine-norepinephrine antagonists (haloperidol and α-methyltyrosine) caused an attenuation of the response. When given into the 3rd ventricle at a pH adjusted to 7.0, both aminophylline (0.4 mg/kg) and theophylline (0.34 mg/kg) caused inhibition of respiration lasting > 30 min whereas control injections of Ringer's solution (pH 6.3) had little effect. Our findings raise doubts that aminophylline stimulates respiratory neurons directly. We suggest that its stimulatory effect, when given systemically, is due to its ability to reduce cerebral blood flow. (Supported by USPHS grants HL-17689, NS-11132 and the Parker B. Francis Foundation)

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EFFECT OF CEREBRAL INTRAVENTRICULAR ADMINISTRATION OF ANIONIC BLOCKING AGENTS ON CEREBROSPINAL FLUID (CSF) ELECTROLYTE DURING RESPIRATORY ACIDOSIS. H.M. Frankel and H. Kazemi, Rutgers University, New Brunswick, N.J. 08903 and Pulmonary Unit, Massachusetts General Hospital, Boston, MA 02114

The possibility that a $[Cl^-]$-$[HCO_3^-]$ exchange occurred in the CSF during respiratory acidosis was investigated by administration of 2 compounds that reportedly block the $[Cl^-]$-$[HCO_3^-]$ exchange transport system. Anesthetized dogs were maintained either normocapnic or hypercapnic and given either pyridoxal 5-phosphate (P-P, 1 mg/kg) or 4,4' diisothiocyano-2, 2'-disulfonate stilbene (DIDS, 10 ug/kg) in the lateral cerebral ventricles (CV). P_{CO_2}, pH, $[Na^+]$ and $[Cl^-]$ were determined in cisternal CSF and arterial blood. $[HCO_3^-]$ was calculated. Samples were drawn before and 4 hrs after administration of the compound. With 4 hrs of hypercapnia CSF P_{CO_2} increased approx 32 torr and $[H^+]$ increased approx 13 mM/L in dogs receiving either compound. CSF $[Cl^-]$ decreased approx 9 and 6 mM/L with CV-P-P and CV-DIDS, respectively; CSF $[HCO_3^-]$ increased approx 9 and 7 mM/L, respectively. There was no significant change in CSF $[Na^+]$ during hypercapnia with either compound. At normocapnia CSF $[Cl^-]$ was decreased 5-6 mM/L with both compounds. With CV-P-P CSF $[HCO_3^-]$ did not change; it decreased with CV-DIDS. CSF $[Na^+]$ decreased 2-3 mM/L with both compounds. The reciprocal relationship between changes in $[Cl^-]$ and $[HCO_3^-]$ observed during respiratory acidosis was not duplicated at normocapnia and requires further explanation. (Supported in part by NIH Research Training Grant HL07354)

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CORRELATION OF RENAL ANATOMY TO RENAL XENON WASHOUT. Robert L. Allen*, John C. Passmore, Carl E. Hock* and William B. Bradford*. Dept. Physiology, Univ. of Louisville, School of Medicine, Louisville, Kentucky 40292.

A correlation of renal anatomical compartments to ^{133}Xe washout rates has been studied. Adult mongrel dogs weighing 19-30 kg were anesthetized with chloralose-urethane. By dissection, we found that the cortex comprises 68.9 ± 1.1% (S.E.) of the total kidney weight; whereas, the outer medulla is 17.9 ± 1.5% of the total kidney weight. Flow rates for the two compartments were determined by the ^{133}Xe disappearance freeze-dissection technique. The average flow rate for the cortex was 4.25 ± .49 ml/g/min and the y intercept for the ^{133}Xe washout rate indicates that 87% of the initial radioactivity was distributed to the cortical compartment. The average flow rate for the outer medulla was 1.9 ± .19 ml/g/min and the y intercept for the ^{133}Xe washout rate indicates that 10% of the initial radioactivity was distributed to the outer medullary compartment. Based on a 100g kidney, total cortical blood flow would be 292.8 ml/min (4.25 ml/g/min x 68.9g) and total outer medullary blood flow would be 34.0 ml/min (1.9 ml/g/min x 17.9g). These calculations indicate that 89.5% of the total flow is distributed to the cortex and 10.4% is distributed to the outer medulla, exactly as the intercept-calculated percentages would indicate. (Supported by Kentucky Heart Association and Heart Association of Louisville and Jefferson County.)

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EFFECTS OF CAPTOPRIL AND SARALASIN ON THE HEMODYNAMIC RESPONSE TO RENAL TUBULAR OBSTRUCTION. Pamela K. Carmines* and George A. Tanner. Indiana Univ. Sch. Med., Indianapolis, IN 46223.

The purpose of this study was to examine the role of the renin-angiotensin system (RAS) in the decreased glomerular blood flow (GBF) that occurs with chronic single tubular obstruction. The effect of pharmacologic interruption of the RAS on blood flow to blocked nephrons was studied in two groups of anesthetized rats treated as follows: (I) Captopril (10 mg/kg, p.o.) or vehicle, and (II) saralasin (10 µg/kg/min, i.v.) or vehicle. Blood flow was determined using nephron microdissection and microsphere techniques for normal tubules and tubules subjected to 24 hr castor oil blockade.

	Glomerular Blood Flow, nl/min			
	Control (5 rats)	Captopril (5 rats)	Control (6 rats)	Saralasin (6 rats)
Normal	235±16	296±40	233±28	210±11
Blocked	116±13**	252±31*	139±20**	152±4**

($\bar{Y}$±SEM. **P<0.001 and *P<0.025 when compared to normal tubules)

Blood flow to blocked nephrons averaged 50±4% of normal in group I control rats; Captopril improved flow to blocked nephrons to 86±4% of normal (P<0.005). In group II control rats, blood flow to blocked nephrons was 59±2% of normal; saralasin increased flow to blocked nephrons to 73±3% of normal (P<0.05). Since both agents improved blood flow to blocked nephrons, and in view of their different modes of action, these data provide evidence for a role of the RAS in maintaining decreased GBF during obstruction. (Supported by NIH grant HL 13929.)

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QUANTIFICATION OF REGIONAL RENAL CORTICAL BLOOD FLOW USING A THERMODYNAMIC TECHNIQUE. T. Adams, W.S. Spielman, J.C. Hartman* and M.A. Steinmetz. Department of Physiology, Michigan State University, East Lansing, MI 48824.

Regional renal blood flow was measured at localized cortical zones in situ at 90 sec, intervals over a 3 hour period in anesthetized (30 $mg.kg^{-1}$ Na pent.; iv) dogs using a new technique (A.J.P. 238:H682-H696, 1980) which involves heat transfer analysis. It requires establishing a weak thermal field in a tissue across which unidirectional heat flux (nom. 8 mW) and a temperature gradient (nom. $0.05^{o}C.mm^{-1}$) are simultaneously measured to allow for the calculation of tissue effective thermal conductivity (k') and the deduction of local blood flow ($ml.min^{-1}.cm^{-3}$). Mean k' for the non-perfused renal cortex (n=3) was 5.34 ± 0.13 (SE) $mW.^{o}C^{-1}.cm^{-1}$. Total renal perfusion measured with an electromagnetic flowmeter was varied with an adjustable arterial clamp. Simultaneous thermodynamic measurements of regional cortical flow correlate (r=.87) with the electromagnetic determinations of total renal blood flow. Advantages of the thermodynamic technique for renal perfusion studies are that it allows for rapid, sequential measurements of regional flow quantitatively in small tissue volumes and its accuracy and precision are unaffected by either local metabolic heat production or tissue temperature.

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EFFECT OF RENAL ISCHEMIA OR URETERAL LIGATION ON THE RENAL BLOOD FLOW RESPONSE TO HYPERONCOTIC DEXTRAN. R.W. Gotshall. Wright State University, School of Medicine, Dayton, OH 45435

Previously, we have shown that the renal vasodilatation response to intrarenal hyperoncotic dextran infusion was absent in nonfiltering canine kidneys. Glomerular filtration was eliminated in these kidneys by a combination of renal ischemia and ureteral ligation. To discriminate between these two effects on the renal response to dextran, hyperoncotic (20%) dextran was infused into renal arteries of kidneys with only ischemia or ureteral ligation. Two hours of ischemia or ureteral ligation was done 4 days prior to the acute experiment.

	RBF (ml/min/100g)		GFR (ml/min/100g)	
	Control	Dextran	Control	Dextran
Ischemic (N=5)	285	323	32	21
Ureteral ligation (N=5)	110	106	--	--

The renal vasodilatation response to dextran is evident only in those kidneys with GFR and not when GFR was not measurable. Thus it appears that ischemia per se does not interfere with the vasodilatation response. The data suggests that the vasodilation by dextran is subsequent to the dextran reduction in GFR and tubular feedback control of the renal vasculature. (Supported by NIH 21382 and MVHA #57-293-801).

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RENAL VASCULAR RESPONSES TO HYPOXEMIA IN SPONTANEOUSLY BREATHING DOGS. W.R. Sexson*, D.S. Miles* and R.W. Gotshall. Wright State University, School of Medicine, Dayton, Ohio 45435

Our previous report (Fed. Proc. 40:554, 1981) demonstrated that RBF and renal function were unchanged during hypoxemia with controlled ventilation until very low PaO_2's (18 torr) when cardiac output decreased. To compare hypoxemia along with hypocapnia and alkalosis, 5 anesthetized spontaneously breathing dogs breathed progressively lower levels of inspired O_2.

O_2 (% inspired)	21%	16%	14%	12%	10%	21%
PaO_2 (torr)	75	53	43	37	29	71
$PaCO_2$ (torr)	39	33	29	26	22	30
pH	7.40	7.46	7.49	7.53	7.56	7.43
C.O. (l/min)	3.42	3.37	3.26	2.97	1.24	1.91
BP (mm Hg)	131	132	136	134	115	95
RBF (ml/min/100g)	520	545	551	558	449	409
GFR (ml/min/100g)	72	68	68	72	55	62
FE_{Na} (%)	0.19	0.16	0.20	0.22	0.08	0.09

Renal function was well maintained until the lower PaO_2's (29 torr) when cardiac output and BP decreased. When hypocapnia and alkalosis are present, the decrease in systemic and renal hemodynamics occurs at a higher PaO_2 (29 torr vs. 18 torr) than when $PaCO_2$ and pH are controlled. This probably results from the left shift in the O_2 dissociation curve due to the low $PaCO_2$ and elevated pH in the present experiment which compromised O_2 delivery to the myocardium. (Supported by NIH 21382)

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RENIN-ANGIOTENSIN AND IMPAIRED AUTOREGULATORY EFFICIENCY DURING PENTOBARBITAL ANESTHESIA IN RATS. L.A. Walker*, M. Gellai, and H. Valtin. Dept. Physiol., Dartmouth Med. Sch., Hanover, NH 03755.

Our previous results indicated depression of renal blood flow (RBF) and glomerular filtration rate (GFR) during pentobarbital anesthesia (AN) in rats. AN also caused reduction in renal perfusion pressure (RPP) to 80-85 mmHg and, according to some reports, stimulation of renin release. In order to determine the role of these factors in the depression of RBF and GFR during AN, studies were performed in: conscious (CON), anesthesia (AN), propranolol (P) pretreatment plus AN, captopril (CAP) pretreatment plus AN, and saralasin (SAR) pretreatment plus AN. All animals were trained and had chronically implanted catheters and, where appropriate, aortic constriction cuffs. Clearances were performed first in the conscious state (at normal RPP), and then in the same rat at RPP of 80-90 mmHg, accomplished by aortic constriction (AC) in CON or by AN. Values in table are at the low RPP, expressed as % of control (normal RPP) values for that particular group.

	CON+AC(7)	AN(9)	P+AN(6)	CAP+AN(6)	SAR+AN(5)
GFR	99	76*	97	107	95
RBF or ERBF	100	74*	88*	94	76*

*p<0.05 compared to control state (i.e., high RPP)

Results suggest: (1)impairment of GFR autoregulation during AN is due largely to renin-angiotensin; (2)angiotensin II may not act predominantly on efferent arterioles. Supported by NKF and NIH.

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EFFECT OF SARALASIN ON THE RENAL CORTICAL VASOCONSTRICTION INDUCED BY NICOTINE INFUSION. C. E. Hock*, J. C. Passmore, R. L. Allen*, W. B. Bradford* and K. C. Huang. Dept. Physiology, School of Medicine, Louisville, Ky. 40292.

Nicotine is known to be a potent sympathomimetic agent. The effects of nicotine infusion (0.024 mg/kg/min) on renal blood flow distribution was investigated using a freeze-dissection ^{133}Xe disappearance technique. Radioactive microspheres measured total renal blood flow (TRBF). Since we have previously found increased renin secretion during nicotine infusion, the angiotensin II antagonist, saralasin, was infused via the renal artery (4 mg/kg/min) to determine the role of the renin-angiotensin system in the nicotine-induced renal cortical vasoconstriction. Nicotine infusion alone caused a 75% increase in mean arterial pressure. TRBF, outer cortical (OC), inner cortical (IC) and outer medullary (OM) flow decreased 64%, 80%, 77% and 68%, respectively, from control. Animals receiving saralasin with the nicotine infusion had a 130% greater OC flow, a 78% greater IC flow and no difference in OM flow when compared to nicotine infused dogs. Although these values are less than untreated control values, they do indicate that a significant portion of the nicotine-induced renal vasoconstriction is due to angiotensin II.
(Supported by Kentucky Heart Association and Heart Association of Louisville and Jefferson County and Louisville Medical Research Foundation. Saralasin provided by Norwich-Eaton.)

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EFFECTS OF CONVERTING ENZYME INHIBITION ON SUPERFICIAL NEPHRON FUNCTION OF THE NONCLIPPED KIDNEY IN GOLDBLATT HYPERTENSIVE RATS. Wann-Chu Huang and L. Gabriel Navar. University of Alabama Medical Center, Birmingham, Alabama 35294

Previous studies have demonstrated that blockade of the renin-angiotensin system enhances GFR, renal blood flow and excretory function of the nonclipped kidney of 2-kidney, 1 clip Goldblatt hypertensive (GH) rats. The present study was performed in 13 GH rats to evaluate superficial nephron responses to converting enzyme inhibition (CEI, SQ 20881, 3 mg/kg.hr). Late proximal and early distal tubule collections were followed by recollection from the same site during CEI. Significant increases in GFR, urine flow, Na^+ excretion, single nephron GFR (25.2 ± 2 to 27.4 ± 1.9 nl/min) and distal tubule flow (4.4 ± 0.4 to 6.9 ± 0.6 nl/min) occurred in spite of reductions in BP (160 ± 5 to 137 ± 6 mmHg) during CEI. Both proximal and distal tubule TF/P inulin ratios were decreased (1.9 ± 0.2 to 1.5 ± 0.1 and 7.4 ± 0.7 to 4.8 ± 0.4, respectively). There were significant decreases in fractional reabsorption of fluid (45 ± 4 to 28 ± 4%), Cl^- (38 ± 6 to 23 ± 3%) and total solute (44 ± 4 to 23 ± 3%) up to the proximal collection site. Fractional reabsorption of the nephron segment between 2 collection sites decreased significantly (72 ± 2 to 63 ± 3% for fluid; 92 ± 1 to 88 ± 2% for Cl^-; and 84 ± 1 to 77 ± 4% for total solute). These results indicate that inhibition of angiotensin II formation reduces superficial tubule reabsorptive function and suggest that an angiotensin mediated alteration of tubular reabsorption exists in the nonclipped kidney of this hypertensive model.

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FACTORS AFFECTING ADSORPTION OF LIPIDS RELATED TO LUNG SURFACTANT AT THE AIR-WATER INTERFACE. Jon Goerke. Cardiovascular Research Inst. and Dept. Physiology, Univ. Calif., San Francisco, CA 94143

We made all measurements at 37°C in cylindrical 6.5 cm diameter Teflon^R cells, containing 15 μM lipid in 30 ml stirred buffer (10 mM HEPES pH 6.9, 6 mM $CaCl_2$, 1 mM EDTA, 100 mM NaCl). Lowering of surface tension (γ), determined with a Wilhelmy plate, was taken as a measure of lipid adsorption. We used large multilayer vesicles (LMV) and small unilamellar vesicles (SUV) prepared both by the French press and by ethanol injection.

Dry dipalmitoyl phosphatidylcholine (DPPC) powder, applied directly to the air-water surface or stirred into the subphase, did not lower γ for up to 2 hr. DPPC as LMV or SUV behaved similarly when prepared between 45 and 50°C. On the other hand, all forms of vesicles adsorbed measureably ($\Delta\gamma$ > 10 mN/m in 30 min) when prepared at or below 37°C. The former SUV suspensions were clear, the latter opalescent. The adsorbability of the latter LMV was destroyed by warming them to 48°C for 20 min followed by slow (20 min) cooling to 37°C. 1 to 16 mol% eggPC, phosphatidylglycerol, lysoPC, cholesterol or palmitic acid in DPPC produced LMV and SUV with graded adsorption rates.

These results suggest that liposome adsorbability is related to the presence of strained structures which, in the case of pure DPPC, can by removed by annealing above the 41°C DPPC phase transition temperature.

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Mechanism of liposomal phosphatidylcholine uptake by granular pneumocytes. A. Chander, W.D. Claypool, Jr., A.B. Fisher. Dept. of Physiology, University of Pennsylvania, Philadelphia, PA 19104.

We have previously shown that granular pneumocytes in primary culture take up exogenous phosphatidylcholine (Fed. Proc. 40:407, 1981). In this study we further investigated this uptake as a model for the clearance of surfactant phospholipids from the alveolar surface. Lung epithelial type II cells were isolated by trypsinization and differential adherence (JAP 48:743, 1980). Liposomes were prepared from mixtures of ^{14}C-DPL-cholesterol (1:1) (neutral) or from ^{14}C-DPL:phosphatidylcholine (egg;hydrogenated):phosphatidylglycerol:cholesterol (50:25:10:15) (anionic) either by sonication or by passage through a French pressure cell (16,000 psi). With neutral liposomes, rates of DPL uptake were 3.01 nmol/h/mg cell protein and 0.63 nmol/h/mg cell protein at final concentrations of 0.33mM and 0.061mM, respectively. Uptake with anionic liposomes was 1.41 nmol/h/mg cell protein at 0.05mM DPL. Uptake was time dependent and was maximal at 2-3 h. 6-Carboxyfluorescein, used as a marker for the liposomal aqueous compartment, was accumulated by cells over 2-3 hrs. Inhibitors of oxidative metabolism had no effect on liposomal uptake, but 2-deoxyglucose (5.6 mM) decreased liposomal uptake by more than 50%. Addition of 0.5 ug/ml surfactant hydrophobic apoprotein (Fed.Proc. 40:408,1981) increased the uptake of liposomes by 2-4 times. These results indicate that granular pneumocytes accumulate exogenous DPL. The uptake is likely mediated, in part, by endocytosis. Surfactant hydrophobic apoproteins may play an important role in modulating the uptake and further metabolism of surfactant phospholipids.

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IN VITRO EFFECTS OF KAOLIN ON DIPALMITOYL LECITHIN (DPL) AND LUNG SURFACTANT. K.C. Weber, J. Ma* and W.E. Wallace*, NIOSH, Morgantown, WV 26505.

Since kaolin was previously found to absorb DPL from solution (J. Colloid Interface Sci. 51: 535-537, 1975), we studied kaolin's absorption of surface active material from the air-liquid interface of a Wilhelmy balance (Kimray-Greenfield). Lung surfactant was obtained from the foam evolved from the lavage of excised rat lungs. After control studies with synthetic DPL and rat lung surfactant (22°C and aqueous subphase), kaolin (<30 mg) was sprinkled unto the balance surface at minimum area and the surface tension vs surface area was recorded for 4 cycles at speeds of 5.5 min per cycle with the pool area changing from 100 to 15%. When DPL was used (3 experiments), the minimum surface tension (γ min) increased from <2 to 31 dynes/cm and the maximum surface tension (γ max) remained constant. The hysteresis decreased by >90%. When lung surfactant was used (3 experiments), γ min increased from 15 to 43 dynes/cm, γ max increased from 41 to 55 dynes/cm and the hysteresis decreased by >90%. These results indicate that workers exposed to kaolin dust may be experiencing changes in their alveolar surfaces due to absorption of the surfactant by the respirable dust particles.

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EFFECTS OF UNSTIRRED WATER LAYERS ON LIPID PERMEABILITY CHARACTERISTICS OF GUINEA PIG TRACHEAL EPITHELIUM. S.F.P.Man*, D.S.K. Park*, and A.B.R. Thomson*. (SPON: R.L. Jones) Dept. of Med., University of Alberta, Edmonton, Alberta, Canada.

The entry of non-electrolytes into the cytosol has several important determinants, among which are the lipid characteristics of the cell membrane, and the overlying unstirred water layer (UWL). We used an in vitro technique to measure the uptake of a homologous series of ^{14}C-labeled saturated fatty acids (FA) and fatty alcohols (Alc) into guinea pig tracheal epithelium. When the bulk phase was not stirred, a linear relationship was noted between the uptake and the number of CH_2 groups for FA 4:0-12:0. In contrast, the uptake reached a plateau from Alc 8:0 to 12:0, indicating that the uptake of these alcohols were limited by diffusion across the UWL. When the bulk phase was stirred at 600 rpm, the resistance of the UWL was markedly reduced, the uptake of Alc10:0 and 12:0 remained limited by diffusion across the UWL, and a linear relationship was again noted between the uptake and the number of CH_2 group for FA 4:0-12:0. From this linear relationship, the incremental change in free energy, $\delta\Delta F_{w\to}$, was calculated to be - 147 cal·mol^{-1}. It is concluded that (1) the guinea pig tracheal epithelium is moderately lipid permeable; (2) the UWL is the major barrier limiting the rate of uptake of medium chain fatty alcohols; and (3) failure to correct for the effects of UWL leads to an under-estimation of the true permeability of tracheal epithelium. (Supported by MRC 6183 and Cystic Fibrosis Foundation of Canada).

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BRONCHODILATOR ACTIVITY OF VASOACTIVE INTESTINAL PEPTIDE (VIP) IN THE CAT IN VIVO. John L. Szarek*, Mark Gillespie* and Louis Diamond. Univ. of Ky., College of Pharmacy, Lexington, KY 40506.

VIP is an octacosapeptide which occurs widely in the animal kingdom, is distributed in many organs and tissues, and has a broad range of biological actions. The present experiments were undertaken to characterize the actions of VIP on feline airways in vivo. For comparative purposes, prostaglandin E_2 (PGE_2) also was studied. A steady state level of bronchoconstriction was induced in anesthetized, atropinized, artificially ventilated cats by means of an iv infusion of serotonin. The increase in lung resistance (R_1) so produced was used as an index of central airways response and the increase in dynamic elastance (E_{dyn}) as an index of peripheral airways response. VIP and PGE_2 (.1-10µg/kg iv) were evaluated for their ability to moderate these indices of heightened bronchomotor tone. Both drugs elicited dose-related bronchodilation which was more prominent in central than in peripheral airways. The mean ratio of % ΔR_1 to % ΔE_{dyn} was 6.6 for VIP and 4.0 for PGE_2. The potency of the 2 drugs was similar: the $ED50_{R_1}$ (dose which reduced R_1 by 50%) was 4.1µg/kg for VIP and 2.7 µg/kg for PGE_2. The bronchodilator action of VIP was not susceptible to beta adrenergic blockade with propranolol or to cyclooxygenase inhibition with indomethacin. These findings indicate that VIP is a potent relaxant of feline airways smooth muscle in vivo and that this effect is not mediated through beta adrenergic stimulation or by prostaglandins.

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INTRINSIC ROLE OF BRONCHIAL DIMENSIONS IN MUCOCILIARY TRANSPORT. M. King and J. Kay.* Meakins-Christie Labs, McGill Univ. and Royal Victoria Hosp. Montreal, Quebec, Canada.

Most, if not all, agents that alter bronchial dimensions also alter mucociliary clearance rates. While many mechanisms for altered mucus transport are possible, it is conceivable that dimensional charges alone could contribute to altered rates of mucociliary clearance. In this study, we examined the effect of mechanical alterations of airway dimensions on mucociliary transport in the absence of the pharmacologic or humoral agents that normally induce airway dimensional change. Mucociliary transport rates were observed in excised dog and rabbit tracheas. Biaxial stretching and compression of the non-cartilagenous portion of the tracheal mucosa was used to simulate mechanically induced bronchodilation and constriction. We found that biaxial compression of the mucosal surface led to a reduction in mucociliary transport rate. Modest degrees of stretching did not affect clearance, but extremes of stretching led to irreversible inhibition of transport. These observations suggest that bronchodilation, within reasonable limits, has no inherent effect on mucociliary clearance rates, while broncho-constriction inherently inhibits the rate of clearance. (Supported by the Canadian Cystic Fibrosis Foundation).

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EFFECTS OF OXYGEN TOXICITY AND ELASTASE TREATMENT ON LUNG FUNCTION IN RATS. Jack R. Harkema* and Joe L. Mauderly. Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185

The purpose of this study was to evaluate the lung function changes in two disease models and examine the combined effects. Twenty female rats were instilled intratracheally with 0.3 IU/gm elastase and 20 were instilled with saline. Half of each group was exposed to room air and half to 100% O_2 for 48 hrs at 1 atm. Tests were performed on anesthetized rats by plethysmography before instillation and after exposure. Function tests included spontaneous breathing patterns, subdivisions of lung volume, quasistatic cord compliance (C_{QS}), CO diffusing capacity (DL_{CO}), and forced expirograms. 100% O_2 exposure induced a "restrictive" lung disease characterized by decreased C_{QS}, vital capacity and DL_{CO}. Rats treated with elastase had increased C_{QS}, total lung capacity, functional residual capacity (FRC), residual volume (RV), forced expiratory volume at 0.1 sec ($FEV_{0.1}$), and reduced expiratory flow rates, characteristic of an "obstructive" disease. Elastase-treated rats exposed to 100% O_2 had decreased C_{QS}, $FEV_{0.1}$, and DL_{CO}, increased FRC and RV, and severely reduced flow rates. These results indicate that separate treatments of oxygen and elastase induced distinct lung disease models. Combined treatments induced some pulmonary function features of both lung diseases. (Research performed under U.S. Department of Energy Contract DE-AC04-76EV01013.)

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AIRWAY MORPHOLOGY IN NORMAL, ALLERGIC AND SO_2 EXPOSED SHEEP. David R. Maurer*, Marek Sielczak*, William M. Abraham and Adam Wanner. Mount Sinai Medical Center, Miami Beach, Florida.

Light and electron microscopy (SEM and TEM) were used to study the airway morphology of 4 groups of adult sheep: 3 normals; 2 aerosol controls; 6 A. suum hypersensitive (allergic) sheep after repeated bronchospasm due to inhalation of this antigen, and 2 sheep with long-term SO_2 exposure (10-50 ppm). The surface epithelium was evaluated by determining cell type frequency, while submucosal muscle, glands, connective tissue and basement membrane were evaluated by morphometric techniques. Proximal airways of normals had 50% ciliated (C), 40% basal/intermediate (B/I), and 10% mucous (M) cells. Bronchioles had 65% C, 24% clara (CL), and only 11% B/I. Aerosol per se produced increases in B/I frequency, overall cell concentration and tracheal submucosal gland volume density. Allergics had intermittent decreases in C and in CL frequency, but increases in B/I and cell concentration. SO_2 exposed sheep had lower M and C, higher B/I frequencies, cell concentration and tracheal gland volume density. No sheep had increases in smooth muscle or basement membrane. In all but the SO_2 exposed sheep, SEM showed a uniformly ciliated epithelium, while TEM indicated little cellular damage. In contrast, the SO_2 group had areas of denudement, vacuolated cells, infiltration, and some squamous metaplasia. We conclude that repeated aerosol exposure caused changes in airway epithelium and submucosal glands but that repeated allergic bronchospasm did not produce histologic lesions consistent with human bronchial asthma. Changes due to SO_2 exposure were consistent with previous models. Supported by NIH HL 20989 and EPRI 1373.

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REFLEX INCREASE OF CANINE TRACHEAL GLAND SECRETION CAUSED BY STIMULATING BRONCHIAL C-FIBERS. B. Davis, A.M. Roberts, H.M. Coleridge and J.C.G. Coleridge. C.V.R.I., Depts. of Physiology, Medicine and Pediatrics, UCSF, San Francisco, CA 94143.

In anesthetized dogs with open chests, we ventilated the lungs through the lower trachea, opened the upper trachea in the midline and retracted the cut edges. We sprayed powdered tantalum onto the exposed mucosa. Secretions from the openings of submucosal gland ducts caused elevations (hillocks) in the tantalum layer which we recorded on videotape with a television camera connected to a microscope. We counted the number of hillocks on an area (1.2 cm^2) of trachea at 10s intervals for 1 min before and 1 min after injecting into the bronchial artery bradykinin (1.5 µg) or capsaicin (3 µg)(chemicals known to stimulate bronchial C-fibers). Bradykinin increased the maximum rate at which hillocks appeared from 2±1 to 22±6 hillocks/10s (mean ± SE; n=9, $p < 0.02$); the latency of response was 21±2s. Capsaicin increased the maximum rate at which hillocks appeared from 2±1 to 25±4 hillocks/10s (n=19, $p < 0.001$); the latency of response was 11±1s. Cooling the vagi to 0°C abolished the responses to bradykinin and capsaicin; responses were restored by rewarming the vagi. We conclude that stimulation of afferent vagal bronchial C-fibers reflexly increases secretion from tracheal submucosal glands. (Supported in part by USPHS. NIH Grants HL-24136, HL-07192 and the Cystic Fibrosis Foundation).

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PENTOBARBITAL POTENTIATES THE INHIBITORY EFFECT OF HALOTHANE ON SYNTHESIS OF LUNG PROTEINS. D. E. Rannels and C. A. Watkins, Physiology and Anesthesia, Hershey Med. Cntr., Penn State Univ., Hershey, PA 17033.

Anesthetic agents may be important modulators of metabolism, especially in lung, where they are present at high concentration. Thus, the effect of pentobarbital (PB) on protein synthesis (PS) in lung was investigated, both alone and in combination with halothane. In rat lungs perfused in situ with buffer containing 5.6 mM glucose, 4.5% bovine serum albumin, plasma levels of 19 amino acids and 690 µM [^{14}C]phenylalanine, addition of PB (50-500 µg/ml) to the perfusate resulted in a dose-related inhibition of PS. Halothane (1-4% in $O_2/N_2/CO_2$, 4:15:1) also rapidly inhibited PS in a dose-dependent manner. The effect of halothane to inhibit PS was potentiated by a dose of PB (100 µg/ml) which had no effect when present alone. At a maximally effective dose of PB, 1-4% halothane further reduced PS, suggesting the agents worked by different mechanisms. Effects of PB and halothane, alone or in combination, were rapidly reversible. A similar dose-related inhibition of protein synthesis by PB was observed in rat hearts perfused by a modified Langendorff technique, suggesting PB was not selectively inhibitory in lung tissue. These observations suggest that metabolic effects of volatile anesthetic agents may be enhanced in the presence of barbiturates. Supported by HL-20344 and HL-00294.

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PROMOTION OF CADMIUM INDUCED PULMONARY LESIONS BY GALACTOSAMINE. P. Chowdhury, L. W. Chang, R. C. Bone, and P. L. Rayford, Depts. of Physiology-Biophysics, Pathology and Medicine, Univ. Ark. Med. Sci., Little Rock, AR 72205.

Previous studies have shown that cadmium (Cd) induces pulmonary lesions. This study was conducted in rats to determine if galactosamine, a known hepatotoxin, will enhance Cd induced pulmonary injury. Methods: Rats in groups of 6 were given either galactosamine (400 mg/kg), cadmium chloride (4 mg/kg) or a combination of the two compounds. Galactosamine was injected i.p. and 24 hours later Cd was administered i.p. Rats were sacrificed 60 min after Cd and blood samples collected by orbital bleeding for measurement of trypsin inhibitory capacity (TIC). Lungs of rats were perfused with saline and fixed in 10% formalin. Light microscopic examinations were made of longitudinal sections of both apical and basal portions of the whole lung. Results: Galactosamine alone produced a reduction in serum TIC by 30% and with Cd, TIC was reduced to 50%. No significant pathology was observed in the lungs of animals treated with either galactosamine or Cd alone. However, severe hemorrhage with polymorphonuclear (PMN) infiltration was observed in all the Gal-Cd treated lungs The most severe hemorrhage was found at the basal portion of the lung while PMN infiltration was found throughout the lung tissue. This is associated with severe distention of alveoli, vascular congestion and vascular leakage. These results indicate that galactosamine and Cd action on TIC are associated and combined effects of these promotes injuries to the lung.

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VESICULAR LUNG SOUND MAPPING BY AUTOMATED FLOW-GATED PHONOPNEUMOGRAPHY. Steve S. Kraman* and Dennis O'Donnell* (SPON: N.K. Burki). Univ. of Kentucky, Lexington, KY 40506

A recently developed automated apparatus capable of determining vesicular sound amplitude rapidly and accurately was used to construct detailed inspiratory vesicular sound amplitude maps in 8 normal subjects in order to determine the normal amplitude patterns on the chest wall. The sounds were recorded in 2 cm steps along the following lines, bilaterally: A) Clavicle to abdomen, 6 cm from the sternal border; B) level of TI to the lung bases, 6 cm from the spine, and C) horizontally, from the sternal border to the spine at the level of the nipple. Sound amplitude was measured at an air flow rate of 1.3 l/s. The resulting amplitude maps revealed considerable intra and intersubject variation with frequent amplitude heterophony. The overall patterns were as follows: A) amplitude decreasing with distance from the clavicle, B) amplitude increasing with distance from TI with a peak at the bases, and C) equal amplitude at all positions. The findings in series B and C are, in general, consistent with an explanation of ventilation following hydrostatic gradients. The series A pattern and the intersubject variability in amplitude suggest that the inspiratory vesicular sound amplitude is not simply a result of ventilation distribution but involves other as yet undefined factors. (Supported by NHLBI grant HL26334-01).

MICROCIRCULATION

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FLEXIBILITY OF CAPILLARIES IN THE HEART. James B. Bassingthwaighte and Edward C. Carlson. University of Washington, Seattle, WA 98195 and University of California, Davis, CA 95616

Capillaries have been considered stiff compared to other vessels. Because the walls are so thin there has been discussion on whether this stiffness lies all within the cells, in the basement membrane, or in the surrounding interstitial gel matrix. Observations on dog and rabbit hearts on 9, 15, and 25μ microspheres within capillaries which were subsequently filled with silicone elastomer, microfil, showed that the silicone elastomere filled the capillaries upstream and downstream from the microspheres of all sizes even though the capillary diameters are only about 5 microns. By electromicroscopy, endothelial cells deformed by microspheres appeared undamaged even though the local deformation was great. Local deformation demonstrates flexibility but does not prove distensibility, i.e. an overall stretching with an increase in total surface area in response to increased luminal pressure. The techniques provide a basis for further work on characterizing the mechanical features of the wall and perhaps for separating out the contributions made by the various components. (Supported by NIH grants HL19135, AM24000, and the Juvenile Diabetes Foundation.)

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ARTERIOLAR VASOMOTION AND IT'S EFFECT ON CAPILLARY BLOOD FLOW. W. Funk* and M. Intaglietta. University of California, San Diego, La Jolla, CA. 92093

Rhythmic arteriolar smooth muscle cell action was investigated looking at changes in diameter and flow velocities in the arterial part of the microcirculation as well as their influence on capillary perfusion patterns. Measurements were performed on skin flap chambers of unanesthetized hamsters using intravital microscopy and television techniques. The macrocirculation was monitored by permanent catheters allowing measurement of central venous/arterial pressure and heart rate. When the criteria for a physiologic state were met, i.e. no pus, edema, hyperemia, microbleedings or leukocyte rolling in the chamber, no permeability for fluorescein labelled dextran 150 within 2 hours, and normovolemia, rhythmic arteriolar vasomotion was present in 72% of the arterioles between 25 and 80μm diameter with an average amplitude of 54% of mean and frequencies of 2.6±1.2 min^{-1}. Terminal arterioles, precapillaries and 1 group of capillaries showed a superposition of the upstream rhythms in their flow velocity profiles. Another group of capillaries showed stop-and-go type flow patterns. We hypothesize, that capillary network geometry is the main factor causing different behavior of capillaries of the same arteriolar trunk. We conclude, that arteriolar vasomotion is a perfusion regulating factor generally present in not manipulated tissues. Since vasomotor activity also affects hydrostatic pressure in the capillaries previous calculations on capillary exchange should be revised. (Supported by USPHS-HL 12493)

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ARTERIOLAR REACTIVITY TO ANGIOTENSIN IN THE CREMASTER MUSCLE OF THE DECEREBRATE RAT. D.A. Bishop*, P.D. Harris, I.G. Joshua*, F.N. Miller*, and D.L. Wiegman. Dalton Research Center, Univ. of Missouri, Columbia, MO. 65211.

Arteriolar reactivity to angiotensin II was studied in 1) Sprague-Dawley rats anesthetized with urethane (800 mg/kg) and α-chloralose (60 mg/kg) and 2) decerebrate rats after a 5 to 10 hour period for dissipation of the initial urethane-chloralose anesthesia. The cremaster muscle with intact circulation and innervation was suspended in a Krebs-bicarbonate bath. Bath temperature (34.5°C), PO_2 (30-40 mmHg), PCO_2 (40-50 mmHg), and pH (7.4) were controlled. Lumenal diameters of second and third order arterioles were measured by television microscopy. Angiotensin II was added to the cremaster bath to produce concentrations between 3 x 10^{-11} and 10^{-7} molar. Second (90±3μm) and third (21±2μm) order arterioles responded differently to angiotensin. Angiotensin did not alter the diameters of second order arterioles in either anesthetized or decerebrate rats. High concentrations of angiotensin produced complete closure of third order arterioles in decerebrate rats; however, angiotensin gave considerably less constriction (to 45% of control diameter) in anesthetized rats. Norepinephrine ($3x10^{-6}$ M) constricted second and third order arterioles in both anesthetized and decerebrate rats. This study shows 1) that the constrictor effect of angiotensin is limited to specific arteriolar levels, and 2) that arteriolar reactivity to angiotensin is markedly depressed by urethane-chloralose anesthesia. (Supported by HL12614 and Mo. Heart Assoc.).

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A COMPARISON OF MICROVASCULAR CHANGES IN SKELETAL MUSCLE OF RENAL AND SPONTANEOUSLY HYPERTENSIVE RATS. R.L. Prewitt, I.I.H. Chen* and R. Dowell*, University of Tennessee Center for the Health Sciences, Memphis, TN 38163

Using stereological methods in vivo, we have investigated the rarefaction of arterioles and capillaries in one-kidney-Goldblatt (1KG), 4 weeks after renal artery clipping, and spontaneously hypertensive rats (SHR), 16-18 weeks old. The gracilis muscle was transilluminated in situ for television microscopy. Vessel length per unit volume of tissue (density), internal diameter, and wall thickness of arterioles were measured in 3 consecutive states: innervated, denervated, and vasodilated with locally applied nitroprusside. Arteriolar density in the denervated state was reduced in the 1KG by 40% and in the SHR by 59% compared to their respective controls. After vasodilation arteriolar density was reduced 26% in the 1KG and 56% in the SHR. Capillary density of 1KG was reduced 45% in the innervated state but not after vasodilation. However, in the SHR, capillary density was reduced 61% in the innervated state and 18% after vasodilation. Innervated arteriolar diameter was 16.7±2.5 μ in the 1KG and 25.9±8.2 μ in the control ($p<0.05$), whereas there was no difference in arteriolar diameter between SHR and controls. The decreased internal diameter of the 1KG arterioles may be related to their increased wall/lumen ratio, which was 0.318±0.037 compared to 0.206±0.026 for the controls ($p<0.05$). There were no differences in the wall/lumen ratio between SHR and controls. (Supported by USPHS GR HL-23480 and HL-18489.)

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EFFECTS OF HEAT-DAMAGED BLOOD ON MICROCIRCULATORY FLOW. M. Mason Guest, M. E. Frazer* and David Wainwright*
Shriners Burns Institute, University of Texas Medical Branch, Galveston, Texas 77550

Blood flow in both heat-damaged tissues and in tissues not subjected to high temperature is altered after extensive burns. Hindrance to flow is resultant of heat-induced changes in physical and chemical properties of blood. 1) Heating erythrocytes to 55°C for 1 minute causes them to become rigid. Consequently they cannot change to the hollow paraboloid shape which permits them to traverse true capillaries; this increases resistance to flow in the microcirculation. Furthermore the rigid cells damage membranes of endothelium when in contact with its luminal surface. 2) Fibrinogen is denatured and becomes insoluble at 55°C. The denatured fibrinogen increases the viscosity of blood and hence resistance to flow. 3) Although clotting enzymes are inactivated by heat, tissue thromboplastin, a lipoprotein complex from cell membranes, is relatively stable at temperatures below 100°C. Fragments of cell membranes (thromboplastin) from formed elements of blood and from endothelium, following damage by heat, are released into the blood and accelerate clotting as it flows through both heat-damaged and heat-undamaged tissues.

(Supported by grant from Shriners of North America.)

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FILTRATION COEFFICIENT OF THE BLOOD-LYMPH BARRIER IN THE POPLITEAL NODE. Thomas H. Adair, Alfred W. Paulsen*, David S. Moffatt*, and Arthur C. Guyton. Univ. Miss. Med. Ctr., Jackson, MS 39216

Popliteal node fluid filtration characteristics were studied in six dogs. The lymph compartment was perfused with various concentrations of homologous plasma (Πa) at several flow rates (Fa), and steady state efferent lymph oncotic pressure (Πe), flow rate (Fe) and systemic plasma oncotic pressure (Πc) were determined. Perfusion with solutions having a high oncotic pressure (OP) caused protein free fluid to be filtered into the lymphatics, which diluted the lymph ($\Pi a > \Pi e$); whereas, perfusion with solutions having a low OP caused protein free fluid to be absorbed into the microvasculature, which concentrated the lymph ($\Pi a < \Pi e$). The lymph OP (Π) which would cause neither absorption nor filtration was determined graphically. By assuming that Πc and the hydrostatic pressure gradient across the blood-lymph barrier remain constant as Fa changes, the net driving pressure for transudation across the barrier was approximated by $\Pi_L - \Pi$, where Π_L is the mean lymph OP. Π_L must lie between Πa and Πe, and was calculated assuming that Πa approaches Πe exponentially, with Π as the asymptote. The rate of fluid filtration or absorption was calculated as Fe-Fa. The filtration coefficient (Kf) was then computed from the slope of the line generated by expressing $\Pi_L - \Pi$ as a function of Fe-Fa. The Kf of the intranodal blood-lymph barrier derived from 40 observations averaged 0.038 $ml \cdot min^{-1} \cdot 100\ gm^{-1} \cdot mmHg^{-1}$.

(Supported by NIH Grants HL 06122 and HL 11678).

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PERMEABILITY OF STOMACH CAPILLARIES TO SMALL AND LARGE MOLECULES. M. A. Perry* and D. N. Granger (Spon.: Gregory Bulkley) University of South Alabama, Mobile, AL 36688

The permeability of gastric capillaries was studied in the dog with the double indicator diffusion technique and in the cat stomach by analysis of steady-state lymph and plasma proteins obtained at different capillary filtration rates. The osmotic reflection coefficient, calculated as 1-L/p when L/p was filtration rate independent, ranged from 0.73 to 0.91 for molecules which ranged in size from albumin (37 A radius) to ß-lipoprotein (120 A radius). The steady-state lymph data was consistent with an effective large pore radius of 250 A, and an effective small pore radius of 47 A. Indicator diffusion studies gave a value for pore radius in gastric capillaries of 53 A. Both techniques indicate that the permeability of gastric capillaries for small solute molecules is similar to values reported for the small intestine. However, steady-state lymph samples suggest that gastric capillaries are more permeable than capillaries in the small intestine and colon to albumin and larger molecules.

Supported by a grant from the Alabama Heart Association.

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HISTAMINE INCREASES CORONARY BLOOD-TISSUE TRANSPORT OF SUCROSE IN DOGS. **Thomas R. Harris, Benjamin R. Bamford* and Jerry C. Collins*. Vanderbilt University, Nashville, TN 37232**

Histamine infusion is known to increase the flow and protein content of lymph from skeletal muscle and lung tissue. We have studied blood-tissue exchange of sucrose in the left anterior descending coronary artery (LADCA) in response to infusions of histamine phosphate solution. In 8 open-chest anesthetized dogs a tubing shunt connecting the carotid artery with the LADCA was used to measure coronary blood flow and to inject a multiple tracer (MT) mixture. ^{51}Cr red blood cells, ^{125}I-albumin, ^{14}C-sucrose, and ^{3}H-water were used to measure sucrose permeability surface area (PS_S) and extravascular water volume (V_E) from MT curves formed by collection of blood samples from the coronary sinus and counting for radioactivity. MT studies were performed at baseline and after steady 20 min infusions of histamine into the cannula sufficient to maintain plasma concentrations at levels from 0.07 to 0.51 micrograms/cc plasma. Histamine infusion generally increased blood flow to the LADCA and PS_S. Concentrations above 0.60 micrograms/cc plasma tended to lower aortic blood pressure, coronary blood flow and PS_S, possibly due to recruitment. V_E did not correlate with histamine concentration. To make the observations comparable among dogs, we normalized LADCA plasma flow (PF) and PS_S to V_E. For all dogs, PF/V_E correlated significantly with plasma concentration ($R = 0.796$, $P < .001$) as did PS_S/V_E ($R = 0.688$, $P < .001$). We conclude that histamine infusion can increase microvascular exchange to small molecules as well as flow in the coronary circulation.

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PAPAVERINE ANTAGONIZES HISTAMINE INDUCED INCREASES IN THE CAPILLARY FILTRATION COEFFICIENT. Ronald J. Korthuis*, C.Y. Wang* and Jerry B. Scott. Michigan State University, East Lansing, MI 48824.

Although many studies show that local histamine increases capillary filtration coefficient (CFC), the mechanism of the increase is uncertain. CFC provides a direct measure of transcapillary hydrodynamic conductivity which, in turn, is a product of the microvascular surface area available for exchange and microvascular permeability. Our intent was to determine the relative contribution of increases in permeability and/or surface area by maximally dilating (increasing surface area to a maximum) the vascular bed of isolated canine gracilis muscle with papaverine (PAP). Any increase in CFC induced by the concomitant infusion of histamine would then be due to increased microvascular permeability. To test this hypothesis, CFC was determined at timed intervals during PAP (1 mg/min) and PAP plus histamine (12 µg base/min) infusion. Propranolol (3 mg/kg) was administered 30 min prior to control CFC determinations. PAP reduced perfusion pressure (Pp) from a control of 110 mg Hg to 30 mm Hg. Concomitant infusion of histamine produced no further reduction in Pp. Histamine infusion alone transiently increased CFC approximately 7-fold. Histamine plus PAP produced a shorter lived 3-fold increase in CFC while PAP alone was without effect on CFC. While the mechanism whereby PAP antagonizes histamine is unclear, it seems more likely that it is related to permeability.

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AMINOPHYLLINE ATTENUATES THE EDEMOGENIC ACTION OF HISTAMINE. J. Dabney, C. Soika*, A. Premen and D. Dobbins. Dept. of Physiology, Uniformed Services University, Bethesda, MD 20014

Histamine may contract fibrils in the cells of post-capillary venules, thus forming endothelial gaps. Bronchial constriction by histamine is reduced by aminophylline. We tested whether aminophylline can limit the increase of lymph flow and protein concentration due to infusion of histamine into the constantly perfused forelimb of the anesthetized dog. Systemic, forelimb perfusion, skin small artery, and vein pressures were recorded every 10 minutes. Lymph was collected from a lymphatic near the elbow. After lymph flow and pressures were steady, an infusion of aminophylline (10 mg/min) and ten minutes later, an infusion of histamine (4 µg base/min) were begun into the arterial supply of the forelimb. Aminophylline was infused for 70 minutes and histamine for 80. Aminophylline alone did not change systemic or small vein pressure, heart rate, lymph flow or its protein concentration. It did, however, lower perfusion and small artery pressure. During infusion of both agents, heart rate and small vein pressure were increased by 10 minutes and systemic pressure was decreased by 50 minutes. Lymph flow was increased by 10 minutes but lymph protein concentration was not statistically different until 50 minutes. With aminophylline present, the increase in lymph flow and protein concentration were markedly attenuated relative to the effects of histamine alone. It is suggested that aminophylline may lessen a constricting action of histamine on fibrils in post-capillary venules.

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ALBUMIN EXCLUSION IN THE LIVER INTERSTITIUM. James A. Barrowman*, M. A. Perry*, P. R. Kvietys and D. Neil Granger, Memorial University of Newfoundland, St. John's and Univ. of South Alabama, Mobile, AL 36688

An important property of the interstitial matrix is the ability of the gel reticulum to exclude solutes from a portion of the available intragel water. In this study, we examined the effect of increased interstitial hydration on albumin exclusion in the cat liver. Tissue blood volume, interstitial volume (V_I) and extravascular albumin space (V_A) were estimated using ^{51}Cr-labeled autologous red cells, ^{99m}Tc-DTPA and ^{125}I-labeled cat albumin or human albumin, respectively. The interstitial concentration of the tracers was obtained from samples of hepatic lymph. The control values (n=12) for interstitial volume (V_I), extravascular cat albumin (V_{AC}) and human albumin (V_{AH}) spaces were 0.194 ± 0.008, 0.112 ± 0.003, and 0.073 ± 0.005, respectively. That is, the fraction of the interstitial space from which albumin was excluded (F_E) was 0.413 ± 0.022 for cat albumin and 0.678 ± 0.016 for human albumin. During venous pressure elevation (8 mmHg) liver lymph flow increased fourfold, V_I increased to 0.240 ± 0.010, V_A for cat albumin increased to 0.157 ± 0.009; however, F_E for cat albumin decreased to 0.338 ± 0.001. The data indicate that exogenous albumin is excluded from the liver interstitium to a much greater extent than endogenous albumin. Elevated venous pressure expands hepatic interstitial volume and reduces the ability of the interstitial matrix to exclude albumin. Supported by NHLBI 26441 and 00816.

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ISOBARIC COUNTERDIFFUSION OF He AGAINST N_2; A PROBE FOR VASCULAR FAT? B.G. D'Aoust. Virginia Mason Res. Ctr., Seattle, WA. 98101

Perfusion theory predicts, and animal experiments demonstrate, that isobaric counterdiffusion of inert gases with unequal tissue/blood partition coefficients can cause transient over or undersaturation depending upon their sequence. By contrast, these over- or undersaturations are not reliably predicted by comparing diffusion coefficients of the respective gases. The simplest consistent model predicting both direction and degree of such transients relates the maximum total inert gas pressure, (Pss) at any point, ie. a potential "site" in the vasculature system to the sum of the pressures of the desaturating gas, (1) and the saturating gas (2) at that point (2).

$$\text{Thus, } Pss = P_1 [\exp.-k_1 t + 1 - \exp.-\gamma k_1 t] \quad 1$$

where P_1 represents the saturation pressure in atmospheres of inert gas 1, k_1 is the reciprocal time constant (ie. proportional to the tissue/blood partition coefficient) of gas 1 at the bubble site, γ is the ratio of k_2/k_1 and k_2 is the tissue/blood partition coefficient of gas 2 at the same bubble "site." Predictions using equation 1 are supported by results of over 50 saturation experiments, many of which have used most of the possible sequence combinations of He, H_2, N_2, N_e, and Ar. Further, equation 1 not only predicts higher supersaturations from fatty tissues but experiments have shown more bubbles at the central venous location; experiments on swine produced many more bubbles than the same experiment on goats, and large variations between goats are probably due to compositional differences. It may therefore be possible to distinguish fatty from aqueous tissue by such methods.

RENAL METABOLISM

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RESTORATION OF PHOSPHATURIA IN PHOSPHATE-DEPRIVED RATS BY PHOSPHATE INFUSION IN THE PRESENCE OF PARATHYROID HORMONE (PTH). Aviad Haramati, Michael Baldwin*, and Franklyn G. Knox, Dept. of Physiology, Mayo Clinic, Rochester, MN 55905

It is well known that rats fed a low phosphate diet (LPD) avidly retain phosphate (Pi) and resist the effects of phosphaturic stimuli. It is not clear, however, whether a combination of factors would evoke a phosphaturia in these animals. We tested this possibility by comparing the effects of Pi infusions in the presence and absence of PTH. Clearance experiments were performed in 12 acute TPTX rats fed LPD (0.07%) and given either PTH (33 U/kg prime, 1 U/kg·min sustaining), or vehicle. After a control clearance, Pi was infused at progressively increasing rates of 1, 2 and 3 μmol/min and fractional Pi excretion (FE_{Pi}) was evaluated.

FE_{Pi}(%)	Pi Infusion (μmol/min)			
	0	1	2	3
Group 1 (vehicle)	0.14 ±.02	0.12 ±.03	0.11 ±.02	0.76 ±.44
Group 2 (PTH)	2.75 ±2.13	9.74 ±4.93	29.12 ±11.66	35.48 ±7.80

These effects were not related to plasma Pi which rose to a greater extent in group 1 (2.26 to 4.91 mM) than in group 2 (2.92 to 3.87 mM). Thus, the phosphaturic response to phosphate infusions was restored in phosphate-deprived rats in the presence of PTH. (Supported by AM19715)

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EFFECT OF METABOLIC ACIDOSIS ON RENAL ADAPTATION TO LOW PHOSPHATE DIET. Stephen A. Kempson. University of Pittsburgh School of Medicine, Pittsburgh, PA 15261

The action of certain phosphaturic stimuli on renal proximal tubules may involve stimulation of gluconeogenesis (GNG) to increase cytoplasmic NAD^+ which inhibits phosphate (Pi) transport across the luminal brush border membrane (BBM). (Endocrinology 108:2005, 1981.) Present study tested whether stimulation of renal GNG by metabolic acidosis (MA) reverses the antiphosphaturic response to low Pi diet. Rats adapted to low Pi diet became acidotic after drinking 1.5% NH_4Cl for 3 days and GNG in renal cortical slices was significantly increased in MA rats compared to pair-fed controls. In MA rats $U_{Pi}V$ was increased compared to controls (106 ± 43 vs. 7 ± 2 nmol Pi/mg creatinine; $p < 0.05$); plasma Pi and creatinine were not different between groups. Results were similar using thyroparathyroidectomized (TPTX) rats. Na^+-gradient dependent Pi transport by BBM vesicles from renal cortex of TPTX rats was decreased in the MA group (1501 ± 55 vs. 3096 ± 158 pmol Pi/mg protein/30 sec; $p < 0.001$) but transport of D-glucose, L-proline and Na^+ were not different from controls. In snap-frozen cortex the $NAD^+/NADH$ ratio was 2·6 ± 0·2 in MA rats compared to 2.1 ± 0.1 in controls ($p < 0.05$). In summary, the MA-induced phosphaturia in low Pi diet rats is due in part to decreased Pi transport across BBM of proximal tubules and is independent of PTH. The intracellular mediator of the change in BBM transport of Pi may be NAD^+ which is increased in MA due to a shift in the $NAD^+/NADH$ ratio following stimulation of GNG.

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EFFECT OF PHOSPHATE (PO_4) LOADING ON URINARY PO_4 EXCRETION (UPO_4V) IN THE BULLFROG RANA CATESBIANA. R.C. Hanson, S.D. Gleason* and E.G. Schneider. Biologic Research Dept., Mead Johnson Pharmaceutical Div., Evansville, IN 47721 and Dept. of Physiol. & Biophys., UTCHS, Memphis, TN 38163.

Net renal PO_4 secretion has been observed following PO_4 infusion in several vertebrate classes. To ascertain if intravenous (IV) PO_4 infusions would cause net renal PO_4 secretion in the amphibian, R. catesbiana, bullfrogs were anesthetized by soaking in a solution of 2% MS 222 and surgically prepared for clearance (C) measurements. Animals were placed in a restraining cage in aerated dechlorinated freshwater and were allowed to recover from the anesthesia for at least 120 minutes before the start of two control C measurements. Frogs then received a PO_4 infusion of either 1.6 μM/min/kgBW(n=2) or 7.0 μM/min/kg(n=5). 60 minutes after the start of the infusion additional C periods were obtained. The low rate of PO_4 infusion increased plasma PO_4(PPO_4) by 64% (Δ1.4±.7μM) and UPO_4V by 11% (0.04±.03 μmol/min/kidney/kg). The high rate of PO_4 infusion increased PPO_4 by 77% (Δ2±.3 μM) and UPO_4V by 126% (Δ0.51±.03 μmol/min/kidney/kg). Neither infusion produced significant alterations in UV or GFR. The CPO_4/Cinulin ratio during the low rate infusion was 0.75 ± .07 and during the high rate infusion was 0.80 ± .05. At no time was this ratio >1. Under these conditions, we were unable to demonstrate net PO_4 secretion by the kidney of the intact bullfrog as has been shown for fishes, reptiles and birds. (Supported in part by USPHS Grant No. HL 16658).

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PHOTOAFFINITY LABELING OF THE RENAL ORGANIC ANION TRANSPORT SITE IN BASOLATERAL MEMBRANE VESICLES. J.M. Goldinger, B.D.S. Khalsa*, and S.K. Hong. Dept. of Physiology, SUNY at Buffalo, Buffalo, New York 14214.

Semi-purified basolateral membrane vesicles from rabbit proximal tubule were prepared according to the method of Scalera et al. (Biochem. J. 186:177, 1980). This method involves centrifugation of a cortical membrane fraction through a 12% Percoll gradient to separate the basolateral and luminal membranes. The distribution of the membranes in the gradient was determined using conventional enzyme markers. The resulting membrane preparation was shown to be vesicular by the demonstration of p-aminohippurate (PAH) transport into an osmotically active space. PAH uptake into these vesicles was shown to be inhibited by probenecid (0.5 mM) and unphotolyzed NAP-taurine, an analogue of PAH. Further, vesicles previously photolyzed in the presence of NAP-taurine show partial inhibition of PAH transport. SDS polyacrylamide gel electrophoresis of basolateral membrane vesicles photolyzed in the presence of (^{3}H) NAP-taurine revealed four labeled protein peaks with molecular weights of approximately 26,000, 52,000, 76,000 and 104,000 daltons. Inclusion of PAH (1.0 mM) in the medium during photolysis prevented NAP-taurine labeling. The fact that labeling these proteins inhibits transport suggests these labeled protein elements may form all or part of the system which serves to actively transport PAH in the renal proximal tubule. (Supported by USPHS Grant AM-18918.)

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ULTRASTRUCTURAL LOCALIZATION OF Na^+,K^+ ATPase IN RAT AND RABBIT KIDNEY MEDULLA. S.A. Ernst and J.H. Schreiber*. University of Michigan, Ann Arbor, MI 48109

The K^+-dependent nitrophenylphosphatase (K^+-NPPase) component of Na^+,K^+-ATPase was localized in rat and rabbit kidney medulla after perfusion-fixation with 1% formaldehyde-0.25% glutaraldehyde. In rat outer medulla (OM), ascending thick limbs (MATL) showed intense activity, whereas descending thick limbs and collecting ducts were barely reactive. While descending thin limbs (DTL) of short loop nephrons were unstained, DTL from long loops in OM exhibited moderate activity. In rat inner medulla (IM), DTL and ascending thin limbs (ATL) were unreactive. In rabbit OM and IM, only MATL were sites of K^+-NPPase activity. The specificity of reaction product localization was demonstrated by its K^+-dependence, restriction to the cytoplasmic side of basolateral plasma membranes, insensitivity to inhibitors of alkaline phosphatase, and in the glycoside-sensitive rabbit kidney, marked inhibition by ouabain. The presence of substantial Na^+,K^+-ATPase in MATL is consistent with its putative role in the countercurrent multiplication system in OM. The absence of activity in ATL and DTL of IM, however, implies that interstitial solute accumulation in IM may occur by passive processes. The presence of Na^+,K^+-ATPase in DTL of long loops in rat OM correlates with structural specialization in this segment and suggests that solute concentration in OM DTL may occur in part by an active salt secretion which might ultimately contribute to IM interstitial hypertonicity and urine concentration. (Supported by NIH AM 27559)

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NET SECRETION OF p-AMINOHIPPURIC ACID (PAH) IN THE URINARY BLADDER OF A CRAB (Cancer borealis). D.S. Miller and C.W. Holliday. Mount Desert Isl. Biol. Lab., Salsbury Cove,ME 04672

Uptake of 10 μM PAH by sections of bladder tissue was concentrative, saturable (K_m 67 μM, V_{max} 1.7 nmoles / mg tissue/ h), inhibitable by other organic anions and dependent on medium Na and glycolytic metabolism. Bladders mounted in flux chambers exhibited net secretory transport of PAH, with serosa-to-lumen fluxes (J_{SL}) being about 4 times J_{LS}. In 60 min experiments, tissue-to-medium ratios exceeded unity, with serosal, but not luminal, PAH. Initial (10 min) fluxes and tissue accumulations (A_C) were measured in the absence and presence of 1-5 mM bromocresol green (BCG) . With serosal PAH, serosal 1mM BCG reduced serosa-to-cell flux (J_{SC}), A_C and J_{CL} by 60-75%. With luminal PAH, luminal 1mM BCG had no effect on J_{LC}, A_C or J_{CS}; increasing the luminal BCG concentration to 5 mM reduced J_{LC}, A_C and J_{CS} by 40-50%. The data are consistent with a model featuring an inwardly-directed PAH pump on the serosal membrane, cellular accumulation and a facilitated carrier on the luminal membrane. Aside from differences in the metabolic pathways that power transport, this simple epithelium provides a convenient model for the study of organic anion transport in the vertebrate renal proximal tubule. Supported by USPHS grants ES-00920, AM-15973 and RR-05764 and NSF grant DEB 7826821.

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RENAL HIPPURATE HANDLING AND AMMONIAGENESIS. T.C. Welbourne and P.D. Dass, LSUMC, Shreveport, LA 71130

γ-Glutamyltransferase, γ-GT, is an extrinsic brush border membrane enzyme reacting with extracellular γ-glutamyl donors (gln and GSH) to form γ-glutamylpeptides/glu. Hippurate (N-benzoylglycine) reacts with the purified enzyme apparently at the γ-glutamyl acceptor site to activate NH_3 formation from gln. To determine whether hippurate would activate the in situ enzyme and renal ammoniagenesis, rat kidneys were isolated and perfused with an artificial plasma solution containing 2 mM L-gln, ^{3}H-inulin and ^{131}I hippurate, 0.5 mM. After perfusion the kidneys were immediately homogenized in 0.44 M sucrose, pH 7.4 and the subcellular distribution of labelled ^{131}I determined. The microsomal fraction containing 80 percent of the total γ-GT activity was then papain treated to free membrane bound γ-GT and ^{131}I. Results. Over the 60 minute perfusion period the kidneys excreted 34 μmoles of hippurate with 62 percent via secretion; tissue to perfusate and tissue to urine ratios were 13 and 2.6 respectively; 75 percent of the tissue hippurate was accumulated in the cytosol and only 1.3 percent in the microsomes. Of that associated with the microsomes, papain released $4x10^{-3}$ μmoles and $2x10^{-3}$ μmoles γ-GT consonant with 2 moles activator per mole enzyme. At this low level of hippurate, the in situ enzyme increased NH_3 production 65 percent while urinary NH_3 excretion rose from 12±4 to 26±6 μmoles 60 min^{-1}. These findings indicate a relatively low level of hippurate maximally activates the in situ γ-GT and stimulates NH_3 formation from L-gln as a consequence of organic acid secretion.

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RENAL ACID EXCRETION IN NORMAL AND ACIDOTIC FISH. Patricia A. King* and Leon Goldstein. Division of Biology and Medicine, Brown University, Providence, R.I. 02912, and the Mount Desert Island Biological Laboratory, Salsbury Cove, ME 14672.

We have examined the renal response to acidosis in the dogfish (Squalus acanthias) and the goldfish (Carassius auratus). Both species show increased renal excretion of titratable acids and ammonia (NH_4^+) when made acidotic either by acid injection into the caudal vessel (dogfish) or by acidification of the aquarium water (goldfish). In the dogfish these increases accounted for the elimination of approximately 15% of the acid load (0.65 mEq/kg) during the 24 hours post-injection; titratable acid excretion increased from 28.6 μEq/hr (pre-injection) to 49.9 μEq/hr (post-injection) and NH_4^+ elimination went from 0.11 μEq/hr to 0.24 μEq/hr (n=8). For the goldfish, titratable acid excretion increased from an average of (-)0.33 μEq/hr before acid stress to (+)0.10 μEq/hr following acid exposure (pH 4.0); urinary NH_4^+ rose from 0.17 μEq/hr to 0.38 μEq/hr excreted (n=7). This increase in NH_4^+ excretion alone restores 3.36 mM HCO_3^- over 24 hours or 36% of the normal goldfish blood HCO_3^- pool. In vitro studies indicate that both species have the capacity for renal NH_4^+ synthesis with glutamine and aspartate serving as the major NH_4^+ precursors. For the dogfish, the simultaneous activities of glutaminase and glutamine synthetase in the kidney mitochondria suggest the presence of a substrate cycle between NH_4^+ plus glutamate and glutamine which could modulate the production of NH_4^+ during acidosis.

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MAGNESIUM METABOLISM IN MAN STUDIED WITH MAGNESIUM-28 AND MAGNESIUM BALANCES. Herta Spencer, Emilie Wlatrowski*, Clemontain Norris*, and Dace Osis*. Metabolic Section, Veterans Administration Hospital, Hines, IL 60141.

Metabolic balances of magnesium were determined in adult males during a constant analyzed dietary magnesium intake for several weeks. The diet and urinary and fecal magnesium excretions were analyzed for magnesium by atomic absorption spectroscopy. The intestinal absorption of magnesium was determined by using oral and intravenous tracer doses of $^{28}MgCl_2$. Plasma levels, urinary and fecal ^{28}Mg excretions were determined. There was good agreement between the absorption of magnesium determined from fecal ^{28}Mg excretions following the oral dose of ^{28}Mg and from the ^{28}Mg plasma levels following the oral and intravenous doses of this tracer. The net absorption values determined from magnesium balances were also in agreement with the ^{28}Mg absorption. The ^{28}Mg absorption averaged 47% of the dose during a low calcium intake of 200 mg/day and did not change when the calcium intake was increased to 800 or 2000 mg/day. In agreement with these results, the magnesium balances also changed little during the higher calcium intakes. The studies have shown that the net absorption of magnesium, determined from magnesium balances, reflects the ^{28}Mg absorption determined with ^{28}Mg and that a calcium intake up to 2000 mg/day did not affect the absorption of magnesium compared to values during lower calcium intakes. (This study was supported by a grant from the USDA.)

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ACUTE EFFECTS OF LEAD ON RENAL HANDLING OF ZINC IN DOGS. Winona Victery, Neil Soifer*, Jonathan Weiss*, and Arthur J. Vander. Univ. of Michigan, Ann Arbor, Mi. 48109.

Urinary zinc excretion was monitored in anesthetized dogs before and during 4 hrs after acute exposure to lead (doses: 0.3 mg Pb (as acetate)/kg, 3 mg Pb/kg, or equimolar sodium acetate in the control group. Zinc excretion in time controls was relatively constant over the 4 hrs, but it rose above baseline values an average of 140 ng/min in 0.3 mg Pb/kg animals, and an average of 300 ng/min in 3 mg Pb/kg animals. Other indices of renal function including excretion of protein, Na, K, and Mg, were relatively constant. Plasma Zn concentration was stable in time control and low Pb animals, but rose significantly after the higher Pb dose. Clearance experiments using ^{65}Zn and in vitro ultrafiltration of plasma were performed in another series of dogs under antidiuretic conditions. Zn excretion (monitored by ^{65}Zn) was 7-fold higher in Pb-treated dogs; plasma Zn was slightly, but not significantly elevated. Ultrafilterable Zn concentration was 2½ fold higher and fractional Zn excretion was 3 times higher in Pb-treated dogs. The stop-flow pattern for Zn after Pb treatment showed no change in the distal tubular handling of Zn, but revealed prominent net proximal tubular secretion of Zn in all animals, a frequency statistically different from that observed in control animals. Thus, acute Pb treatment in dogs produced an increase in urinary Zn excretion which was related both to an increase in ultrafilterable plasma Zn and a change in renal tubular Zn transport. (Supported by NIOSH 5R01 OH00913-05.)

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NATURE OF URANIUM INHIBITION OF TUBULAR AMINO ACID (AA) REABSORPTION. E.C. Foulkes and S. Blanck*. Depts. Environ. Health & Physiol., Univ. Cincinnati Med. Cen., Cincinnati, OH 45267.

Heavy metals are well-known to inhibit proximal tubular AA reabsorption. We analyzed the nature of this inhibition in rabbits injected s.c. 10 days previously with 0.5 mg U as $UO_2(NO_3)_2$/kg. Absorption parameters (max. transport/ml GFR: T_M; affinity constant: K_M) of the non-metabolizable AA cycloleucine or AIB were indeterminately high. Further studies utilized U-^{14}C-ASP. In order to 1) avoid possible pharmacological effects of high systemic AA levels, 2) abolish need for repeated long equilibration periods, and thus 3) minimize ASP metabolism with likely formation of competing AA, an arterial gradient infusion was used (JPET 150:406, 1965). This permitted rapid attainment of a constant arterial ASP concentration. ^{3}H-inulin served as glomerular marker, and clearances were calculated from 1 min collections of ureteral urine. In 6 controls, T_M = 5.1±2.0 µmol/ml GFR, K_M=5.1±2.0 mM. Addition of ALA (n=4) caused little change in T_M (4.1±1.8) or K_M (4.1±2.0). Use of the competitive inhibitor GLU instead of ALA, as expected, raised K_M (to 9.4±2.0) with little effect on T_M (7.2±1.7) (n=6). In 5 U-poisoned animals, both T_M and K_M were greatly lowered (to 0.7 and 0.5, resp.). Future work will test whether such mixed non-competitive inhibition describes the action of other metals on absorption of ASP and other AA. (Supported by NIH grants ES 02453 and ES 00159.)

NEURAL CONTROL OF CIRCULATION II

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EFFECTS OF SYMPATHETIC NERVES ON CEREBRAL BLOOD FLOW DURING HYPERCAPNIA IN CATS. David W. Busija* and Donald D. Heistad. Dept. of Int. Med. and CV Center, University of Iowa and VA Hospital, Iowa City, Iowa 52242

Although sympathetic nerves play an important role in attenuating increases in cerebral blood flow (CBF) during sudden severe hypertension, it is not clear whether sympathetic nerves have important effects during other stimuli. The purpose of this study was to determine whether reflex or electrical activation of sympathetic nerves attenuates increases in CBF during hypercapnia. Sympathetic nerves supplying cerebral vessels were interrupted on one or both sides in 20 chloralose anesthetized cats. CBF was measured with 15 µm microspheres. During hypercapnia (PCO_2 > 55 mmHg), CBF increased from 53 ± 5 to 120 ± 9 ml/min per 100 g (mean ± SE). Electrical stimulation (10 Hz) of sympathetic nerves to one hemisphere reduced blood flow to the ipsilateral cerebrum by 12 ± 2% ($p < 0.05$). Bilateral stimulation reduced CBF more (30 ± 5%) than unilateral stimulation ($p < 0.05$). Unilateral or bilateral section of sympathetic nerves, however, did not change CBF during hypercapnia. Thus, in anesthetized cats, although intense electrical stimulation of sympathetic nerves attenuates increases in CBF during hypercapnia, reflex activation of nerves has little or no effect on CBF during hypercapnia.

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REGIONAL CEREBRAL BLOOD FLOW (CBF) RESPONSE TO POSTSYNAPTIC α-BLOCKADE IN HYPOXEMIC NEWBORN LAMBS. L.C. Wagerle*, T.M. Heffernan*, C.N. Roper*, L.M. Sacks*, and M. Delivoria-Papadopoulos. Univ. of Pennsylvania, Philadelphia, PA 19104

Adrenergic effects on CBF in adult animals have shown controversial results. The present study investigates the response of total and regional CBF during hypoxemia in newborn lambs following infusion of prazosin HCl, a postsynaptic α-antagonist. Hypoxemia was induced in 12 newborn lambs by decreased F_IO_2 during mechanical ventilation at constant $PaCO_2$ (38.2±0.5 torr). Six lambs received 0.5 mg/kg prazosin (Gr II) while six served as controls (Gr I). Measurements of [Hb], blood gases, O_2 sat., and regional blood flow by microspheres, were made prior to and following decreased F_IO_2 in all animals. During hypoxemia, PaO_2 decreased to 24.1±2.0 torr reducing O_2 content to 8.4±1.2 ml/dl and to 6.9±1.1 ml/dl in Gr I and II respectively. During hypoxemia total CBF increased from 119.4±7.2 ml/min·100g^{-1} to 185.5±28.8 ml/min·100g^{-1} in Gr I and to 179.3±19.4 ml/min·100g^{-1} in Gr II indicating no difference between the two experimental groups. Regional blood flow to the cerebrum, cerebellum, caudate, hippocampus, thalamus, midbrain, pons, and medulla increased during hypoxemia in all animals; the observed increase to each region was not different between controls and those receiving α-blockade. These data indicate that adrenergic effects do not influence either total or regional brain blood flow in the hypoxemic newborn lamb suggesting that the circulatory response to hypoxemia, mediated by potent metabolic factors, is not influenced by adrenergic stimulation. (Supported by NIH #2-T32-HL-07027-06 and #1PO-HL-19737.)

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SYSTEMIC AND RENAL HEMODYNAMIC RESPONSE TO LEFT VENTRICULAR FAILURE (LVF), CAROTID OCCLUSION (CO) AND VAGAL BLOCK (VB) IN CONSCIOUS CALVES. J.E. Chimoskey and S.W. Ely*. Dept. of Physiology, MI State Univ., East Lansing, MI 48824

Male Jersey calves were chronically instrumented with electromagnetic detectors to measure pulmonary and renal blood flow and with catheters for pressure in the aorta (AoP) and right atrium (RAP) to compute total peripheral (TPR) and renal resistances (RR). Occluders were placed on the ascending aorta, both common carotid arteries and the left renal artery. Catheters were also placed in one carotid artery and the left atrium to monitor CO and LVF. Coils of stainless steel tubing were placed on the vagus nerves to produce (VB). RAP did not change during CO or LVF with or without VB. The % changes r.e. control of AoP, CO, TPR and RR during LVF, CO, VB, LVF+VB and CO+VB shown in the table are significant at the 5% level or better.

	LVF	CO	VB	LVF+VB	CO+VB
AoP	no change	+25	+14	+27	+41
CO	-15	no change	no change	-15	- 7
TPR	+13	+25	+17	+39	+52
RR	no change	+27	no change	+24	+39

Competition between the high and low pressure baroreflexes occurs during LVF and is abolished by VB. Competition between the two high pressure baroreflexes occurs during CO and is abolished by VB. LVF+VB and CO+VB are similar.

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INFLUENCE OF LOWER BODY NEGATIVE PRESSURE (LBNP) ON UNANESTHETIZED MALE RATS. T. G. Bedford* and C. M. Tipton. Exercise Science Program, University of Iowa, Iowa City, Iowa 52242

The decrease in arterial blood pressure with LBNP in humans and anesthetized animals has been used as a test of cardiovascular functioning. Application of LBNP to trained anesthetized rats has yielded blood pressure responses similar to those reported from trained humans. However no tachycardia was observed, presumably due to anesthesia. Therefore, we sought to expand the LBNP test to include unanesthetized rats. Cannulas were inserted into the jugular vein and ascending aorta (from the left carotid) in 6 Sprague-Dawley rats (350±15 g). After 1-2 days recovery, measurements were made while the animals rested in their cages, within an LBNP chamber and during LBNP. Results obtained were as follows (X̄±SE):

Parameter	Cage	Chamber	At -5mmHg	At -10mmHg
HR (bpm)	382±10	427±10	481±14	505±11
SBP (mmHg)	148±7	152±4	135±6	103±10
CVP (cmH2O)	1.8±0.3	2.0±0.3	1.3±0.4	-0.4±0.4
Resp Rate (f)	106±7	121±3	130±14	126±5

Compared to our published results from anesthetized rats, tachycardia was present, blood pressure fell 10-30% less, and CVP changes were similar. Administration of Valium (150 µg/kg) changed only the degree of tachycardia during LBNP (20 bpm less) but reduced the total testing time and muscular activity during LBNP. Supported in part by HL-21245-04 and GM-07045-03.

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EFFECTS OF CHOLINERGIC AND ADRENERIC BLOCKADE ON CARDIOVASCULAR DEPRESSION OCCURRING WITH LUNG INFLATION

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The goal of this study was to determine the role of efferent neural pathways in mediating depression of cardiovascular function evoked by lung inflation (LI). Direct mechanical cardiovascular effects were eliminated and gas exchange was maintained by diverting all blood flow and ventilation to the right lung during left LI in 14 open-chest dogs. Mean arterial pressure (MAP), hindlimb vascular resistance (HVR), and heart-rate (HR) were measured prior to (PI) and during left LI to 30 cm H_2O. Left LI was repeated after atropine blockade (ATR), after atropine plus β-blockade (ATR+β), or after α blockade (α). Maximum changes occurring with left LI are expressed as a percent of PI, %ΔMax (*=p<.05). † indicates a significant change in response following blockade, p<.05.

	ATR		ATR +β		α	
%ΔMax	Before	After	Before	After	Before	After
MAP	-34± 5*	-31± 5*	-28±4*	-22± 4*	-40±5*	-14±8 †
HVR	-15±13*	-19±15*	--	--	-28±6*	- 5±3 †
HR	-35± 8*	-15± 3*†	-22±3*	0±0 †	-27±6*	-20±5*

This vasodilation is primarily mediated via α-adrenergic pathways, and bradycardia is mediated via β-adrenergic, as well as cholinergic, pathways. These data indicate that LI causes increased vagal stimulation and withdrawal of α and β adrenergic activity, confirming the presence of a refexly mediated cardiovascular inhibition in response to lung inflation.

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THE EFFECT OF CARDIAC DENERVATION ON CARDIOVASCULAR FUNCTION BEFORE AND AFTER AUTONOMIC BLOCKADE. Joyce M. Evans*, David C. Randall, Charles F. Knapp. Wenner-Gren Res. Lab. and Dept. of Physiol. and Biophysics, U. of Ky., Lexington, KY 40506.

A comparison of various cardiovascular variables for normal (N) and cardiac denervated (D) dogs was made before and after alpha and beta adrenergic and muscarinic blockades (*n*= number of dogs per group). All dogs were studied in the supine position three weeks after instrumentation/denervation surgery under Innovar tranquilization with the following results:

	HR	CO	SV	TPR	AP	LV VOL	PV	HCT	EPI	NOR EPI	PRA	ADH	OSM
	b/m	L/m	ml	mmHg L/m	mmHg	cc	L	%	ng ml	ng ml	ng ml/h	pg ml	mos L
						UNBLOCKED							
N	97	2.4	24	41	92	28	1.1	35	0.4	0.6	2.2	20	306
n	*10*	*10*	*10*	*10*	*10*	*10*	*5*	*9*	*8*	*8*	*11*	*11*	*11*
D	94	2.3	24	43	97	33	0.8	40	0.2	0.3	0.5	27	306
n	*10*	*10*	*10*	*10*	*10*	*10*	*4*	*7*	*5*	*5*	*6*	*7*	*7*
						FOLLOWING AUTONOMIC BLOCKADE (SAME DOGS)							
N	144	2.5	17	34	67	34	-	35	4.9	10	6.4	76	323
D	102	2.2	21	31	71	42	-	39	1.4	6	5.6	85	318

These results suggest differences between unblocked normal and cardiac denervated dogs for hematocrit plasma volume, renin activity, epinephrine and norepinephrine. In the autonomically blocked state, additional differences in heart rate, stroke volume and mean left ventricular volume appear. SUPPORTED BY AFOSR GRANT: 80-0039 and NIH: HL 19343

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REFLEX CARDIOVASCULAR RESPONSES TO TOPICAL APPLICATION OF BRADYKININ ON THE GALL BLADDER OF CATS. G.A. Ordway and J.C. Longhurst. Univ. of Texas Health Sci. Ctr., Dallas, TX 75235

Pharmacological stimulation of the gall bladder with capsaicin reflexly activates the cardiovascular system in cats. The reflex responses to endogenous substances, however, have not been shown. Therefore, in 14 cats anesthetized with methoxyflurane, we studied the cardiovascular responses to topical application of bradykinin (0.5μg) on the serosal surface of the gall bladder. After a latency of 13±.92 sec, there were significant (p<.05) increases in mean arterial pressure (101± 4.0 to 118±5.0mmHg), heart rate (193±7.4 to 199±7.3beats/min), dP/dt at 40mmHg developed pressure (dP/dt 40) (2777±159 to 3286±173mmHg/sec), and left ventricular end diastolic pressure (2.6±.56 to 3.7±.81mmHg), while aortic flow was not changed (269±38 to 272±40ml/min). Overdrive right atrial pacing did not alter the increase in dP/dt 40. Celiac and superior mesenteric ganglionectomy eliminated all responses to application of bradykinin on the gall bladder. Further, serosal application of bradykinin to the neurally intact liver, adjacent to the gall bladder, did not evoke any cardiovascular changes. These data demonstrate that, in cats, local serosal application of bradykinin to the gall bladder activates spinal afferents to increase myocardial performance, heart rate and peripheral vascular resistance. Thus, bradykinin may be formed in bile or in the gall bladder wall and induce reflexes that are manifested as cardiovascular abnormalities known to be associated with gall bladder disease.

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Chemical Depolarization of Left Ventricular (LV) Mechanoreceptor Nerve Endings by KCl in Verapamil Asystolic Hearts. J.A. Estrin*, A.M. Booth*, G.M. Wahler*, C.R. Swayze* and I.J. Fox. University of Minnesota, Minneapolis, MN 55455

The LV mechanoreceptor reflex is normally initiated, e.g. in exercise, by increased LV contractility mechanically depolarizing LV mechanoreceptors to reduce the systemic (SX) resistance. In beating hearts, intracoronary KCl, a chemical depolarizing agent, produces ventricular asystole or fibrillation, unloading LV mechanoreceptors, causing a reflex rise in SX resistance, indicating mechanical effects predominate in beating hearts. To test if chemical depolarization of LV mechanoreceptors is possible in asystolic hearts, 4 pneumonectomized dogs were studied on total cardiac by-pass (chloralose-Flaxedil^R) with SX and coronary circulations isolated and perfused separately (constant-rate SX perfusion). In hearts asystolic from intracoronary verapamil (80 mg) intracoronary injection of 5 mEq KCl caused an 8 ± 2% fall in pressure (resistance) of the SX circulation (P <0.01) from a control of 93 ± 4 mm Hg, a fall abolished, attenuated or unchanged by vagotomy. Thus, KCl can depolarize LV mechanoreceptors in verapamil asystolic hearts to cause reflex SX hypotension, an effect overshadowed by mechanical effects of KCl in beating hearts.

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GABA MODULATION OF THE EFFECT OF AUTONOMIC NEUROTRANSMITTERS IN THE CANINE SINUS NODE. Brett H. Neely*, Gilbert R. Hageman and Thomas N. James*. University of Alabama Medical Center, Birmingham, Alabama 35294.

Gamma- amminobutyric acid (GABA) is an important CNS neurotransmitter. In seven pentobarbital anesthetized open chested dogs we investigated the local effects of GABA upon the neurohumoral regulation within the sinus node. Stimulus frequency-response curves (8-32Hz.) of right stellate ganglion (RSS) and right cervical vagus (RCV) as well as selective perfusions of the sinus node (via the sinus node artery (SNA)) with norepinephrine and acetylcholine (0.01 and 0.1 μg/ml) were performed before and after GABA (1 to 1000 μg/ml) was perfused via the SNA. All changes in heart rate were expressed as percent of control. GABA had no significant effects upon spontaneous sinus rate. At 1 μg/ml GABA potentiated by 23% (p<.001) the tachycardia produced by RSS; at 100 μg/ml GABA potentiated the response to RSS by 15% (p<.05). The bradycardia produced by RCV was significantly attenuated by 17% (p<.05) with 1 μg/ml of GABA; by 27% (p<.001) with 100 μg/ml of GABA; and 38% (p<.001) with 1000 μg/ml of GABA. The direct effects of norepinephrine and acetylcholine (via the SNA) were not significantly affected by any concentration of GABA used. These effects of GABA were entirely reversed by perfusion of picrotoxin (1000 μg/ml) via the SNA. Thus, GABA exerts a peripheral effect by modulating the neural regulation of the canine sinus node. (Supported by NHLBI program project grant HL 11,310 and the American Heart Association)

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AN INTRACELLULAR STUDY OF EFFERENT NEURONS OF THE CELIAC PLEXUS AND THEIR CONNECTIONS IN CELIAC GANGLIA (CG). D.L. Decktor* and W.A. Weems, Univ. of TX. Med. Sch., Houston, TX 77030.

Recent evidence has accumulated indicating that sympathetic prevertebral ganglia integrate neural input of both central and peripheral origin. This study was designed to identify the soma of neurons whose axons are located in the celiac plexus and determine the origin of their preganglionic inputs. Feline solar plexus were superfused in vitro with Krebs solution. Stimulating electrodes were placed on the celiac and superior mesenteric plexus and the ipsilateral and contralateral splanchnic nerves. The soma of efferent neurons whose axons are located in the celiac plexus were identified by antidromic activation. A number of these neurons were splenic efferents. Synaptic input to both efferent and non-efferent neurons was generated upon stimulation of either the celiac or mesenteric plexus. Included in this suspected peripheral input was synaptic activity initiated by splenic nerve stimulation. Seventy-one percent of the CG neurons impaled received synaptic input upon stimulation of the ipsilateral splanchnic nerves. No synaptic input was observed upon stimulation of the contralateral splanchnic nerves. These findings demonstrate that (1) splenic efferent neurons can be identified in the CG, (2) these neurons receive both central and peripheral synaptic input, and (3) central nervous input to these neurons is provided by the ipsilateral splanchnic nerve exclusively. (Supported by NIH Grant HL 21351-03 and Heart, Lung and Blood Institute Research Career Development Award.)

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EFFECTS OF ELEVATED INTRACRANIAL PRESSURE ON PLASMA VASOPRESSIN. Richard P. Menninger, University of South Florida, College of Medicine, Department of Physiology, Tampa, FL 33612.

Several intracranial lesions, including subdural and intraventricular hemorrhage have been associated with the syndrome of inappropriate secretion of arginine vasopressin (AVP). Many of these same lesions are also associated with increased intracranial pressure (ICP). The present studies were conducted in anesthetized cats to determine whether elevated ICP can alter plasma AVP levels. ICP was elevated with a hydrostatic column applied to a cannula in the cisterna magna, a lateral ventricle or to a subdural balloon. Increasing ICP 50 to 200mmH_2O for periods up to 20 minutes had no effect on mean arterial pressure (MAP) or plasma AVP. Increasing ICP 150mm H_2O did not alter the AVP response curve to increasing plasma osmolality. Increasing ICP 50mmHg resulted in a rise in plasma AVP from 39 to 80pg/ml (P<.001) and increase in MAP from 117 to 150mmHg (P<.05) within 10 minutes. There were no changes in central venous pressure or plasma osmolality during this time. Since elevated MAP reflexly inhibits AVP release, it is hypothesized that some central or brainstem reflex is responsible for the elevated AVP. This reflex could be initiated by central pressoreceptors or the generalized decrease in cerebral blood flow reported at these levels of ICP.

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HEMODYNAMIC SIGNALS ARRIVING AT THE HYPOTHALAMUS MAY TRAVERSE A DISCRETE PONTINE AREA. Drew E. Carlson, Anne Dornhorst*, Janice W. Maran, and Donald S. Gann. Brown University, Rhode Island Hospital, Providence, RI. 02902.

To identify the pontine area through which the input from cardiovascular receptors might pass from the medulla to the hypothalamus, we recorded extracellularly from hypothalamic neurons in 13 cats anesthetized with chloralose-urethane, artificially respired, and immobilized with gallamine. Constriction of supradiaphragmatic inferior vena cava (CVC), that reduced both venous return and arterial pressure was used as a stimulus. Neurons were also tested for orthodromic responses to single electrical shocks (0.05 msec, 100-800μa, 0.5/sec) delivered with bipolar coaxial electrodes placed at 3 or 4 pontine sites in each cat. These sites occupied a region that extended laterally from the dorsal tegmental nucleus to and including the parabrachial nuclei. Of 29 neurons tested, 8 increased and 10 decreased their firing during CVC. Eleven of the CVC-responsive neurons were tested with stimulation of a total of 27 pontine sites. Three other sites drove neurons not responsive to CVC. Only 4 sites drove CVC-responsive neurons. However, 3 of these 4 sites were located in the lateral locus ceruleus within 300μ of an area shown previously to contain CVC-responsive neurons. In contrast, only 5 of the remaining 26 sites were located within 300μ of the above region. This difference in distribution is significant ($p<0.025$, X^2-test). Thus, it appears that hemodynamic information enters the hypothalamus from a very discrete region in the pons. Further, these hemodynamic neurons do not seem to receive additional input from the parabrachial or the dorsal tegmental nuclei. Supported in part by NIH grant AM26831.

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A TECHNIQUE FOR MEASURING DEFORMATION OF THE AORTIC VALVE RING DURING THE CARDIAC CYCLE. R.J. van Renterghem*, T. Arts*, A.A. van Steenhoven*, R.S. Reneman, University of Limburg, Maastricht and University of Technology, Eindhoven, Netherlands.

The deformation of the aortic valve ring (ring to which the leaflets are attached) is assumed to be determined by the natural strains between the commissures (cs), the bases of the aortic valve leaflets (bs) as well as the commissures and the bases (cbs). Natural strain is measured by using the induction principle. A magnetic field, generated in coil G induces a voltage in coil R. From the amplitude of this voltage the natural strain between G and R can be determined because the strength of the magnetic field decreases with distance. In vitro over a range of 2.5 to 30 mm, natural strains $\leq$ 20% can be measured with an accuracy of 0.1%. The frequency response is 0-150 Hz (-3dB). In dogs on total cardiopulmonary bypass, 6 coils (D: 1.5mm; thickness: 1.3 mm) could be attached to the commissures and the annulus at the base of each leaflet. Two coils can generate magnetic fields synchronously, but at different frequencies. The remaining 4 coils act as receivers. By varying the generator and receiver assignment over 6 coils the above mentioned natural strains can be measured. Preliminary results show that in the anesthetized open-chest dog 7 natural strains (3cs, 1bs, 3cbs) can be determined as an instantaneous function of time simultaneously with the pressures in the left ventricle and the ascending aorta, so that information can be obtained about the deformation of the aortic ring during the cardiac cycle. (Supported by the Dutch Heart Foundation).

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ARTERIAL HEMODYNAMICS OF ACUTE MITRAL INSUFFICIENCY. M. M. Lane*, J. A. Glasgow*, M. G. Nagle*, and R. C. Elkins. Veterans Administration Medical Center, Oklahoma City, Oklahoma 73104.

The hemodynamic consequences of the development of acute mitral insufficiency (MI) have not been described. Aortic impedance was studied in 6 dogs with induced acute MI, and the changes occurring in the first 5 min of MI were analyzed. With a sustained rise in mean left atrial pressure (from 5.9 $\pm$ .9 mmHg to 10.7 $\pm$ .6 mmHg at 5 min, $p < .005$) and coincident drop in mean aortic pressure, (from 114 $\pm$ 13 mmHg to 86 $\pm$ 12 mmHg at 5 min, $p < .05$), cardiac output decreased such that input impedance did not change. Characteristic impedance increased significantly after only 30 sec of MI (from 219 $\pm$ 75 dyne-sec cm^5 to 302 $\pm$ 85 ds/cm^5, $p < .02$), and remained significantly elevated for the 5 min of study (349 $\pm$ 88 ds/cm^5 at 5 min, $p < .05$). The magnitude of the oscillations of the impedance modulus with frequency increased by 30 sec but returned toward baseline values by 3 min; no change was observed in the frequency at which the first minimum of the impedance modulus occurred, nor in the frequency at which the impedance phase changed sign. These alterations in aortic impedance are consistent with an increase in wave velocity and an increase in aortic wall stiffness. The acute reduction in left ventricular (LV) afterload which occurs with the development of acute MI appears to be associated with prompt alteration in aortic wall properties. These changes have significant consequences for LV function.

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INDICES OF VENTRICULAR CONTRACTILE STATE: COMPARATIVE SENSITIVITY AND SPECIFICITY. Charles R. Lambert Jr. and Carl J.Pepine* and Wilmer W. Nichols, Dept. of Medicine,University of Florida, Gainesville, FL 32610.

Twenty-four indices of ventricular contractile state were compared as to inotropic sensitivity (dobutamine) as well as preload (dextran) and afterload (phenylephrine) independence. Experiments were done in open-chest instrumented dogs and signal processing was done off-line by digital techniques. The indices studied, listed in order of decreasing sensitivity, are (1) power-averaged rate of generation of power density, (2) peak isovolumic rate of change of power, (3)ejection rate of change of power at peak tension, (4) peak second time derivative of ventricular pressure, (5) peak ejection rate of change of power, (6) peak isovolumic power, (7) energy-averaged power density, (8) mean aortic blood acceleration, (9) peak aortic blood acceleration, (10) peak first time derivative of ventricular pressure, (11) peak normalized fiber velocity, (12) peak fiber velocity, (13) peak aortic blood flow, (14) peak power, (15) extrapolated Vmax (total pressure), (16) mean normalized fiber velocity, (17) mean fiber velocity, (18) extrapolated Vmax (developed pressure), (19) mean aortic blood flow, (20) mean power, (21) stroke volume, (22) peak wall tension, (23) mean wall tension, (24) time-tension index. The most sensitive index which was independent of preload and afterload manipulation was the ejection rate of change of power at peak tension. (Supported by the Southern Medical Association and NIH Biomedical Research Support Grant, 79-113).

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COMPARATIVE EFFECTS OF ISOPROTERENOL AND CALCIUM CHLORIDE ON LEFT VENTRICULAR PERFORMANCE. R.G.Johnson*,L.J.Drop*,G.A.Geffin*, B.N.Fowler*,D.D.O'Keefe,G.S.Haas*,W.M.Daggett. Surg. Cardiovascular Unit, Massachusetts General Hospital, Boston, MA 02114

We compared the effects of isoproterenol (ISU) with those of $CaCl_2$ on left ventricular (LV) performance depressed by hypocalcemia in dogs on right heart bypass.In 22 dogs,LVend-diastolic pressure (EDP),dP/dt and myocardial oxygen consumption ($M\dot{V}O_2$) at constant (c) stroke work (SW), and LV function curves at c mean aortic pressure and heart rate, were obtained during normocalcemia (A&BI) and during stable citrate-induced hypocalcemia(AII,BII).In group A (n=12),ISU(0.16μg/kg/min) was infused (AIII);in group B (n=10),$CaCl_2$ was infused (BIII) to match the EDP changes of A. LV end-diastolic segment length was obtained with circumferential gauges in 17 of the dogs.

	A&BI	AII	AIII	BII	BIII
[Ca++]*(mM)	1.1±0.04	0.59±0.04	0.58±0.03	0.53±0.02	1.00±0.06¶
LVEDP§	5.4±0.5	13.2±0.5	6.4±0.6¶	13.0±0.8	6.3±0.7¶
dP/dt	2309±106	1692±737	2958±278¶	1719±152	2469±323¶
$M\dot{V}O_2$ **	10.6±0.4	10.5±0.3	12.5±0.8†	12.4±0.9	12.1±0.8
SW@EDP=14§	34.6±1.6	11.4±1.2	30.4±2.1¶	13.9±2.5	32.7±2.5¶
SW@cEDSL	29.5±2.4	9.5±2.9	21.7±3.1¶	10.5±2.3	30.2±3.4¶

†p<0.05 ¶p<0.01(all vs II) *ionized calcium §cm H_2O

**ml/min/100g LV. Conclusions: ISU (0.16μg/kg/min) is equivalent to a [Ca++] rise of 0.44 mM from a hypocalcemic baseline as shown by the decrease in LVEDP at c SW and by the increase in SW at c LVEDP, but increased LV performance secondary to ISU was associated with increased oxygen cost whereas that secondary to $CaCl_2$ was not.(Supported in part by NIH grant HL 12777)

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EFFECTS OF PLASMA IONIZED CALCIUM CONCENTRATION ON VENTRICULAR FUNCTION DURING REGIONAL ISCHEMIA. G.A.Geffin,* L.J.Drop*, D.D.O'Keefe, M.A.Jacocks,* W.M.Daggett. Massachusetts General Hospital, Boston, MA 02114.

We assessed the effect of plasma ionized calcium ([Ca++]) on global and regional left ventricular (LV) function(F) in 10 anesthetized dogs on right heart bypass with mean aortic pressure and heart rate held constant. Control of cardiac output enabled paired comparisons to be made at matched preloads: stroke work (SW) at iso-LV-end-diastolic pressures and, using piezoelectric crystals in control(C) and ischemic(I) regions, normalized systolic shortening (ΔL) at iso-end-diastolic chord lengths. LVF was studied before(Pre) and after coronary artery ligation(CAL) during normocalcemia(N) and then after stable ionized hypercalcemia(↑Ca) or citrate-induced hypocalcemia(↓Ca), established in random order,each compared to F in the immediately preceding N:-

	[Ca++](mM)	SW(g.m.)	ΔL(C)(mm)	ΔL(I)(mm)
Pre	1.04±0.03	38.4±2.8↘§	1.67±0.13↘*	2.21±0.38↘+
CAL	1.05±0.03	25.5±2.6↙§	1.32±0.17↙*	-0.90±0.17↙+
N	1.11±0.02↘§	26.4±2.5↘+	1.47±0.12↘+	-0.65±0.20↘+
↑Ca	1.71±0.01↗§	32.5±3.1↗+	2.00±0.15↗+	-0.11±0.21↗
N	1.04±0.03↘§	25.4±3.1↘+	1.53±0.09↘§	-0.37±0.10↘+
↓Ca	0.75±0.02↙§	14.7±2.9↙§	0.76±0.11↙§	-0.65±0.12↙

Thus, ↓Ca depressed and ↑Ca improved F in C and I, (as well as global LVF), but the effects in I were small compared to the ischemia-induced depression. ↑Ca returned F in C,but not global LVF ($p<.003$), to preligation levels. *$p<0.02$, +$p<.01$, §$p<.001$

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VENTRICULAR FUNCTION IN CATECHOLAMINE-INDUCED CARDIOMYOPATHIC RABBITS. J.C. Lee and S.E. Downing, Yale University School of Medicine, Dept. of Pathology, New Haven, Ct. 06510

Catecholamine cardiomyopathy (CM) was produced in rabbits by a 90-min infusion of norepinephrine (NE, 2 μg/kg/min). Left ventricular (LV) contractility and pump function (VF) were examined 2 days later and compared with control animals. The effects of hypercapnia (PCO_2 >70 mmHg) and inotropic responsiveness to NE were also determined. VF was assessed by means of left ventricular function curves obtained with constant aortic pressure and heart rate, and quantified by determining stroke volume at LVEDP 10 cmH_2O (SV_{10}). Mean SV_{10} was 1.16 (±0.06) ml in controls, but averaged only 0.93 (±0.05) ml in CM ($P<0.02$). Hypercapnia caused significantly greater depression of VF in CM than in controls. NE dose-response curves demonstrated increases in both LV dP/dt_{max} and SV_{10} in each group. The percent increase in LV dP/dt_{max} was markedly attenuated in CM, but the increments in SV_{10} did not differ. The mean histological score in the CM animals was 1.6 (±0.1), indicating extensive myofiber injury. No histological abnormalities were observed in the controls. Thus, functional defects correlated with the presence of histopathological changes. In addition, a disscoiation of velocity (dP/dt_{max}) and force (SV_{10}) responsiveness to inotropic stimulation was identified in the CM group. (Supported in part by NIH Grant #HL-20401 and HL-08659)

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PARASYMPATHETIC STIMULATION AND THE SYSTOLIC INTRAMYOCARDIAL PRESSURE GRADIENT IN THE DOG. D. Nematzadeh*, P.A. Kot and J.C. Rose. Georgetown U. Med. Ctr., Washington, D.C. 20007

During measurement of intramyocardial pressure (IMP) at specific myocardial depths, the peripheral stump of the transected left vagus nerve was stimulated in 12 dogs (10 volts, 10 cps, 10-30 sec. duration). Left ventricular pressure (LVP) was recorded simultaneously. Heart rate decreased up to 50%. A decrease in pressures occurred during stimulation followed by a slight increase of pressures upon cessation of stimulation. Computer linear regression analysis was performed on 59 data points obtained before and during stimulation. During control, the systolic IMP (SIMP) expressed in percent of systolic LVP (SLVP) increased linearly with a slope .88 from about 15% of SLVP at subepicardium to as high as 103% at the subendocardium. However, upon vagus stimulation the slope decreased to .78 and SIMP increased linearly from about 13% of SLVP in subepicardium to 91% in the subendocardial layer. Vagus stimulation caused the SIMP gradient to shift to the right and the slope to decrease by 11.5% from that of control. This indicates an inhomogeneous negative inotropic response across the myocardium in response to left vagus stimulation. These results emphasize a functional role for the left vagus nerve in modulating LV contractility in the intact canine heart. The intrinsic mechanisms are complex and involve peripheral autonomic interactions across the LV wall.

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NEGATIVE CHRONOTROPIC EFFECT OF ADENOSINE ON ISOLATED RAT HEARTS. Lois Jane Heller. U. Minnesota, Duluth, Sch. of Med., Duluth, Mn. 55812

Isolated rat hearts were perfused with modified Krebs-Henseleit solution (Langendorf method-constant flow) and left ventricular isovolumic pressure measured. When adenosine was added to the perfusate (10^{-7} to 10^{-5}M), a dose-dependent decrease in spontaneous beating rate was observed (to 45% with 10^{-5}M adenosine, n=32). Neither propranolol nor atropine eliminated this adenosine effect. Electrocardiograms indicated that the pacemaker site usually remained constant and that gradual slowing of pacemaker firing rate usually accounted for the negative chronotropic effect. In a few instances, the higher doses of adenosine produced a second-degree AV nodal block causing an abrupt halving of heart rate. Increased systolic pressure development accompanied the adenosine-dependent decrease in heart rate reflecting the negative staircase of the force-frequency relationship of rat cardiac muscle. When hearts were paced to maintain constant rate, adenosine produced the expected coronary vasodilation and had a slight negative inotropic effect. These data support previous suggestions that, in addition to effects on coronary vasculature, adenosine also has direct influences on cardiac function.

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INFLUENCE OF POSITIVE END EXPIRATORY PRESSURE(PEEP), ON LEFT VENTRICULAR PERFORMANCE. Frances L. Bosse*, George P. Shedd, Jr.*, Richard W. Stremel and William B. Mead*. Dept. of Physiology and Biophysics, University of Louisville, Health Sciences Center, Louisville, Kentucky 40292.

The influence of PEEP on cardiac function has been extensively investigated. The purpose of our study was to observe the effects of PEEP on left ventricular (LV) performance in the closed chest dog. LV pressures and diameters were recorded with the Pieper left ventricular diameter-pressure transducer. Acute, mongrel dogs were anesthetized with chloralose and urethan and pancuronium bromide was given as needed to prevent spontaneous respiration. The following parameters were recorded at 0, 10, and 20 cm H_2O PEEP (at control and increased respiratory rates): intrapleural, aortic, pulmonary artery (PA) and LV pressures, heart rate, LV dp/dt, LV diameters and cardiac output. Control values were obtained at a tidal volume of 15 ml/kg, 12 breaths/min, and 0 PEEP. In addition to a significant decrease in cardiac output, we observed an increase in PA pressures and a decrease in LV end-diastolic diameters (LVEDD) that were directly related to increasing levels of PEEP. At a PEEP of 10 cm H_2O, LVEDD's were reduced 11% and at 20 cm H_2O, LVEDD's were decreased 18% from control values. These results suggest that the reduction in cardiac output and LV performance associated with PEEP are consistent with decreased LV preload.

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IONIZED CALCIUM: A MAJOR DETERMINANT OF THE LEFT VENTRICULAR RESPONSE TO CALCIUM INFUSION. L.J.Drop,* R.G.Johnson,* G.A. Geffin,* D.D.O'Keefe, W.M.Daggett. Surg. Cardiov. Unit, Massachusetts General Hospital, Boston, MA.

We tested the hypothesis that the left ventricular (LV) response to calcium infusion is dependent upon the preexisting plasma ionized calcium ([Ca++]) level.Dogs were placed on right heart bypass;LV end-diastolic pressure(EDP), peak LV dP/dt and myocardial oxygen consumption were obtained at constant(c) mean aortic pressure(MAP), cardiac output and heart rate(HR) and LV function curves were obtained at c MAP and HR during normocalcemia(A1,B1).In group A(n=10) [Ca++] was then lowered to 0.53±0.03mM (steady state) by citrate infusion(A2).$CaCl_2$ was administered to raise [Ca++] to normal (A3).In group B(n=13) $CaCl_2$ was infused to raise [Ca++] from normal(B-1) to hypercalcemia (steady state)(B2).In 8 dogs of each group,LVend-diastolic segment length (EDSL) was measured with circumferential gauges. Delta values (Δ) (A2→A3 vs B1→B2) were compared.

	A1	A2	A3	B1	B2	Δ
[Ca++](mM)	1.09±0.04	0.53±0.03	1.00±0.06	1.08±0.02	1.69±0.01	+
LVEDP§	4.6±0.7	13.0±0.8	6.3±0.7	6.0±0.8	4.4±0.5	+
peakLVdP/dt	2265±182	1719±152	2469±323	2670±260	3294±226	
SW@EDP=14§	39.4±1.6	13.9±2.5	32.6±2.5	36.8±2.3	40.3±2.5	¶
SW@c EDSL	38.6±1.8	10.5±2.3	30.1±3.4	34.6±2.5	40.7±3.9	¶

Δ : A2→A3 vs B1→B2: +$p<0.025$ ¶$p<0.01$ §cm H_2O

Conclusions: The initial [Ca++] (or its associated cardiac contractile state) is an important determinant of the LV response to $CaCl_2$ infusion.(Supported in part by NIH Grant HL 12777)

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CALIBRATION OF VENTRICULAR END DIASTOLIC VOLUME BY A BLOOD-BASED IDEAL ATTENUATION COEFFICIENT. Richard D. Baldwin*, Richard P. Spencer, Judith Gouldin*, Joseph Caulder*, John Burkes*. Williamsport Hospital, Williamsport, PA and Univ. of Connecticut Health Center, Farmington, CT 06032.

Calibration of end diastolic volume is needed to determine cardiac work. We are studying a technique which may allow this calibration, by comparing end diastolic counts with activity in a tube of blood drawn during blood pool imaging (Tc-99m in vivo labeled RBC). Venous blood, in a heparinized tube, was placed on a lead rectangle and counted under a gamma camera after being taped in place at the axilla. The ideal attenuation coefficient (IAC) was defined by: (end diastolic counts)/[(counts in tube)(IAC)] = end diastolic volume. After background correction, the ratio of tube counts to end diastolic counts was taken as an index of the difference between the 2 sources at the crystal face. Data were converted to a cardiac index and compared with the index calculated at the time of cardiac catheterization. Plots of IAC as a function of the ratio of tube counts/end diastolic counts showed a linear relationship: IAC = 0.263 - 0.279·Ratio. This suggests further refinement could be obtained by using correction factors for body size and apparent cardiac depth. In more general terms, a venous blood/cardiac ratio could be compared with other organs during studies of perfusion and function.

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ACUTE ANOXIA IN RAT HEART : EFFECT OF AGE. Colleen George* and M.T. Kopetzky. Texas Tech U. School of Medicine, Dept. of Physiology, Lubbock, TX 79430

Young (3 months, 32 animals) and middle- aged (11 months, 32 animals) male Sprague-Dawley ratswere respired with nitrogen to determine the effects of acute anoxia (AA) on heart rate (HR), peak aortic flow (PAF) and myocardial contractility. Thoracotomy was done after anesthesia, tracheal intubation, adrenectomy and obstruction of blood flow to the brain. Right and left ventricles were cannulated by direct puncture with bevelled PE tubing connected to pressure transducers. An electromagnetic probe was placed around ascending aorta. Measurements were made during initial room air period, AA period, and recovery room air period. The statistical model was a split plot factorial anova. The 11 months old animals had significantly lower HR and higher PAF on room air. AA significantly depressed HR and PAF, but age differences in HR and PAF were not significant; however, the age differences in right vs. left ventricle positive and negative dP/dt_{max} were significant. Myocardial contractility in AA varies with age and apparently is related to contraction and relaxation changes specific to right and left ventricle.

CONTROL OF BREATHING: RECEPTORS

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AUGMENTED EFFERENT INHIBITION OF CAROTID BODY CHEMORECEPTORS IN CHRONICALLY HYPOXIC CATS. N. Smatresk, S. Lahiri, M. Pokorski* and P. Barnard*. Dept. of Physiol. and Inst. for Environ. Med., Univ. of Penna., Philadelphia, Pa. 19104.

Chronic hypoxia leads to hypertrophy, increased vascular volume and an elevated dopamine and norepinephrine content in the carotid body. Since both catecholamine release and local blood flow may be regulated by sinus nerve efferents, these changes provide a basis for a greater efferent effect during chronic hypoxia. We studied this possibility by testing chemoreceptor responses before and after complete section of carotid sinus nerves in two groups of cats, one exposed to 10% O_2 for 21-30 days and another to air at sea level. The cats were anesthetized with α-chloralose, and single or pauci-fiber chemoreceptor afferents were recorded from a fine slip of an otherwise intact sinus nerve. Chemoreceptor responses were measured at several levels of PaO_2 and $PaCO_2$. While still recording from the slip, the remaining part of the nerve was cut and the measurements were repeated. In chronically hypoxic cats, carotid chemoreceptor activity consistently rose after sectioning the nerve, with the greatest stimulation seen in hypoxia. In normoxic cats, the effects of sinus nerve section were marginal. Thus, the inhibitory effect of sinus nerve efferents is augmented in chronically hypoxic cats, possibly via elevated dopamine release, which inhibits chemoreceptor activity, or through changes in local flow of the carotid body. (Supported in part by NHLBI Grant # 19737-05)

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EFFECTS OF NALOXONE ON CAROTID CHEMORECEPTOR ACTIVITY AND VENTILATION IN CHRONICALLY HYPOXIC CATS. M. Pokorski*, S. Lahiri, N. Smatresk and A. Mokashi. Inst. for Environ. Med. and Dept. of Physiol., University of Pennsylvania, Philadelphia, Pennsylvania 19104.

The mechanism of "blunted" ventilatory response to hypoxia in cats exposed to severe chronic hypoxia (Tenney et al. 1971) is still not known, although endogenous opiates which suppress ventilatory response to hypoxia may play a role. We investigated this possibility utilizing opiate antagonist, naloxone, in chronically hypoxic cats which, in a companion study (Barnard et al. 1981), were found to show an attenuated ventilatory response to acute changes in PaO_2. Cats were exposed to a 10% O_2 environment for 21-30 days, then anesthetized with α-chloralose. The activity of pauci-fiber chemoreceptor afferents from a cut sinus nerve was recorded, and ventilatory responses before and after naloxone (0.4 $mg.kg^{-1}$; i.v.) at various steady-state levels of PaO_2 were studied. We found that naloxone raised the level of ventilation at any PaO_2 level and increased ventilatory effect of a given carotid chemoreceptor input, but did not change the blunted pattern of ventilatory response, nor chemoreceptor activity appreciably regardless of the PaO_2 level. These findings argue against the possibility that the increased secretion and release of endogenous opiates play any significant role in the attenuation of respiratory response to chronic hypoxia. (Supported in part by NHLBI Grants HL-08899-17 and HL-19737-05)

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CAROTID CHEMORECEPTOR AND VENTILATORY RESPONSES IN CHRONICALLY HYPOXIC CATS, P. Barnard*, R. Zhang*, N. Smatresk, M. Pokorski*, A. Mokashi*, and S. Lahiri. Dept. of Physiol. and Inst. for Environ. Med., Univ. of Penna., Pa. 19104.

Attenuated hypoxic ventilatory responses in cats exposed to chronic hypoxia have been reported (Tenney et al., 1971). However, the contribution of carotid chemoreceptor activity to this attenuation is unknown. We studied the carotid chemoreceptor and ventilatory responses under steady state conditions to both hypoxia and hypercapnia in cats acclimatized to 70 torr PIO_2 for 21-30 days and those in normoxic cats at sea level. Cats were anesthetized with α-chloralose. Carotid chemoreceptor activity from a slip of an otherwise intact sinus nerve, ventilation, end-tidal PaO_2 and $PaCO_2$, and arterial blood pressure were continuously monitored. The chronically hypoxic cats had on the average lower $PaCO_2$ values on hyperoxia than did the controls; however, ventilation increased linearly with $PaCO_2$ in both groups. The chronically hypoxic cats exhibited a lower PaO_2 threshold for ventilatory responses than did the control cats. However, the percent increases in ventilation at PaO_2 values of less than 40 torr were similar in the two groups. Chemoreceptor activity increased hyperbollically with decreasing PaO_2 in both groups. Whether the carotid chemoreflex response is responsible for the lowered PaO_2 threshold for ventilation has not been settled by these data. (Supported in part by NHLBI Grant #19737-05.)

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CAROTID SINUS BARORESPIRATORY INHIBITION IN PENTOBARBITALIZED CATS. H.L. Borison , R. Borison*, M.J. Purves* and T. Sadig*. Dartmouth Med. Sch., Hanover, NH and Univ. Bristol, England.

Pressure-controlled bilateral autoperfusion of the carotid sinus was effected by means of a peristaltic roller pump redirecting heparinized blood from a common carotid artery. Pump oscillations were damped with an air cushion. Blood supply to the carotid body was preserved while major arterial branches were ligated. The cat was maintained on O_2 inhalation, with F_ACO_2 measured continuously and ventilation recorded as the integrated pneumotachogram. Rapid elevation of intrasinual pressure (ISP), within the physiological range, produced a sharp inhibition of breathing evident as a fall in V_T and/or a change in timing of the cycle in progress depending on the phase of respiration coincident with the stimulus. Further expression of the inhibitory effect with sustained ISP was related both to the amplitude of the rise and to its slope; in any case, recovery occurred in less than a minute. Cardiodeceleration also began promptly and showed a similar tendency to recover after a step shift in ISP. Vasodepression on the other hand developed more slowly to a non-adapting level. Respiratory steady-state was altered slightly if at all from the prior condition after any change in ISP. Vagotomy enhanced the vasomotor and respiratory responses. The order of ISP thresholds for eliciting steady-state effects was V_T>HR>BP. All responses to ΔISP were abolished by carotid sinus neurotomy.

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FUNCTIONAL LOCALIZATION OF PULMONARY STRETCH RECEPTORS IN THE NEWBORN KITTEN. D. Marlot*, J.P. Mortola and B. Duron*. Dept. Neurophysiology, Univ. Picardie, Amiens, France and Dept. Physiology, McGill Univ., Montreal, Canada.

Six kittens between 5 and 8 days of life have been anesthetized with ketamine, tracheotomized, cannulated just below the larynx, paralyzed and passively ventilated. The thorax was widely open and an expiratory load equal to the transpulmonary pressure at functional residual capacity ($P_{L_{FRC}}$) was added. Single vagal fibers were dissected from the peripheral cut end of the right vagus nerve. Of 38 pulmonary stretch receptors (PSR) studied 10.5% were firing at $P_{L_{FRC}}$ while the remaining had a threshold between 1.2 and 7.6 cm H_2O, increased their activity with higher pressures reaching a plateau between 5-10 cm H_2O. By occluding the airways at different levels of the tracheobronchial tree 32 PSR have been functionally localized: 0% were located in the extrathoracic trachea, 9.5% in the intrathoracic trachea, 37.5% at the carina, main bronchi and lobar bronchi, 53% inside the lobes. All the tracheal receptors were tonic PSR. Previous data in adult mammals indicated that 40-60% PSR had tonic activity and most of them were located in the trachea. An immaturity of PSR is probably the explanation of the low tonic vagal activity in the kitten.

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RESPONSE OF SLOWLY ADAPTING RECEPTORS IN THE TRACHEA TO SINUSOIDAL STRETCHES AT FREQUENCIES UP TO 40 Hz. C. Sant'Ambrogio and P.W. Davenport. Dept. of Physiology and Biophysics, U.T.M.B. Galveston, Texas 77550

In 5 dogs anesthetized and spontaneously breathing we recorded from thin vagal filaments action potentials from 5 slowly adapting receptors (SAR) of the extrathoracic trachea (ETT). The ETT was cut longitudinally, the cut ends of the cartilage corresponding to the site of the receptor in the trachealis muscle were stretched sinusoidally at frequencies up to 40 Hz. The number of spikes per cycle decreased with increasing frequency. At the highest frequency (40 Hz) SARs still responded to each oscillation with a single action potential. In 4 of the SARs the number of action potentials per second increased with increasing frequency. A decrease in smooth muscle tone, following vagotomy, decreased the firing of these endings at rates of oscillations below 20 Hz. Vice-versa an increase in smooth muscle tone, as obtained by acetylcholine applied topically, increased the receptors discharge at rates of oscillations below 8 Hz. These latter results are consistent with an "in series" arrangement of SAR with the muscle fibers. The increase in tracheal stretch receptors activity per second as the oscillatory frequency increases might explain the inhibitory influences on respiration observed with high frequency ventilation (A. Jonzon, Acta Anesth. Scand., Suppl. 64, 29-35, 1977).

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TRACHEOBRONCHIAL VAGAL AFFERENTS IN THE NEWBORN DOG. John T. Fisher and Giuseppe Sant'Ambrogio. Dept. of Physiology and Biophysics, U.T.M.B. Galveston, Texas 77550.

Activity from vagal afferents of respiratory origin were recorded from thin filaments of the vagus nerve in newborn (NB) puppies (age 1-5 days). The single fibre discharge was classified as arising from slowly or rapidly adapting receptors (SAR and RAR respectively) on the basis of their response to lung inflation and deflation. A total of 79 receptors were recorded of which 92% (75/79) were identified as SARs and 5% (4/79) as RARs. Further classification of the SARs was made on the presence or absence of activity at functional residual capacity (FRC). The SARs with FRC activity accounted for only 8% (6/75) of the SAR recordings while 92% (69/75) had no FRC activity. In 13 SARs the discharge frequency (f) vs static transpulmonary pressure (P_{tp}) curve was obtained. The response curves were of 2 types: an increase in discharge f with increasing P_{tp} after which a plateau was observed while in the second type no plateau of f was present. Fourteen SARs were localized by direct probing and of the lung and dissection of the lung parenchyma while recording from the fibre; 7 were intrapulmonary and 7 extrapulmonary. Compared to the adult dog (A) the NB has much less SAR activity at FRC (8% NB vs 50% A) and the NB appears to have fewer RARs.

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FLOW SENSITIVITY OF PULMONARY STRETCH RECEPTORS. Steve Iscoe* (SPON. J.V. Milligan). Dept. of Physiology, Queen's University Kingston, Ontario, Canada K7L 3N6.

The contribution of flow to the discharge of pulmonary stretch receptors (PSR) has not been established. In this study, the instantaneous discharge frequency of a single PSR was related to inspiratory flow in spontaneously breathing, pentobarbital-anesthetized cats. Inspiratory flow was increased by allowing the cats to rebreathe a hypercapnic gas mixture (5.5% CO_2, 50% O_2 and N_2) from a spirometer. Instantaneous discharge frequencies and flows were measured at selected volumes above the cat's end-expiratory level. At volumes below 40 ml, instantaneous discharge frequency decreased as flow increased. Between 50 and 120 ml, instantaneous discharge frequency increased as flow increased. The average flow sensitivity in this latter range was 0.070 spikes/s per ml/s. During CO_2 rebreathing, tidal volume increased by 61±21 (SD) ml and flow by 131±30 ml/s. Associated with these increases was an increase in peak discharge frequency of 37.8± 16.1 spikes/s. Increases in flow alone would account for an increase in frequency of 9.2 spikes/s, or 24% of the observed change. Moreover, since CO_2 inhibits PSR, this value may underestimate the contribution of flow to PSR discharge during increased ventilation in air. These data also indicate that the flow sensitive component of PSR discharge must be included in any model of the inspiratory off-switch mechanism.

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RESPIRATORY RESPONSES TO FLOW RESISTIVE LOADS DURING VAGAL BLOCKADE IN AWAKE DOGS. B. Simhai* and S. Kelsen, Dept. of Medicine, Case Western Reserve Univ., Cleveland, Ohio 44106.

In awake animals and man, external flow resistive loading of ventilation (FRL) elicits increases in respiratory muscle electrical activity and contraction force (occlusion pressure). Although the motor response to FRL appears to involve neural rather than chemical mechanisms, the location(s) of the mechanoreceptor(s) mediating this response are not clear. The present study examined the response to FRL when sensory input to the respiratory neurons from lung and tracheal mechanoreceptors was eliminated (vagal blockade) and receptors in the mouth and upper airway were bypassed (tracheostomy breathing). Inspiratory FRL (12 $cmH_2O/L/sec$) were applied during complete vagal blockade produced by cooling exteriorized cervical vagal loops in 4 awake dogs. Respiratory responses to FRL were assessed from changes in ventilation and occlusion pressure (P100). Respiratory activity under control and loaded conditions was compared at the same level of chemical drive by adding FRL during CO_2 rebreathing. FRL produced no consistent change in either the duration of inspiration or expiration but increased the P100 at a given level of PCO_2 in each animal. P100 at P_ACO_2 55 mmHg during FRL was 168 ± 33% SE of control ($p = 0.01$). We conclude that FRL can augment respiratory motor activity in the absence of sensory input from the lungs and airways. Presumably chest wall mechanoreceptors are responsible for the response to FRL under these conditions.

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CENTRAL CHEMORECEPTOR BLOOD FLOW ESTIMATED BY HYDROGEN CLEARANCE. **P.J. Feustel, M.J. Stafford, J. Allen* and J.W. Severinghaus. Cardiovascular Research Inst. and Dept. of Anesthesia, Univ. of Calif., San Francisco CA 94143.**

To verify conclusions concerning central chemoreceptor blood flow made from observations of ventilatory responses to step changes in end tidal Pco_2, we have used the H_2 clearance technique to measure flow independent of ventilatory system parameters. In 6 cats, 25μ teflon coated platinum wire electrodes were implanted and polarized for H_2 determinations. To insure that perfusion rather than diffusion dominates the clearance, flow was determined both during a step decrease in H_2 and following bolus H_2 inhalations. If flows were independent of technique they were judged to be perfusion limited. The flows measured from 24 electrodes placed in the ventrolateral surface of the medulla (area 'M') and in 14 electrodes placed in the adjacent pyramidal tracts were (Mean ± S.D.):

P_tco_2 (torr)	Blood Flow (ml/min/100g)	
	Area 'M'	White Matter
21.8±1.6	55.7±34.3	24.1±16.5
31.9±2.2	59.4±38.5	30.5±21.1
43.5±3.3	84.2±47.9	40.3±21.7

These results confirm that flow in central chemoreceptors exceeds that of white matter ($p<0.05$) and is sensitive to variations in arterial Pco_2. **(GM-15571)**

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Blood Flow to the Respiratory Centers (RC) and Central Chemosensitive Areas (CCA) in the Dog. P. J. Buco, J. C. Passmore and R. W. Stremel. Dept. Physiology and Biophysics, University of Louisville, HSC, Louisville, Kentucky 40292.

Brain blood flow and its distribution are critical in considerations of respiratory control. We, therefore, wished to determine in dogs the total blood flow, and the contribution from the common carotid arterial flow (CCAF) and vertebral arterial flow (VAF) to the pneumotaxic center (PNC), apneustic center (APC), dorsal respiratory group (DRG), ventral respiratory group (VRG) and CCA. Anesthetized dogs were surgically prepared with non-occlusive catheters in the right femoral, right vertebral and right common carotid arteries. Each artery received one of three radioactively-labeled 15 ± 3μ diameter microspheres. The results are in the table below.

	TBF*	VAF**	CCAF**
PNC	67.4 ± 0.1	93.2 ± 0.1	6.8 ± 0.1
APC	76.1 ± 0.1	82.8 ± 0.2	17.2 ± 0.2
DRG	122.1 ± 0.2	98.1 ± 0.0	1.9 ± 0.0
VRG	89.9 ± 0.1	98.3 ± 0.0	1.7 ± 0.0
CCA	80.5 ± 0.2	99.2 ± 0.0	0.8 ± 0.0

* Total Blood Flow ($\bar{X}$ ± S.E. ml/100g·min).
** Contributions as % ± S.E. for right side structures.

The contributions of VAF and CCAF to the TBF for the contralateral structures are similar. The results suggest that the vertebral artery is the principal artery for perfusion of the RC and CCA. (Supported by Academic Excellence Commission of the University of Louisville and USPHS - HL23546.)

SHOCK II

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NOREPINEPHRINE TURNOVER IN HEART AND SPLEEN DURING ENDOTOXICOSIS. B. J. Pardini, S. B. Jones and J. P. Filkins. Dept. of Physiology, Loyola Univ. Medical Center, Maywood, IL 60153.

Hyperactivity of the sympathetic nervous system during endotoxin shock is mainly supported by findings of increased serum levels of catecholamines and depressed tissue content of norepinephrine (NE). The present study is the first quantitation of sympathetic activity in endotoxic rats using measurements of the turnover rate of NE. NE turnovers in the heart and spleen were evaluated by the ^{3}H-NE decay method. Fasted rats were injected iv with high specific activity ^{3}H-NE one minute before injection with either saline (S) or S. enteritidis endotoxin (E) (2 mg/300gm rat; LD 5% at 24 hrs). Rats were sacrificed at preselected times up to 24 hrs later (4-7 rats per time group). Tissues were analyzed for NE content (μg/gm) and the specific activity of ^{3}H-NE. Least squares regression analysis of log specific activity vs time was performed. Turnover rate (μg NE x gm^{-1} x hr^{-1}) was derived from the slope and NE content.

Group		N	NE Content	Slope	Turnover Rate
Heart	(S)	19	.69±.02	-.0066	.011
	(E)	22	.70±.02^{NS}	-.0307$^{p<.001}$	.049
Spleen	(S)	19	.94±.04	-.0091	.020
	(E)	22	.84±.05^{NS}	-.0485$^{p<.001}$	.093

NE turnover is increased in spleens and hearts of E rats indicating increased peripheral sympathetic nerve activity and increased rate of NE synthesis. (Supp. by NIH Grant HL 08682.)

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Inactivation of Catecholamines by Endogenously Released Peroxidase During Endotoxin Shock. H. F. Janssen and M. B. Grisham*. Depts. of Orthopaedic Surgery and Biochemistry. Texas Tech Hlth. Sci. Ctr. Lubbock. Texas 79430

The cardiovascular system is, for the most part, insensitive to catecholamines during endotoxin shock. The rapid fall in mean arterial pressure (MAP) which occurs following an intravenous bolus of endotoxin results mainly from vasodilation due to an apparent loss of sympathetic tone. Numerous reports indicate that the decrease in MAP closely correlates to the removal of white blood cells (WBC's) from the circulating plasma. The present study explored a possible implication of this correlation in adult mongrel dogs given a bolus injection (0.5 mg/kg) of E. coli endotoxin. The analysis of plasma collected from these animals showed a rapid increase in peroxidase activity as early as 4 min. following the endotoxin injection and reaching a plateau at 90 min. Additional tests suggest that this peroxidase activity is due to myloperoxidase (MPO) released from neutrophils. The effect of the MPO upon catecholamines was then investigated. Dopamine, epinephrine, and norepinephrine were separately incubated with MPO (harvested from dog WBC'S) in the presence of H_2O_2. The subsequent intravenous injection of these incubated compounds into naive dogs produced a significantly reduced cardiovascular effect as compared to a similar dose of the original drug or the drug incubated with H_2O_2 only.

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EFFECT OF THE THROMBOXANE (Tx) A_2 SYNTHETASE INHIBITOR, UK37, 248, IN ENDOTOXIN (LPS) SHOCK: PREVENTION OF SPLANCHNIC INFARCTION AND IMPROVED FUNCTIONAL PARAMETERS. J.A. Cook, P.V. Halushka*, and W.C. Wise, Med. Univ. of S.C., Charleston, S.C.

Our previous studies have suggested that TxA_2, a platelet aggregator and vasoconstrictor, plays a pathogenic role in LPS shock. In this study we evaluated the actions of the clinically effective Tx synthetase inhibitor, UK37,248(UK)(Pfizer Inc.) in rats injected iv with S. enteritidis LPS (30 mg/kg). Plasma TxB_2, the stable metabolite of TxA_2, and PGE were measured by RIA, 30 minutes after LPS. LPS increased TxB_2 from <200 pg/ml to 1013±116 pg/ml whereas UK pretreatment 30 mg/kg reduced TxB_2 to <200 pg/ml ($P<0.01$) but did not affect plasma PGE. UK attenuated the severity of LPS shock at 4 hours as denoted below. UK

	Blood Glucose (mg%)	Serum β-glucuronidase (units/ml)	Plasma Fibrin Split Products(μg/ml)	Platelet Count ($x10^3/mm^3$)
UK (N)	57±6*(21)	127±24*(16)	10±3*(6)	404±38(20)
Control(N)	39±6(27)	253±48(18)	26±6(6)	301±27(21)

*P<0.05 compared to control

prevented splanchnic infarction as determined by gross and histological examination. Disruption of mucosal integrity and hemorrhage in the bowel were present in 18 of 20 controls and only 1 of 16 UK pretreated rats ($P<0.01$). These observations further support the notion that TxA_2 is an early pathogenic factor in LPS shock and suggest that it may be an important mediator of splanchnic ischemia. (Supported by NIH GM27672 and GM20387 and RR1070).

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EXTRACORPOREAL PERFUSION WITHOUT EXOGENOUS ANTICOAGULATION: LIMITATIONS OF ITS PROTECTIVE ROLE IN ENDOTOXIN SHOCK. L.B. Hinshaw, A.C.K. Chang*, B. Beller-Todd* and L.T. Archer*. VA Medical Center, Oklahoma City, OK 73104

Our previous work demonstrated that after 90 min. of arteriovenous perfusion without anticoagulation dogs are protected from lethal endotoxin. We extended this work by administering endotoxin simultaneously with the onset of perfusion and by excluding the open air reservoir from the system. Anesthetized dogs (N=24) were divided equally into 4 groups and perfused for 240 min. and/or infused with LD_{85} E. coli endotoxin for 30 min. Group A (endotoxin; no perfusion); Group B (perfusion; no endotoxin); Group C (perfusion; endotoxin initiated after 90 min.); and Group D (perfusion and endotoxin initiated simultaneously). Percent 7 day survival: Group A = 17%, Group B = 100%, Group C = 83%, and Group D = 17%. Mean aortic pressures, glucose, platelets, and fibrinogen concentrations fell in Groups A, C, and D but remained stable in B. PTT increased markedly in Groups A, C, and D. White blood cell counts decreased in Groups A, C, and D but increased in B. Lee White whole blood clotting times were prolonged in Groups C and B, were unchanged in D and decreased in A. Groups B and C confirm the stability of the perfusion system and its defense against shock. The lethal effects of endotoxin are prevented if extracorporeal perfusion is begun 90 min. before endotoxin administration (Group C), but not if extracorporeal perfusion and endotoxin infusion are started simultaneously (Group D). (Supported by VAMC, NIH, and U.S. Navy)

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CHARACTERISTICS IDENTIFYING SURVIVORS IN BABOONS CHALLENGED WITH E. COLI SHOCK. Daniel J. Brackett, Michael F. Wilson and Lerner B. Hinshaw. VA Medical Center and OU Health Sciences Center, Oklahoma City, OK. 73104

The pathophysiological mechanisms of septic shock have not been completely identified. Ineffective treatment is partly related to this lack of understanding. Infusion of E. coli in the baboon is a recognized experimental septic shock model; in this study we have administered an LD_{100} dose to 39 baboons followed by different therapy regimens in 31. There were 18 permanent survivors (S) (7 days or more), all receiving an antibiotic/steroid combination therapy. If the early responses and their temporal patterns which are characteristic of S could be identified, specific supportive therapy to enhance them may be beneficial in the treatment of septic shock. Responses were measured during the first 12 hours from the onset of E. coli infusion to evaluate the circulatory and metabolic status of the animals. Non-survivors (NS) were compared to S during the 12 hour observation period (unpaired t test, $p<.05$) and measurements at each time period were compared to control within each group (paired t test, $p<.05$). Lactate, heart rate and blood urea nitrogen were lower in S than NS. Glucose and insulin levels were higher in S while blood pressure, white blood cell count, and blood gases were the same. A greater lactic acidosis with the same respiratory compensation in NS was evident as early as 4 hours. We conclude that S had a lesser impairment of renal, hepatic, and pancreatic function during the early phase of septic shock in the baboon.

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INSULIN-LIKE ACTIVITY OF ENDOTOXIC LIPID A. J. P. Filkins and L. Witek-Janusek. Depts. of Physiology and Maternal Child Health Nursing, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL 60153.

A comparative analysis of various endotoxin preparations suggested that the insulin-like activity (ILA) of Gram-negative lipopolysaccharides resides in the lipid A moiety (*The Physiologist* 23:131, 1980). The current study evaluated lipid A as purified from Salm. minnesota Re595 for in vivo and in vitro evidence of ILA. Lipid A -- either as complexed with bovine serum albumin (BSA) or as the triethylamine salt (TEA) -- induced a hypoglycemic shock syndrome in lead-sensitized assay rats. Lipid A-BSA also induced hypoglycemic deaths in adrenalectomized assay rats. Lipid A-BSA iv to donor rats elicited increased ILA as assessed by enhanced glucose oxidation in epididymal fat pads (EFP). In contrast, neither lipid A-BSA nor-TEA exerted a direct ILA on EFP as assessed in vitro; however, addition of lipid A-BSA to inactivated alkaline hydrolysates of S. enteritidis Boivin lipopolysaccharide resulted in restoration of ILA. The data indicate that lipid A is indeed the active ILA moiety of endotoxin, but that it requires additional components of the lipopolysaccharide complex in order to exert in vitro actions. The ILA of lipid A may play a major role in development of endotoxic hypoglycemia and shock. (Supported by NIH grant HL 08682.)

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BASAL INSULIN AND GLUCAGON RESPONSES TO PORTAL VERSUS SYSTEMIC VENOUS ADMINISTRATION OF ENDOTOXIN IN FASTED RATS. Robert P. Cornell. Northeast Missouri State Univ., Kirksville, MO 63501.

Intravenous administration of bacterial endotoxins causes basal plasma hyperinsulinemia and hyperglucagonemia in rats, dogs, and humans. Kupffer cells of the liver are well recognized for their phagocytic removal of circulating endotoxins. In the present study Salmonella enteritidis endotoxin was injected slowly over a 1 min interval into the portal vein or systemic inferior vena cava of fasted, anesthetized rats at a range of doses (10,33,100,333, and 1000 µg/100 g). Compared to saline control values at 4 hr postinjection (portal and systemic plasma levels, respectively, insulin = 43±6.6 and 16±1.8 µU/ml and glucagon = 0.70±0.04 and 0.53±0.05 ng/ml), systemic administration of endotoxin usually resulted in significantly greater hyperinsulinemia and hyperglucagonemia than did portal administration for all but the lowest (10 µg/100 g) and highest (1000 µg/100 g) doses. For example, at the 100 µg/100 g dose, portal injection of endotoxin yielded values of 58±5.2 and 17±2.4 µU/ml for insulin and 1.29±0.30 and 0.70±0.09 ng/ml for glucagon while the values after systemic injection were 71±9.8 and 26±3.1 µU/ml for insulin and 1.97±0.22 and 1.22±0.18 ng/ml for glucagon. The results suggest that Kupffer cells of the liver normally provide an effective barrier against the influence of bacterial endotoxins on pancreatic hormone secretion. (Suported by DCWA of St. Louis, MO and NIH Grant 22102.)

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EFFECTS OF ATP-$MgCl_2$ ON HEPATIC GLUCOSE METABOLISM AND OXYGEN CONSUMPTION. M.G. Clemens, I.H. Chaudry, P.H. McDermott* and A.E. Baue. Yale University School of Medicine, Department of Surgery, New Haven, Connecticut 06510.

Salutory effects of ATP-$MgCl_2$ in low flow states have been documented but the mechanisms remain unclear. This study describes the effects of ATP-$MgCl_2$ on hepatic oxygen consumption (VO_2) and glucose metabolism. Livers from fed or 40 hr fasted rats were isolated and perfused at a constant flow. Gluconeogenesis was estimated from glucose release by livers from fasted rats when 5mM lactate was added and glycogenolysis from glucose release by livers from fed rats without substrate. ATP-$MgCl_2$ in equimolar amounts was infused to give final concentrations of 10^{-6} to 10^{-4}M. In fasted rats, 10^{-6}M ATP-$MgCl_2$ increased glucose production from 17.4 ± 1.14 to 19.2 ± 1.4 µmoles/hr/g liver ($p<.001$ by t-test for paired data), with no change in VO_2. At concentrations $>5x10^{-5}$M, glucose production decreased with concomitant decrease in VO_2. ATP-$MgCl_2$ at $>5x10^{-6}$M stimulated glycogenolysis (maximum effect 227% of control). Steady state VO_2 showed little change except for a transient decrease at $>5x10^{-5}$M. These results demonstrate that exogenously applied ATP-$MgCl_2$ in micromolar amounts have direct cellular effects on glycogenolysis and gluconeogenesis with little effect on VO_2. At higher concentrations, however, gluconeogenesis and VO_2 are decreased.

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EFFECTS OF EARLY AND LATE SEPSIS ON HEPATIC OXYGEN SUPPLY AND SELECTED BLOOD PARAMETERS. Kathleen A. Fitch* and Richard D. Rink. Univ. of Louisville, Louisville, Ky. 40292

Hepatic oxygen supply and related parameters were evaluated during early (8-10 h) and late (18-30 h) stages of lethal septic peritonitis induced in rats by cecal ligation and puncture (CLP). Mortality was 65% in 30 h. In the early phase, hepatic PO_2 was reduced significantly (mean 9.3 versus 22.2 mm Hg in sham-operated controls). This was accompanied by elevations of serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase ($P<0.02$ and $P<0.10$, respectively), moderate hyperglycemia ($P<0.02$), and hemoconcentration (56.7%, $P<0.001$). Total body oxygen consumption was decreased by 21% ($P<0.001$). By the late stage of sepsis hepatic oxygen supply was depressed profoundly (mean 2.0 versus 24.5 mm Hg in controls) concomitant with further elevations of serum transaminases. Lactacidemia, respiratory alkalosis, and tachycardia were also present. No additional changes of total body oxygen consumption or hematocrit were recorded. Hypoxemia and hypotension were not observed during either early or late stages. While it has been proposed that the CLP model develops a hyperdynamic state in early sepsis, the hemoconcentration we recorded is interpreted as evidence of hypovolemia. Our results suggest hypoperfusion leading to early impairment of hepatic nutrient flow sufficient to establish hypoxic foci and hepatocellular damage.

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EFFECTS OF INTESTINAL BLOOD FLOW REDUCTION AND SUPEROXIDE RADICALS ON MUCOSAL ALBUMIN CLEARANCE. Dale A. Parks,* Bjarne Grogaard,* and D. Neil Granger, Dept. of Physiology, Univ. South Alabama, Mobile, Ala. 36688.

The purpose of this study was to determine if intestinal arterial occlusion (of varying durations) or superoxide radicals, generated by the hypoxanthine-xanthine oxidase reaction, influence the clearance of albumin across the intestinal mucosa. Albumin clearance was measured in jejunal segments of 23 dogs which were injected with I-125albumin 12 hrs. prior to the experiment. In addition, the RBCs were labelled with Cr-51. Clearance rates (R) were estimated from the luminal perfusion rate and the activity of protein bound I-125 in the perfusate and plasma. R was 0.00035 ± .00012 ml/min/cm under control conditions and increased progressively with arterial occlusions of 15 min (.00084 ± .00019) to 240 min (.0296 ± .0094) duration. Intraluminal perfusion with hypoxanthine-xanthine oxidase (H-XO) significantly increased R (.00133 ± .0002). Superoxide dismutase prevented the R increase produced by H-XO while H or XO alone did not affect R. The results of this study indicate that arterial occlusion and enzymatically generated superoxide radicals increase mucosal albumin clearance.
Supported by NHLBI 26441 and 00816

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CARDIORESPIRATORY EFFECTS OF ACUTE SMOKE INHALATION, R.Dunn, M. Pindok, E.Sukowski and V.V.Glaviano, University of Health Sciences/The Chicago Medical School, North Chicago,Il.60064.

Cardiorespiratory alterations in the experimental animal subjected to acute smoke inhalation have not been precisely defined. Mongrel dogs anesthetized with morphine-chloralose were intubated for inhaling smoke from burning white pine chips for 5 min. The smoke inhaled contained 1.6% carbon monoxide and 10.1% O_2 . Aortic blood pressure, right and left intraventricular pressures and heart rate were measured before, during and 20 min following smoke inhalation. Inhalation produced a decrease in aortic diastolic pressure and marked elevations of left and right ventricular end diastolic pressures and right ventricular systolic pressure. A return to control values occurred gradually during recovery except for right ventricular systolic pressure which remained elevated. Smoke inhalation increased carboxyhemoglobin saturation from 2.1 to 73.8% and arterial lactate from 1.12 to 1.66 mM. Twenty minutes of recovery failed to decrease carboxyhemoglobin saturation during which time a further rise in arterial lactate to 4.97 mM occurred. Arterial pCO_2 increased and PO_2 and pH decreased with smoke inhalation but returned to near control values in the recovery period. Smoke inhalation increased hematocrit from 41.5 to 53.5%. Analysis of the data indicates that acute smoke inhalation caused a combination of hypoxic hypoxia, carbon monoxide poisoning and pulmonary vasoconstriction that likely act synergistically to produce cardiorespiratory collapse.

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PRIMATE ENDOTOXEMIC SHOCK REVERSED BY OPIATE RECEPTOR BLOCKADE WITH NALOXONE. Nelson J. Gurll, David G. Reynolds, Thomas Vargish*, Stephen A. Lutz*, and Eric Ganes*. Univ. Iowa Coll. Med., Iowa City, IA 52242.

Naloxone (nal) attenuates the cardiovascular depression found with hemorrhage or endotoxemia in rats and dogs with resultant increased survival. This presumably occurs by blocking opiate receptors from endorphins released by stress. Since primate endorphin systems may be under different control mechanisms (Science 209:827, 1980) we investigated the effect of nal on mean arterial pressure (MAP), cardiac output (CO), and left ventricular contractility (LV dp/dt max) in cynomulgus monkeys. Monkeys lightly anesthetized with N_2O/O_2 were given E. coli endotoxin 5 mg/kg i.v. When MAP reached 75 mmHg or its nadir at 60-90 min the animals were treated with either nal 2 mg/kg plus 2 mg/kg·hr i.v. for 4 hours (N=6) or 0.9% NaCl in equivalent volumes as a control (con, N=6). Nal significantly increased MAP by 20-30 mmHg and LV dp/dt max by 400-800 mmHg/sec over controls. Differences between nal and con groups remained significant during treatment (repeated measurement analysis of variance) for MAP ($F(1,10)=14.5$, $p<.003$) and LV dp/dt max ($F(1,9)=13.3$, $p<.005$). Nal significantly enhanced survival at 48 hrs (6/6 alive cf 1/6 con alive, $p<.05$). Endorphins, acting on opiate receptors, are activated in and contribute to the cardiovascular depression in primate endotoxemia like other species. (Supported by U.S. Army Contract DAMD-17-80-C-0094).

MYOSIN PHOSPHORYLATION AND MUSCLE CHEMISTRY

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IN VITRO MECHANICAL PROPERTIES OF SMOOTH MUSCLE FROM FELINE LOWER ESOPHAGEAL SPHINCTER (LES). N.W. Weisbrodt and R.A. Murphy, Dept. of Physiology, University of Virginia School of Medicine, Charlottesville, VA 22908

The circular layer of the LES differs from most smooth muscles in developing a high level of spontaneous tone and undergoing relaxation when electrically stimulated. LES strips were connected to an electronic isotonic lever system. Spontaneous tone after equilibration was 0.57 ± 0.08 (SEM) x 10^5 N/m^2 at the optimum length for force development (L_0). Active stress increased to 1.08 ± 0.19 x 10^5 N/m^2 in the presence of 10^{-6}M carbachol. Field stimulation (8 Hz, 1 ms) for 30 s resulted in complete relaxation, and 95% of maximum stress was redeveloped within 30-60 s after stimulation ceased. Isotonic shortening velocity increased rapidly to a peak value 10 s after cessation of stimulation and then rapidly declined. The maximum shortening velocities with no external load (V_0) were 0.121 ± 0.032 at 10 s and 0.038 ± 0.003 L_0/sec at 10 min. The isotonic estimates of average crossbridge cycling rates were confirmed by similar changes in the rate of isometric force redevelopment with time following a 0.05-0.07 L_0 step-shortening. We conclude that the LES exhibits properties observed in arterial smooth muscle (Dillon et al., Science 211:495, 1981). The relaxing system rapidly inhibits crossbridge interactions. On cessation of stimulation, rapid crossbridge cycling occurs but this is converted to an economical slow cycling during maintained tone. [Supported by NIH grants HL19242, AM19886 and DA00022.]

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MYOSIN PHOSPHORYLATION AND CONTRACTION OF AIRWAY SMOOTH MUSCLE. W.T. Gerthoffer* and R.A. Murphy. Dept. of Physiology, Univ. of Virginia School of Medicine, Charlottesville, VA 22908

The hypothesis that Ca^{++} activates a crossbridge in smooth muscle by stimulating phosphorylation of the 20,000 dalton light chain of myosin (LC 20) was supported by a correlation between LC 20 phosphorylation and active stress in canine trachealis (deLanerolle & Stull, J. Biol. Chem. 255:9993, 1980). However, in the carotid artery, LC 20 phosphorylation correlated with isotonic shortening velocity and crossbridge cycling rate rather than developed stress (Dillon et al., Science 211: 495, 1981). The latter study suggested that the myosin light chain kinase/phosphatase system can arrest the crossbridge cycle in the attached state, maintaining force with high economy while slowing shortening velocity. We tested the applicability of this hypothesis to the rabbit trachealis, where short diffusion distances (<100μm) allow detection of rapid changes in LC 20 phosphorylation and shortening velocity. At 30 sec after stimulation with carbachol, active stress was 0.6 ± 0.12 (SEM) x 10^5 N/m^2 (0.73 F_0) at the optimum tissue length (L_0); shortening velocity at zero afterload (V_0) was 0.37 ± 0.02 L_0/sec, and LC 20 phosphorylation was 0.42 ± 0.02 mol P_i/mol LC 20. However, at 5 min, active stress increased to 0.8 ± 0.1 x 10^5 N/m^2 (0.96 F_0), while V_0 and LC 20 phosphorylation declined to 0.24 ± 0.03 L_0/sec and 0.24 ± 0.004 mol P_i/mol LC 20 respectively. We conclude that the regulatory scheme proposed for arterial smooth muscle may apply to other tonic smooth muscles. [Supported by NIH grants 2P01 HL 19242 and F HL 5991.]

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PHOSPHORYLATION OF MYOSIN LIGHT CHAIN KINASE IN TRACHEAL SMOOTH MUSCLE. J.R. Miller* and J.T. Stull* (SPON: G. Weiss). Univ. Texas Health Science Center, Dallas, TX 75235

Phosphorylation of smooth muscle myosin light chain kinase (MLCK) in vitro by the catalytic subunit of cyclic AMP-dependent protein kinase (C) is accompanied by a decrease in kinase activity at limiting concentrations of Ca^{2+}-calmodulin. This has been postulated to partially mediate relaxation by agents which increase intracellular cyclic AMP. We have developed a method for assessing the extent of phosphorylation of MLCK in intact smooth muscle (SM) based upon the ratio of MLCK activities measured in the presence of low (4 μM) and high (100 μM) concentrations of Ca^{2+}, and 1 μM calmodulin. Phosphorylation of purified MLCK from bovine aortic SM by C produced a decrease in this activity ratio (AR) from 0.79 to 0.21. Incubation of a bovine tracheal SM homogenate with C similarly decreased AR from 0.68 to 0.32. When intact tracheal SM strips were treated for 5-6 min with 5 μM isoproterenol, which relaxes smooth muscle, a smaller but significant ($p < 0.001$) decrease in AR of the extracts, from 0.75 to 0.66, was observed. However, 80 mM KCl and 0.1 μM carbachol, both of which elicit contraction, decreased AR, from 0.79 to 0.57 and from 0.81 to 0.62, respectively. The effects of these agents correspond to relatively small (1.5-2.7 fold) decreases in MLCK sensitivity to activation by Ca^{2+}-calmodulin. Thus, there does not appear to be a clear association between the extent of MLCK phosphorylation and relaxation in tracheal smooth muscle. (Supported by NIH grant HL 26043)

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MYOSIN LIGHT CHAIN PHOSPHORYLATION AND PHOSPHORYLASE a FORMATION DURING CHANGES IN THE CONTRACTILE STATE OF TRACHEAL SMOOTH MUSCLE. P.J. Silver* and J.T. Stull* (SPON: G.B. Weiss), Univ. Tex. Hlth. Sci. Ctr., Dallas, Texas 75235

The activity of phosphorylase kinase and smooth muscle myosin light chain kinase can be regulated by Ca^{2+}-calmodulin or the cAMP system. This study relates temporal changes in phosphorylase a (Ps a) formation and phosphorylation of the phosphorylatable light chain (P-LC) of myosin with isometric tension (I.T.) development in intact strips of bovine tracheal smooth muscle during cholinergic and/or β-adrenergic stimulation. After recording changes in I.T., each strip (15 mg) was quick-frozen and assayed for Ps a levels [activity -AMP/+AMP] and P-LC phosphate content (PC) [mol P/mol P-LC] as shown:

	C;C+I*	C;C+I	C;C+I	C;C+I	C	C;C+I
time	0	15"	30"	1'	2'	3'
I.T. (g)	0;0	3.5;0.8	6.7;1.9	9.7;3.9	11	11;6.3
Ps a†	.16;.40	.33;.50	.45;.63	.61;.56	.59	.58;.61
P-LC PC†	.13;.09	.25;.15	.35;.24	.75;.38	.55	.48;.30

*C=1 μM carbachol; C+I=pretreatment with isoproterenol (5 μM-5') followed by 1 μM C--†$\bar{x}$ values-SEM range from .02-.05.

These results show that increases in Ps a and P-LC PC reach maximal values prior to the development of maximum I.T.; P-LC PC subsequently declines as Ps a and I.T. remain elevated. Isoproterenol alone increases Ps a formation without affecting I.T. and also attenuates carbachol-mediated increases in I.T. and P-LC PC while not attenuating Ps a formation. (Supported by NIH HL26043)

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TEMPORAL RELATIONS AMONG ACTIVE ISOMETRIC FORCE (ΔP_o), cAMP-DEPENDENT PROTEIN KINASES (cPKs) AND PHOSPHORYLASE (P'lase) IN BOVINE CORONARY ARTERIES. P. Galvas*, C. Kuettner*, J. DiSalvo, and R. Paul (Spon.: D.L. Kline) Dept. Physiology, U. of Cincinnati, Coll. of Medicine, Cincinnati, OH 45267

Vascular smooth muscle (VSM) contractility is tightly coupled to ATP production by intermediary metabolism. To elucidate mechanisms underlying coordination of metabolism and contractility we measured the time-course of ΔP_o, activation of cPKs and P'lase in VSM. Strips of bovine circumflex coronary artery were mounted for recording isometric force. The strips were contracted by addition of 30mM KCl (ED_{90}), frozen in liquid freon (-78°C) at 2',3',10',20' and 30' of contraction and homogenized in 20 vols. of buffer. Aliquots were analyzed for P'lase (activity ratio, -/+2mM 5'AMP) and cPKs (activity ratio, -/+2 μM cAMP) activities. ΔP_o increased to maximal values within 6'-10' of contraction and remained constant throughout the period of study. In contrast, P'lase activity increased to approximately 180% of the control value at 3' ($p<.05$) and decreased significantly ($p<.05$) to about 140% of the control value at 20' ($p<.05$). The activities of cPK isozymes-type I and type II-however, did not vary from control values at the same time points. These findings suggest that activation of P'lase during K^+ induced contraction is independent of the cAMP system and may be attributable to Ca^{++} activation of the phosphorylase cascade. The decline in P'lase activity is of particular interest in light of the reported decrease with time in the phosphorylation state of myosin light chains of VSM during contraction, an effect presumably ascribable to an enzyme cascade similar to P'lase in terms of Ca^{++} and calmodulin dependence. Supported in part by NIH 22619, 23240, and 20196.

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EFFECTS OF CALMODULIN (CaM) cAMP-DEPENDENT PROTEIN KINASE (cPK) ON THE Ca^{2+} SENSITIVITY OF SKINNED VASCULAR SMOOTH MUSCLE. J. Caspar Rüegg* and Richard J. Paul, Departments of Physiology University of Heidelberg (FRG) and University of Cincinnati, College of Medicine, Cincinnati, OH 45267.

Recent work on VSM actomyosin has indicated that the Ca^{2+} sensitivity of both ATPase and superprecipitation are affected by CaM and cPK. Using a "chemically skinned" arterial preparation, we have extended these observations to the intact structured contractile system. Media from hog carotid artery was cut into strips approximately 1mm wide, which were fixed at 1.25 slack length and treated at 0°C with an EGTA-isosmotic relaxing solution (RS), RS + 1% Triton X-100, followed by a 50% glycerol-ATP salt solution, in which the strips were stored at -25°C. Small strips (.1-.3mm d.) were teased and relaxed in a Mg-ATP salt solution, pH 6.7, $Ca^{2+} < 10^{-8}$M, 30°C. Ca^{2+} elicited a contraction with an ED50 of 10^{-6}M. Isometric force was between 1-4mN, consistent with the force observed before skinning. With time, the preparation became less sensitive with an increase in ED50 to $10^{-5.7}$M. CaM (4 μM) reverses this loss, stabilizes the preparation and sharply accelerates the rate of tension development. The ED50 in the presence of 4 μM CaM shifts to about 10^{-7}M. This effect is dose-dependent with the half maximal effect at about 0.4 μM CaM. Submaximal Ca^{2+} contractions can be reversibly depressed by preincubation of relaxed fibres with cPK catalytic subunit (300U/ml), even in the presence of 4 μM CaM. An inhibition of about 50% of the contraction at 0.2 μM Ca^{2+} was obtained, whereas only 20% inhibition was found at 6 μM Ca^{2+}. Supported in part by NIH 23240, 22619, AHA 78-1080, and DFG-RU-154/14-1.

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BOVINE AORTIC MYOSIN LIGHT CHAIN PHOSPHATASE D.S. Gifford*, P. Roberts*, and J. DiSalvo. Dept. Physiol., Univ. Cinn. Coll. Med., Cinn., OH 45267

Contraction of a variety of smooth muscles, including vascular smooth muscle, is associated with phosphorylation of the 20,000 dalton myosin light chains (MLC). Moreover, relaxation is associated with dephosphorylation of MLC suggesting that such phosphorylation-dephosphorylation cycles may participate in regulating contractility of smooth muscle. Although information regarding MLC kinases is accumulating rapidly, relatively little is known of MLC phosphatases. We partially purified aortic MLC phosphatase by procedures involving precipitation with $(NH_4)_2SO_4$, and ion exchange and affinity chromatography. The specific activity of the preparation was 0.1-1.0 μmol ^{32}P/mg/min when measured with phosphorylated MLC from bovine cardiac or rabbit skeletal muscle. Phosphorylated aortic myosin was also dephosphorylated but virtually no activity was manifested against a synthetic substrate (p-nitrophenyl phosphate) or phosphorylated histone IIA. Enzymic activity was unaffected by Ca^{++} (.1-5mM) but it was progressively and markedly inhibited by either ATP (.5-8mM), Mn^{++} (1-20mM) or Mg^{++} (1-20mM). However, further purification eliminated sensitivity to Mg^{++} perhaps suggesting that Mg^{++} dependent modulators of MLC phosphatase exist in aortic muscularis. This mammalian MLC phosphatase may function in modulating contractile responses in vascular smooth muscle. (Supported by NIH grant HL20196).

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THE EFFECT OF REPETITIVE STIMULATION ON MYOSIN P-LIGHT CHAIN PHOSPHORYLATION IN SITU. G.A. Klug*, B.R. Botterman*, and J.T. Stull* (SPON: G.B. Weiss), Univ. of TX Hlth. Sci. Ctr., Dallas, Texas 75235

Calcium-dependent phosphorylation of the P-light chain of myosin (P-LC) has been shown to be correlated to post-tetanic potentiation of twitch tension. The purpose of this study was to determine if a similar relationship exists between P-LC phosphorylation and the potentiation of twitch tension observed in the rat gastrocnemius muscle during repetitive stimulation (staircase phenomenon) of the sciatic nerve in situ. The magnitude of P-LC phosphorylation was found to be a function of stimulus frequency as phosphate content increased from a control value of 0.18 mol phos/mol P-LC to 0.52 and 0.80 following 100 pulses at 1 Hz and 20 Hz, respectively. The time course of phosphorylation measured at 5 Hz was characterized by an initial rapid increase during the first four sec (0.18-0.43) followed by a secondary gradual increase (0.43-0.71 over 12 sec). Potentiation of isometric twitch tension displayed a time and frequency dependence similar to that of phosphorylation. Maximum twitch tension increased to 180% of control and 1/2 relaxation time decreased 20% during the period of maximum P-LC phosphorylation whereas contraction time remained unchanged. These data demonstrate that in situ phosphorylation of P-LC can occur with low frequency stimulation with a time course and frequency dependence that would permit myosin phosphorylation to play a role in the alteration of twitch characteristics during low frequency stimulation.

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THE ABSENCE OF A CHANGE IN PHOSPHAGEN LEVELS IN VASCULAR SMOOTH MUSCLE DURING CONTRACTION. J.M. Krisanda and R.J. Paul Department of Physiology, University of Cincinnati, College of Medicine, OH 45267

Active isometric force (ΔP_o) in vascular smooth muscle (VSM) is critically dependent on oxidative metabolism. The rate of oxygen consumption during maintenance of maximal ΔP_o is nearly twice the basal level. Stimulation of oxidative phosphorylation has been correlated with changes in the [ATP] / [ADP] [Pi] ratio in other tissues. We tested the hypothesis that a change in the $[ADP]_{free}$ during contraction is sufficient to stimulate oxidative phosphorylation in VSM. Media strips from porcine carotid artery were equilibrated in Krebs-PSS at 37°C, at l_o where the average ΔP_o, stimulated with 50mM KCl, of 165 9 mN/mm2 (n=13) was attained with a $t_{\frac{1}{2}}$ of 2.0±0.2 min. Strips were rapidly frozen in freon cooled in liquid N_2 at 0, 0.5, 1 and 15 min. after K^+-depolarization. Methanol-EDTA extracts of the frozen tissues were analyzed using an LKB Analytical Isotachophor. Basal [ATP], [ADP] and [PCr] were 0.57 ±0.03, 0.20± 0.02 and 0.79±0.05 μmol/gm wet wt., (n=24). No significant changes from these values were observed during stimulation suggesting that a change in the ADP_{free} does not correlate with the elevated rate of oxidative metabolism. Assuming that the Lohman reaction is in equilibrium (Keq=20), one can calculate using the measured $[Cr]_{total}$ = 2.34 ±0.19 μmol/gm wet wt. (n=4) an $[ADP]_{free}$ of 56 μM, which is similar to values reported for skeletal muscle. In the absence of a detectable change in the $[ADP]_{free}$ during contraction we conclude that alternate mechanisms, such as changes in $[Ca^{2+}]_i$ or $[Pi]_i$, may be operating to couple ΔP_o with oxidative metabolism in VSM. (Supported by NIH 1 F32 HL06051-01, AHA 78-1040 and NIH 23240.)

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IMPARED ENERGY TRANSPORT IN THE MYOCARDIUM OF PHOSPHATE DEPLETED (PD) RATS. N. Brautbar, R. Baczynski*, P. Geiger* and S.G. Massry. Dept. Med., Div. Nephrol., USC Sch. of Med. Los Angeles, Ca. 90033

Myocardial dysfunction occurs in PD but the molecular basis is not understood. Myocardial ATP remains unchanged after 4 and 8 weeks (W) of PD, but fell at 12 W of PD. While CP was reduced at 8 and 12W. Suggesting: intact ATP production but impaired energy transfer. This study examined this question by evaluating mitochondrial function from hearts of PD and control (C) rats, after 4, 8 and 12W. Respiratory control rate was not altered 13.6±1.3, 10.0±1.0, 15.8±1.8 in PD rats vs 15.2±1.8, 12.7±1.7, 17.3±1.0±SE in C at 4, 8 and 12W respectively. ADP:O ratio in PD 3.6±0.12, 3.6±0.7, 3.5±1.0 was not different from C 3.6±0.2, 3.6±0.2, 3.3±0.09 SE. Oxygen consumption QO_2 was significantly reduced in PD rats 65.4±4.0, 82.0±8.0 vs 94.0±10.0, 114.0±9.2 SE nmoles per mg protein. CPK activity was markedly reduced in PD 1.05±0.1, 0.86±0.05, 0.77±0.08 vs 1.71±0.12, 1.5±0.20, 1.6±0.08: SE IU/mg protein ($p<0.01$). The results show: 1) ATP production via oxidative phosphorylation is intact 2) energy transport through the CPK-CP shuttle is impaired. The data suggest that the initial step leading to myocardial dysfunction during PD is impairment in energy transport from mitochondria to cytosolic compartments.

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CHANGING STEADY STATE ATPASE ACTIVITY OF CONTRACTING ACTOMYOSINS. G. Kaldor and W. J. DiBattista*. VA Medical Center, Allen Park, Michigan and Wayne State Univ., Detroit, Michigan.

Previous work done in this laboratory showed that the "extra-phosphate production" of the superprecipitating actomyosins 14 nmole per nmole actomyosins (Physiol. Chem. and Phys. 6, 67, 1974). This "burst" is 7 times higher than the stochiometric "burst" and, therefore, it was difficult to explain on the basis of presteady state phosphate production. A filter was attached to the Durrum Multi-mixing System right after the second mixer. Actomyosin and ATP were mixed in the first mixer and interaction was permitted to proceed in the delay time. After various time intervals the actomyosin was forced through the second mixer and retained on the filter.

The actomyosin was removed from the filter, washed and analyzed for protein and phosphate. This method showed 2 nmoles of phosphate per nmole of actomyosin. Thus the "high extraphosphate production" was not caused by increased "presteady state burst". Analysis of the filtrate showed that the superprecipitating actomyosin during the first 800 millisecond has very high "steady state" ATPase which continuously decreases to the "steady state" level of the "superprecipitated" actomyosin. This initial high ATPase activity of the "contracting" actomyosin was not demonstrated with myosin, NMM, denatured actomyosin and 85% of it was missing when previously superprecipitated actomyosin was used instead of the native protein.

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DIFFERENCES IN F/G ACTIN RATIOS IN VASCULAR AND STRIATED MUSCLES. C.L. Seidel, M. Snabes* and Janis McLeod*. Dept. of Medicine, Baylor College of Medicine, Houston, Texas 77030

Many of the characteristics of smooth muscle contractile proteins are more similar to non-muscle than to striated muscle proteins. Because non-muscle tissues exhibit a low filamentous to globular (F/G) actin ratio, the nature of this ratio in smooth muscle is of interest, both from a comparative and functional standpoint. Rat aorta, gastrocnemius and left ventricular muscles were homogenized under conditions favoring F-actin formation (150mM NaCl, 2mM $MgCl_2$, 5mM K_2HPO_4, 0.2mM ATP, 0.2mM DTT, 0.5% triton, pH 7.6, 4°C). After centrifugation at 2500 xg, the supernatant was analyzed for G-actin by determining its inhibition of DNase I activity relative to that of known amounts of purified G-actin. This determination was made before and after treatment of the supernatant with 1.5M guanindine-HCl (depolymerizes F-actin) and indicates G and total actin, respectively, with the difference being F-actin. The amount of G (% total) was 11 $\pm$ 2, 13 $\pm$ 2 and 39 $\pm$ 5 for skeletal, cardiac and vascular, respectively ($p<0.05$ relative to vascular) giving F/G ratios of 9:1, 8:1 and 2:1. These differences in F/G ratio between smooth and striated muscles may reflect differences in the conditions necessary for actin polymerization, as has been suggested by other investigators, or may reflect differences in the in situ filamentous organization of actin such that smooth muscle actin is more similar to non-muscle actin. (Supported by NIH HL 25349).

TEACHING OF PHYSIOLOGY

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MICROCOMPUTER DEMONSTRATION OF PHARMACOKINETICS. James E. Randall and Donald J. Costello.* Indiana University School of Medicine, Bloomington, 47405.

Biomedical students frequently have difficulty with dynamic concepts, such as the plasma level of a drug as a function of time. Microcomputers can now provide graphic simulations in which hypothesized changes in drug kinetics and dosage regimes may be demonstrated in the lecture room and for individual study. An instructional program has been written which is based upon a single compartment model with single first-order absorption and elimination rates. The program asks for the size of the initial dose, the size and frequency of booster doses, and half-lives of the absorption and elimination processes. Video monitors display the computed plasma concentrations over time spans matched to the concepts being explored. Concepts of loading doses and long-term steady state with multiple doses are much easier to grasp from graphic presentations. Demonstrations also include the effects of different modes of administration and matching doses to half-lives to maintain a desired steady-state concentration.

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Satellite Meeting

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SESSIONS AND ABSTRACTS BY DAY

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PERFORMANCE OF GAS EXCHANGE ORGANS OF VERTEBRATES
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The performance of the various gas exchange organs of vertebrates is determined by a number of factors (J. Piiper and P. Scheid: Internat. Rev. Physiol., vol. 14, 219-253, 1977). The following factors will be analyzed on the basis of specific examples.

(1) The external respiratory medium: water or air.

(2) The magnitude and the nature (tissue, water, air) of the resistance to gas transfer between the external medium and blood.

(3) The arrangement of external medium and blood flow directions at the site of gas exchange (counter-current, cross-current, ventilated pool).

(4) The extent of functional inhomogeneity.

2

ACID-BASE STRESS AND CENTRAL CONTROL OF VENTILATION IN TURTLES.
Bernard M. Hitzig and Eugene E. Nattie. Dept. of Physiology, Dartmouth Medical School, Hanover, N.H. 03755

Central chemical control of ventilation has been demonstrated in the turtle, Pseudemys scripta. It has also been shown that the central response consists of alterations in breathing frequency (f). To assess the effects of hypercapnia and/or anoxia on the central ventilatory response, 3 groups of adult Pseudemys (1-2Kg; n=6/group) were subjected to 2 hrs of nitrogen (N_2) breathing, hypercapnia (8% CO_2 in air), or hypercapnia plus anoxia (8% CO_2 in N_2). Respiratory minute volume ($\dot{V}_E$), tidal volume (V_T), and f were continuously measured. At the end of 2 hrs arterial blood and cerebrospinal fluid (CSF) acid-base variables were measured. Results show that after the 1st .5 hrs f was elevated 2.5 times control in all groups. However, f fell to control values by the end of the 1st hr of anoxia, while rising continually in hypercapnia to 3.1 times control by 2 hrs. Anoxia plus hypercapnia increased f to 2.5 times control which was maintained for 1.5 hrs and then decreased to 1.8 times control during the final .5 hr. $\dot{V}_E$ followed the same pattern as f, while V_T was elevated to similar levels in all groups. These experiments show that after 2 hrs f and therefore $\dot{V}_E$ are not behaving as a single function of CSF pH since it was lowest (7.10) in anoxia plus hypercapnia, slightly higher in anoxia (7.19), and highest in hypercapnia (7.37). Our results strongly suggest that the central effects of anoxia (accumulation of lactate in CSF) produces centrally mediated ventilatory changes in a fundamentally different way than hypercapnia in Pseudemys.

3

EFFECTS OF HYPOXIA ON SEA BASS (Morone labrax).
G M Hughes and S Thomas. Research Unit for Comparative Animal Respiration, Bristol University, Bristol BS8 1UG England and Laboratoire de Physiologie Animale, University de Bretagne Occidentale, Brest, France.

An extracoporeal circulation has been used for continuous recording of arterial P_{O_2}, P_{CO_2}, and pH. Moderate hypoxia (40 mmHg) is accompanied by a respiratory alkalosis, pH_a increases from 8.0 to 8.13 associated with hyperventilation and a fall in P_aCO_2. Blood lactate concentration (0.40 meq.L^{-1}) is unchanged but rises if the ypoxia is continued for 24 hours; pH_a falls to 7.86 and ventilatory frequency increases.
Deep hypoxia (10 mmHg) was sustained for 60 mins during which, following an initial brief increase, pH_a returns to normal levels as lactate concentration rises and metabolic acidosis develops. On return to normoxia there is a very marked decrease in pH_a (8.0 - 7.73) and rise in lactate (6.2 meq.L^{-1}) during the first 5 mins. Recovery of P_aO_2 from levels below P_{insp} is more rapid than recovery of P_aCO_2 associated with residual hyperventilation indicate that the fish is paying-off an oxygen debt because of persistent lactate (4.63 meq.L^{-1}) in the blood 1 hour later. These results will be compared with those obtained with rainbow trout under comparable conditions.

4

RESPONSE TO HYPERCAPNIA OF TRACHEAL AND INTRAPULMONARY AIRWAY STRETCH RECEPTORS IN NEWBORN PUPPIES.
John T. Fisher and Giuseppe Sant'Ambrogio. Dept. of Physiology and Biophysics, U.T.M.B. Galveston, Texas 77550.

We have recorded action potentials from single vagal fibers originating from airway slowly adapting stretch receptors in 3 newborn puppies anesthetized with a mixture of chloralose and urethane, with the chest open and artificially ventilated. Both vagus nerves were cut in the neck and the pressure in the trachea was also recorded. Four slowly adapting stretch receptors, localized in the trachea, were inhibited by carbon dioxide (10% in the inspired air); their discharge in expiration being more affected (15% of control) than that in inspiration (71% of control). Eight slowly adapting stretch receptors were localized within the lung parenchyma and found to remain largely unaffected by carbon dioxide.With carbon dioxide inhalation there were marginal changes,in both directions,of the tracheal pressure with no apparent relationship with the modifications in receptors discharge. Therefore the action of carbon dioxide on airway stretch receptors appears to be quite different in newborn and adult dogs.In fact in this latter group bronchial, but not tracheal stretch receptors, are inhibited by carbon dioxide (Bartlett and Sant'Ambrogio, Respir.Physiol. 26: 91, 1976).

Supported by N.I.H. grant HL-20122.

5

THE EFFECT OF INSPIRED GASES, BODY TEMPERATURE AND BILATERAL VAGOTOMY ON VENTILATION IN SNAKES.
Ronald K. Gratz and Jay B. Dean. Department of Biological Sciences, Michigan Technological University, Houghton, Michigan, 49931.

Water snakes (Genus Nerodia) increase tidal volume (Vt) but decrease respiratory frequency (Fresp) in response to breathing increased concentrations of CO_2 in air (2 - 6% $FiCO_2$). Hypoxic breathing (to 5% FiO_2) elicits the same response. In neither case does oxygen consumption ($\dot{M}O_2$) change significantly. Increased body temperature from 15 to 30°C results in an approximately 8-fold increase in oxygen consumption ($\dot{M}O_2$) but only a 4-fold increase in ventilation ($\dot{V}$), the latter being due almost entirely to an increase in Fresp. Arterial pH changes by a factor of -0.024 units/°C over this temperature range. While breathing 5.2% CO_2 in air, the snakes' arterial pH changes by a factor of -0.034 units/°C over the same temperature range. Bilateral vagotomy results in a markedly increased Vt but a much reduced Fresp in snakes breathing room air. Breathing 5.2% CO_2 following vagotomy produces no further change in Vt but does produce a further reduction in Fresp.

6

THE EFFECT OF BODY TEMPERATURE ON VENTILATORY SENSITIVITY TO CO_2 IN THE ALLIGATOR, A. MISSISSIPIENSIS.
D. G. Davies. Department of Physiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Changes in minute ventilation and blood acid-base balance were measured in 6 conscious alligators during hypercapnia at 15, 25 and 35°C to determine whether body temperature affects ventilatory sensitivity to CO_2. Three definitions for ventilatory sensitivity were used: 1) $\Delta\dot{V}E/\Delta PaCO_2$; 2) $\Delta(\dot{V}E/\dot{V}O_2)/\Delta PaCO_2$; 3) $\Delta(\dot{V}E/\dot{V}O_2)/\Delta\alpha Pr$, where αPr is the fractional dissociation of blood imidazole. Results: $\Delta\dot{V}E/\Delta PaCO_2$ was greater at 35°C than at either 15 or 25°C while $\Delta(\dot{V}E/\dot{V}O_2)/\Delta PaCO_2$ was greater at 15°C than at either 25 or 35°C. However, the values for $\Delta(\dot{V}E/\dot{V}O_2)/\Delta\alpha Pr$ were similar at each temperature. It is concluded that the interpretation of the effect of body temperature on ventilatory sensitivity to CO_2 in the alligator depends on the definition for sensitivity used in analysis. (Supported by USPHS, NIH grant HL 25984.)

7

NARIAL RESISTANCE DURING BUCCAL AND LUNG VENTILATION IN Bufo marinus. Ronald M. Jones, Department of Physiology, Dartmouth Medical School, Hanover, NH 03755.

The external nares rarely close completely during positive pressure lung filling in B. marinus. Simultaneous measurement of airflow at the nares and transnarial pressure revealed continuous airflow (out) during lung emptying (nares open) and the subsequent lung filling (nares partially closed). $\dot{V}_E$ measured at the nares is consistently greater than $\dot{V}_E$ from the lungs because the buccal contents are being simultaneously forced into the lungs and out the partially closed nares.

The relation between narial resistance and ventilatory parameters during hypercapnia was investigated to determine if control of the narial aperture is an important variable related to the volume of air transferred to and from the lungs and buccal cavity. Buccal f decreased (73/min → 30/min) and buccal T_E increased (0.28 → 0.41 sec) when breathing 2% CO2. Mean narial resistance was 0.11 cm H2O/l-min, maximum narial resistance was 0.12 cm H2O/l-min, and both were uninfluenced by CO2.

Lung ventilation f increased with 2% CO2 (5.3 → 20.8/min). T_E of lung ventilation cycles (time for expiratory airflow at the nares) remained constant (about 0.45 sec) while V_{TE}(at the nares) increased from 0.73 → 0.90 ml/100g. Mean narial resistance during lung ventilations decreased from 1.04 to .48 cm H2O/l-min with 2% CO2. Maximum narial resistance during lung ventilations was unchanged. It is concluded that the nares may remain open for a longer proportion of each lung ventilation cycle during hypercapnic hyperpnea.

8

THE RESPIRATORY ROLE OF THE CARDIAC CHRONOTROPIC RESPONSE TO HYPOXIA AND ITS NERVOUS CONTROL IN THE DOGFISH SCYLIORHINUS CANICULA. E.W.Taylor and P.J.Butler, Zoology & Comparative Physiology, University of Birmingham, Birmingham B15 2TT, U.K.

During hypoxia the dogfish exhibits a reflex bradycardia accompanied by an increase in stroke volume such that cardiac output is unchanged except at the slowest heart rates. Cardiac vagotomy abolishes the bradycardia and reveals that it can serve to increase blood oxygen saturation during hypoxia and decrease apparent power output by the heart, thus reducing oxygen demand. Anaesthetised, decerebrate dogfish were infused with a relaxant. The cardiac nerves were exposed via a lateral incision into the anterior cardinal sinus and lifted clear of the blood flowing along the floor of the sinus. En passant activity included small units firing continuously at 2-4 sec^{-1} and larger units which fired in bursts of 5-8 spikes per burst at approximately 2 second intervals. These bursts were synchronised with ventilatory movements of the pharynx and may serve to optimise the concurrence of periods of most rapid flow of blood and water over the counter-current gas exchange system at the gills. When the level of relaxant was increased in order to reduce ventilatory movements the bursts decreased in frequency and number of spikes and could be abolished. Occasional events such as a 'cough' or violent expiration, were accompanied by a burst of activity in the cardiac vagus and cardiac slowing. During hypoxia there was a bradycardia accompanied by an increase in the rate of firing of the small units to 10 sec^{-1}.

9

Neuroepithelial cells in fish gill primary lamellae: a possible O_2 sensor. P. Laurent, S. Dunel-Erb* and Y. Bailly.* LPCR, CNRS,* BP20CR, 67037 Strasbourg, France.

Falck and Hillarp method reveals numerous yellow-fluorescent aminergic cells within the gill primary epithelium. Cells are isolated or clustered and supported by the epithelial basal lamina but they never reach the external medium. They are found exclusively on the internal side of the lamellae facing the respiratory water flow. With the electronmicroscop these cells are found to contain granular vesicles of 80 to 100 nm, they have a round nucleus and clear cytoplasm. Sometimes basal part of the cell threads its way through interrupted basal lamina down to subepithelial region. Nerve profiles displaying a green fluorescence are consistently found close to the granular cells. With the electronmicroscop nerve terminals are seen crossing the basal lamina finally ending on vesiculated cells. These terminals display granular and agranular vesicles and are in direct contact with the cells. Specific membrane alterations are suggestive of efferent synapses. These neuroepithelial cells remind neuroepithelial bodies of lung airways in mammalian and submammalian Vertebrates as well as carotid bodies type I cells. Structure and localization are suggestive of an external O_2 sensor.

10

Significance of unidirectional ventilation for avian pulmonary gas exchange. P. Scheid, Abteilung Physiol. Max-Planck-Inst. f. exp. Med., D 3400 Goettingen,FRG

Airflow through the open-ended parabronchial tubes of avian lungs is unidirectional, i.e. assumes the same flow direction during both inspiration and expiration (cf. Scheid, 1979). Although theoretical and experimental evidence predict independence of gas exchange efficacy on flow direction in the isolated parabronchus, the effect of unidirectional, as opposed to bidirectional, ventilation is to reduce the respiratory air shunt (equivalent to alveolar dead space ventilation). In fact, with bidirectional flow, the entire cranial air sac ventilation would by-pass the parabronchi. Further reduction in respiratory air shunts with unidirectional ventilation is provided by the following functional valving mechanisms for which recent experimental evidence has been provided: (1) No inspiratory flow from main bronchus into ventrobonchi; (2) No (or little) expiratory flow from caudal air sacs through main bronchus, past parabronchi. It is concluded that the unidirectional ventilation, in conjunction with the functional valving, is advantageous for pulmonary gas exchange in the avian respiratory tract.

Scheid, P.: Mechanisms of gas exchange in bird lungs. Rev. Physiol. Biochem. Pharmacol. 86: 137-186, 1979.

11

EFFECTS OF DEAD SPACE ON CAUDAL AIR SAC GAS COMPOSITION IN THE GOOSE. M.R. Fedde, R.E. Burger*, J. Geiser*, R.K. Gratz*, J.A. Estavillo* and P. Scheid. Dept. Physiol., Max Planck Inst. Exp. Med., D-3400 Göttingen, W. Germany.

The relative contributions of gas exchange by neopulmonic parabronchi and reinhalation of dead space gas to the high CO_2 and low O_2 concentrations in the caudal air sacs is currently under debate. We altered the dead space in adult, anesthetized geese and observed the influence on ventilation, air sac gas concentrations and arterial blood gases. Changing the dead space from low values (about 3 ml, by allowing the bird to inhale through its mouth or tracheal cannula and exhale out a clavicular air sac cannula) to high values (>100 ml, by adding tubing to the tracheal cannula) caused a marked increase in V_T, $\dot{V}_I$ and V_D/V_T ratio but very little change in respiratory frequency, effective ventilation, arterial blood gases and pH, O_2 and CO_2 concentrations in end-expired, clavicular or cranial thoracic air sac gases, and respiratory exchange ratio (R) in these gases. There were progressive increases in $[CO_2]$ and decreases in $[O_2]$ and R values in the gas of the caudal thoracic and abdominal air sacs with added dead space, with larger R values in the abdominal than in the caudal thoracic air sac gas. CO_2 concentration was approximately 2 to 2.5% greater in these sacs than predicted if the CO_2 came only from reinhaled dead space gas. We conclude that a significant proportion of the CO_2 in the caudal air sacs is derived from gas exchange in the neopulmo and that there are different $\dot{V}/\dot{Q}$ ratios in the exchange system leading to these two sacs.

12

Effects of changes in lung $[CO_2]$ on the timing and amplitude of the ongoing breath in awake Roosters. T.L. Clanton, G.O. Ballam, R.K. Moore, A.L. Kunz. Ohio State University Department of Physiology, Columbus, Ohio 43210.

The breathing patterns of birds appear to depend in part upon feedback from intrapulmonary chemoreceptors which can be stimulated by changes in $[CO_2]$ within the lungs (F_LCO_2). In an attempt to study the reflex effects of stimulation of these receptors, we have given brief pulses or step changes of F_LCO_2 in the gas blowing through the lungs of unidirectionally ventilated roosters and observed the effects on the pattern of the ongoing breath. Within 200 to 500 msec., a noticeable change in inspiratory or expiratory airflow occurred; increases in F_LCO_2 caused airflow and tidal volume to increase while decreases in F_LCO_2 caused airflow and tidal volume to decrease. Expiratory duration (T_E) was prolonged by decreases in F_LCO_2 and shortened by increases, whereas inspiratory duration (T_I) was not appreciably altered. When the amplitude of the steps was changed, the responses changed almost proportionally. When the time in which pulses were given within the breath cycle was changed, the response often reached a peak at mid-cycle. The results are consistent with a first order model coupling F_LCO_2 and respiratory motor output. (Supported in part by NHLBI Grant HL23780 and Central Ohio Heart Chapter, AHA).

13

LIMITATIONS OF GAS EXCHANGE IN AVIAN LUNGS. Frank L. Powell and Peter D. Wagner. Dept. of Med., Univ. of Calif., San Diego, La Jolla, CA 92093

To better understand gas exchange in bird lungs, the effects of $\dot{V}/\dot{Q}$ inequality on O_2 and CO_2 exchange in cross-current lungs were studied using a computer model which incorporated physiologic dissociation curves and the Bohr-Haldane effect. Q was considered uniform along a cross-current gas exchange unit, viz. parabronchus, and inhomogeneity was introduced between parabronchi. Acutely increasing the standard deviation (σ) of log normal distributions of $\dot{V}$ or $\dot{Q}$ reduced both O_2 and CO_2 transfer quantitatively similarly to alveolar lungs. In steady state, CO_2 transfer is less affected by inequality in that the negative $(E-a)O_2$ predicted for homogeneous cross-current lungs is abolished at σ=0.5, but the negative $(a-E)CO_2$ persists to σ=1.2. The consequences of $\dot{V}/\dot{Q}$ maldistribution as determined with the multiple inert gas elimination technique in 3 normoxic geese were also modeled. $(E-a)O_2$ was positive, in contrast to ideal cross-current predictions, but $(a-E)CO_2$ was negative similar to log normal model predictions for mild (σ=0.6) $\dot{V}/\dot{Q}$ inequality. However, modeled $(E-a)O_2$ was always more negative than measured differences suggesting that other factors besides $\dot{V}/\dot{Q}$ inequality (e.g. diffusion impairments) may reduce normoxic O_2 exchange efficacy in birds. This latter finding is in contrast to healthy men or dogs under similar conditions.

14

GAS EXCHANGE DURING HIGH FREQUENCY VENTILATION OF THE CHICKEN. R.B. Banzett and J.L. Lehr*, with the technical assistance of B.A. Geffroy. Harvard School of Public Health, Boston, MA 02115.

High frequency ventilation (HFV) at 1 to 30 Hz is capable of maintaining adequate gas exchange in humans and dogs with tidal volumes substantially less than dead space. We evaluated the effectiveness of gas exchange in the avian lung by comparing CO_2 elimination during various frequencies and tidal volumes of HFV with CO_2 elimination during conventional mechanical ventilation. Anesthetized adult roosters were tracheotomized and paralyzed. Approximately sinusoidal oscillations were applied at the tracheal cannula and their amplitude was determined by integrating the output of Fleisch pneumotachograph calibrated to 30 Hz. A bias flow provided fresh gas at the top of the tracheal cannula. CO_2 concentration was measured in the exiting bias flow. Three conclusions emerge from the data. 1) HFV enhances gas transport in the chicken, as it does in mammals. 2) At low oscillatory flows (amplitude x frequency) CO_2 elimination depends on both frequency and tidal volume, while at higher flows CO_2 elimination depends almost entirely on tidal volume. The flow at which this transition occurs is relatively lower than in humans and much lower than in dogs. 3) HFV at volumes below dead space is usually not capable of maintaining adequate gas exchange in the chicken in contrast to results in dog and man. (Supported by NIH grants HL14580 and HL26566)

15

EFFECTS OF CO_2 AND AIR SAC VOLUME ON THE ACTIVITY OF MEDULLARY RESPIRATORY NEURONS OF THE CHICKEN. E.K. Michal, G.O. Ballam, and A.L. Kunz. Dept. of Physiol. Ohio State University, Columbus, Ohio 43210.

Much is known about rapid pulmonary reflex responses to changes in CO_2 concentration and stretch in birds. The afferent limb of these reflexes has been studied and the functional characteristics of intrapulmonary chemoreceptors described. Much is also known about the effector response of these reflexes; but little is known of the information processing within the CNS, which connects the two limbs. This is a preliminary report on a study investigating these reflexes through extracellular recordings of the activities of neurons in the medulla of the chicken. Decorticate, upright, unanesthetized roosters were stereotaxically positioned for neural recording. Breathing movements were recorded by measuring sternal position and air sac pressure. During unidirectional ventilation, the insufflated CO_2 concentration and air sac volume could be altered independently. The effects of steady state and pulsed changes were studied. Both inspiratory and expiratory units were recorded. Most decreased firing rate when $[CO_2]$ was decreased and increased firing rate when $[CO_2]$ was increased. These changes occurred within 300 msec of the $[CO_2]$ change at the trachea. Expiratory units were responsive to stretch inputs, increases in volume causing excitation. Supported by NHBLI Grant #HL 23780.

16

EFFECT OF CARDIOVASCULAR VARIABLES ON HYPERPNEA DURING RECOVERY FROM DIVING IN DUCKS. Richard Lillo and David R. Jones. Zoology Dept., University of British Columbia, Vancouver, B.C., Canada.

Control of hyperpnea during recovery from diving in unanesthetized White Pekin ducks, Anas platyrhynchos, was examined. Post-dive minute ventilation ($\dot{V}_E$) increased 5 times regardless of the length of the preceding dive (1-4 min) although longer dives resulted in slower return of ventilation towards pre-dive levels. Manipulation of arterial blood gases showed that both hypoxia and hypercapnia contributed to hyperpnea on emergence. Although chronic bilateral carotid body denervation depressed $\dot{V}_E$ before and after diving, $\dot{V}_E$ still increased 4 times after 1 min dives. Post-dive hyperpnea was accompanied by dramatic elevations in heart rate, cardiac output, and the ventilation/perfusion ratio. However, artificially maintaining heart rate at abnormally low levels did not affect the post-dive hyperpnea. In addition, post-dive hyperpnea was unaffected by systemic arterial baroreceptor denervation. Post-dive hyperpnea in ducks depends on blood gas changes occurring during a dive yet a substantial part of the response is independent of input from carotid body chemoreceptors and the accompanying rises in heart rate and cardiac output.

17

DEPOSITION AND CLEARANCE OF INHALED AEROSOL IN THE RESPIRATORY TRACT OF CHICKENS. George A. Mensah*and Joseph D. Brain, Department of Physiology, Harvard School of Public Health, Boston, MA. 02115.

Sixteen unanesthetized adult White Leghorn hens (Gallus domesticus), were exposed to an aerosol of ^{99m}Tc labelled submicrometric particles and sacrificed 0, 1, 12, or 36 hrs later. The amount and distribution of radioactive particles retained in the lungs and skeletal system were measured to describe regional deposition and clearance. There was deposition in the air sacs and skeletal system immediately after exposures. Reduction in activity with time suggested clearance of aerosol from the pneumatized bones. Aerosol particles were not distributed uniformly within the lungs; there was greater retention in the caudal regions. No dorsal-ventral gradients were observed. Of the initial lung deposition, only 54 ± 13.9% (S.D.) remained at one hr post-exposure, however, 35.6 ± 20.9% (S.D.) remained 36 hrs later. There was no statistically significant decline in retention between 12 and 36 hrs post-exposure. These data suggest an early fast phase of lung clearance followed by a slower phase. Detailed morphological studies are needed to understand the underlying clearance mechanisms and the basis for the differences in regional deposition. (Supported by NIH grants ES-01016 and ES-00002).

18

EFFECT OF $[CO_2]$ CHANGES ON VOLUME TIME THRESHOLD (VTT) CURVES IN CHICKENS. G.O. Ballam, T.L. Clanton and A.L. Kunz. Dept. of Physiology, Ohio State University, Columbus, OH 43210.

We have previously demonstrated that in birds, both the I→E and E→I phase switches are triggered by the bird's volume crossing a threshold value, which changes with time. The present study was to determine if these volume thresholds are CO_2 dependent. Awake, White Leghorn roosters were unidirectionally ventilated with rates of inspiratory and/or expiratory air flows that could be mechanically limited. The $[CO_2]$ of the insufflated gas was then raised or lowered ½ to 1% for a period of 2 minutes. VTT curves were generated by repeating this CO_2 step at a variety of inspiratory and expiratory flow rates and measuring threshold during 5 breaths immediately after the step and then again 60 to 90 seconds later. In response to step increases in $[CO_2]$: I→E VTT curves showed a small shift initially to either the left or right, followed by a larger shift to the right after 60 seconds; while the E→I VTT curves shifted immediately to the right. In response to step decreases in $[CO_2]$: I→E VTT curves shifted first to the right and then later to the left of control curves; while E→I VTT curves shifted initially to the right and later further to the right. Summary: Changes in lung or arterial $[CO_2]$ shift the VTT curves for both I→E and E→I. For the I→E VTT curve, the early shift is in a different direction than the later. Therefore, during normal ventilation, $[CO_2]$ may affect T_I and T_E by changing VTT in addition to changing respiratory motor output. (Supported in part by NHLBI Grant HL23780 and Bremer Foundation).

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INTRAPULMONARY CO_2 RECEPTOR DISCHARGE AT DIFFERENT LEVELS OF VENOUS CO_2. R.D. Tallman, Jr. and F.S. Grodins. Dept. of Biomedical Engineering, U.S.C., Los Angeles, Calif. 90007

It has been suggested that avian intrapulmonary CO_2 sensitive receptors (IPC) may be capable of affecting ventilation in response to changes in lung CO_2 load. The purpose of this study was to record IPC discharge activity in spontaneously breathing ducks when venous P_{CO_2} was elevated or lowered from resting levels. Venous CO_2 loading and unloading was accomplished using an extracorporeal veno-venous blood circuit which included a 0.25 m^2 silicone membrane blood oxygenator and heat exchanger. Adult, male Pekin ducks (3.06 kg avg. wt.) were Urethane anesthetized and tracheostomized. Single unit vagal activity was recorded from 23 IPC. During the loading state, the rate of CO_2 excretion was increased to twice the resting level. There was no difference in the IPC discharge during CO_2 loading as compared to the control discharge despite an increase in end-tidal P_{CO_2} of 14 torr. Similarly, venous CO_2 unloading was without affect on IPC discharge. Peak inspiratory and expiratory tracheal flow did increase during CO_2 loading and decrease during unloading. This finding may explain how IPC discharge remains high despite large increases in lung CO_2 flux. (This work was supported by HL07012).

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EFFECT OF CAROTID BODY DENERVATION ON THE CARDIAC RESPONSE TO SPONTANEOUS DIVING IN TUFTED DUCKS. P.J.Butler and A.J.Woakes, Dept. Zool. & Comp. Physiol., Univ. of Birmingham, Birmingham B15 2TT, England.

In intact tufted ducks there is an immediate reduction in heart rate, upon spontaneous diving, from its elevated pre-dive level. There is then a slow increase during the remainder of the dive so that after 10-15s, heart rate is similar to that recorded when the duck is swimming fairly vigorously at the surface. The carotid bodies were effectively denervated, as indicated by the abolition of the ventilatory responses to hypoxia and hyperoxia. Qualitatively the cardiac response to spontaneous diving was not altered, although heart rate was higher during all stages of diving after carotid body denervation. This difference was at its greatest towards the end of the dive. It is concluded that the carotid bodies are not involved in the initial reduction in heart rate from its elevated level upon diving but that they do exert some inhibitory influence on the heart particularly during the latter stages of submersion.

21

CONTROL OF RESPIRATORY PATTERN IN EXERCISING FOWL. J. Brackenbury, M. Gleeson and P. Avery. Univ. of Salford, Salford M5 4WT, England.

Mean ventilation ($\dot{V}$), respiratory rate (f) and tidal volume (V_T) were measured between the 5-10th minutes of treadmill exercise at speeds of 1.24-4.3 $km.h^{-1}$ and environmental temperatures of 13±2°C and 35±2°C. At 13°C the increases in $\dot{V}$ with work load were brought about mainly by increased f, V_T increasing by less than 25% except during maximal exercise. At 35°C the resting f was higher and V_T lower than at 13°C but increases in $\dot{V}$ with work load were produced mainly by increased V_T. At maximal work loads respiratory pattern was similar at both temperatures. Comparison with the steady-state respiratory responses at rest to combined hyperthermia and hypoxia/hypercapnia suggests that interaction between CO_2-dependent and thermal factors is important in determining respiratory response to exercise. (Supported by U.K. Science and Agricultural Research Councils).

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ACTION OF VARIOUS AMBIENT FACTORS ON CO_2 AND IONIC EXCHANGES AND BLOOD ACID BASE BALANCE IN WATER BREATHERS: A STUDY ON CRAYFISH. Pierre Dejours. CNRS, 67087 Strasbourg, France.

The branchial CO_2 output and the acid base balance, ABB, of the hemolymph in the crayfish Astacus leptodactylus depend on several factors in the ambient water: 1) oxygenation; 2) ionic composition, particularly [Cl]; 3) titration alkalinity, TA; 4) P_{CO_2} and pH; 5) temperature. Changing the first four factors in directions which either increase or decrease hemolymph pH and P_{CO_2} resulted in extreme values of the hemolymph ABB. The table shows the composition of three waters at 13 °C and the corresponding hemolymph P_{CO_2} and pH. Line A is the reference water and hemolymph ABB. Line B and C show the effects on hemolymph ABB of changing the first four factors either side of the reference water values.

	Water (13 °C)					Hemolymph	
	Cl^- meq·L^{-1}	TA meq·L^{-1}	P_{CO_2} Torr	pH	P_{O_2} Torr	P_{CO_2} Torr	pH
A	1.0	5.0	0.80	8.39	152	2.53	7.84
B	9.7	0.5	2.0	6.99	550	8.91	7.69
C	0.20	10.0	0.30	9.07	40	0.77	8.34

23

A COMPARATIVE STUDY OF THE FUNCTION OF EMBRYONIC CHICKEN HEMOGLOBIN IN SOLUTION AND RED CELLS. R. Baumann, Zentrum Physiology, Medizinische Hochschule Hannover, F.R.G.

The O_2-binding curve of early embryonic chicken blood, is bi(poly)phasic, reflecting the presence of the 4 embryonic hemoglobins (HbP, P', M, E). The "n"-value of the O_2-binding curve changes continuously from < 1 at low O_2-saturation to a maximum value of ~8 at the middle to high O_2-saturation range. The high cooperativity in the middle and upper range of the O_2-binding curve, is coupled with a low O_2-affinity (P_{50} ~84 mmHg at day 6 and pH7.4 37°C), but arterial oxygenation is unimpaired. At day 6 80% of total hemoglobin bound O_2 can be released at a PO_2 >40 mmHg, thus creating excellent conditions for diffusion. Between 3-6 days of development, the position and form of the O_2-binding curve change continuously, although the concentration of red cell ATP and the hemoglobin pattern remain stable. In purified embryonic hemolysate (or with the isolated embryonic hemoglobins) at physiological concentrations of H^+, ATP, and hemoglobin, one cannot simulate the O_2-binding curve of embryonic red cell suspensions. Under these conditions the O_2-affinity of the isolated embryonic hemoglobins is still 3 to 4 times higher than that of blood and likewise the n-value never exceeds 3. Freshly prepared hemolysate shows, however, the same binding characteristics as whole blood. Additional experiments indicate that embryonic red cells contain other low molecular weight factors, not competitive with organic phosphates, that reduce the O_2-affinity and increase the cooperativity of embryonic hemoglobins P and P' probably by promoting tetramer-tetramer aggregation. Supp. by DFG SFB 146.

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ERYTHROCYTIC ORGANIC PHOSPHATES IN AMPHIBIANS AND REPTILES. V.H. Hutchison, A.G. Hughes* and E.S. Hazard*. Univ. of Oklahoma, Norman, Oklahoma 73019

Concentrations of organic phosphates (2,3-diphosphoglycerate {DPG}, nucleoside triphosphates {NTP}, inositol pentaphosphate {IPP}, and total phosphate (P_{tot}}) within the erythrocytes of 55 species of amphibians and reptiles were determinded by enzymatic and/or ion exchange chromatographic methods. Qualitatively and quantitatively the organic phosphate concentration of amphibian erythrocytes ranged from reptilian to mammalian values. All species of amphibians examined had DPG. The DPG:Hemoglobin (Hb) molar ratios ranged from 0.07 - 1.9. DPG concentrations exceeded NTP concentrations in 18 species. NTP was primarily adenosine triphosphate (ATP); the mean guanosine triphosphate:ATP ratio was 0.128. NTP:Hb molar ratios ranged from 0.32 - 1.3. IPP was detected in only 5 species of amphibians and never exceeded a molar ratio of 0.03. Molar ratios of organic phosphates correlate with aerobic scope for activity in amphibians. NTP (primarily ATP) was present in high concentrations in all species of reptiles examined. The NTP:Hb molar ratios always exceeded 0.81 and ranged up to 3.93. IPP was present in lesser concentrations in all turtles examined except softshelled turtles (Trionyx). Substantial concentrations of DPG were observed only in erythrocytes of softshelled turtles, where DPG:Hb molar ratios ranged from 0.63 - 1.29.

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CAN THE GAS GLAND OF TELOSTS SECRETE HIGHLY DIFFUSIBLE GASES? Brian G. D'Aoust and Wayne A. Gerth. Virginia Mason Research Ctr., Seattle WA 98101

Inert gas secretion into deep-sea fish swimbladders evidently proceeds by the countercurrent multiplication (ccm) of minute dissolved gas tension differences between counterfluent blood in the arterial and venous limbs of the *rete mirabile*. For the inert gases, these A-V gas tension differences are induced via the salting out effect (soe) presumed to be due to the addition of lactic acid to the rete venous blood as it circulates through the gas gland. Theoretical treatments of this mechanism currently consider only radial gas diffusion between the rete arterial and venous capillaries, while diffusion along the rete capillary axes is neglected. This axial "back diffusion," which tends to short-circuit ccm and reduce the maximum attainable swimbladder gas pressures and gas secretion rates, is an insignificant feature of rete countercurrent performance only when the rete capillary blood flow velocities exceed twice the ratio of the gas diffusion coefficient in the blood plasma to the effective capillary diameter. Thus, in a given rete countercurrent system, backdiffusion imposes a more severe limitation on countercurrent performance for highly diffusible gases such as H_2 and He than for less diffusible gases such as N_2 and Ar. Recent theoretical estimates of rete countercurrent performance based on measurements of the soe of lactic acid in water indicate that in order to account for the production of observed swimbladder N_2 pressures in some deep-sea species, the rete capillary blood flow velocities must be in the range where N_2 backdiffusion is important. The latter result suggests that gases more diffusible than N_2 may not be secreted into the swimbladders of these species. This suggestion can be tested for a given species by measuring the swimbladder gas compositions in specimens pressurized to a hydrostatic pressure of 10 atm in water equilibrated at 1 atm with N_2 and He.

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COMPARATIVE ASPECTS OF OXYGEN DELIVERY AND RESISTANCE TO ANOXIA IN TURTLES AND RATS. Thomas J. Sick, Peter L. Lutz, Joseph C. LaManna and Myron Rosenthal. Depts. of Neurol. and Marine Sci., Univ. of Miami, Miami, FL. 33101.

The minimum pO_2 that an animal can endure is determined by the tissue in which oxidative metabolism is most critical. For air-breathing vertebrates, this is the central nervous system but causes of this sensitivity remain unknown. In these studies, we compare metabolic and electrophysiological changes in brains of animals extremely sensitive to anoxia (rat) with brains of animals which show great endurance to anoxia (turtle). Such changes were recorded in situ by reflection spectrophotometry and electrode probes for tissue pO_2 and K^+. In both species, N_2 respiration produced decreases in tissue pO_2 accompanied by reduction of cytochrome a,a$_3$. In rat, maximal changes occurred within 3-4 min while in turtles, such responses required up to an hour. In contrast to rapid EEG suppression and large efflux of K^+ seen during anoxia in rat, EEG and K^+ remained near control levels (2-4 mM) during anoxia in turtle brain. Difference spectra showing redox changes of many mitochondrial enzymes obtained under normoxic and anoxic conditions were similar in the two species, demonstrating that resistance to anoxia in these two species does not result from differences in mitochondrial components. Rather, other pathways for producing cellular energy appear sufficient to maintain ion homeostasis during long periods of inhibition of oxidative metabolism. This capacity may provide a basis to evaluate the vulnerability of mammalian brain to oxygen deprivation. (Suppported by PHS grants NS16655, NS14325, NS14319 and NS06300)

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INTERPRETING OXYGEN DISSOCIATION CURVES IN VERTEBRATES WITH CENTRAL VASCULAR SHUNTS. S.C. Wood. University of New Mexico School of Medicine, Albuquerque, N.M. 87131

The oxygen equilibrium curve of blood (O2EC) is conventionally drawn as % Sat. = f(PO2). However, when the O2EC is determined in vitro by the "mixing-method", PO2 = f(% Sat). The principle of this method should also apply in vivo if venous admixture occurs. Therefore, PO2, the independent variable of open systems (tonometers or pulmonary capillaries), becomes the dependent variable in closed systems (mixing syringes or central shunts). Furthermore, arterial PO2 (PaO2) for a given % Sat. should be inversely related to Hb-O2 affinity. For a given reduced % Sat. due to shunt, a right-shifted O2EC will provide increased PaO2. This, in turn, could increase the rate of O2 diffusion to tissues. Limiting factors of this hypothesis are environmental PO2 and lung (or gill, skin) O2 diffusing capacity. The presence of low Hb-O2 affinity in many amphibians and reptiles (the "shunt" vertebrates) is indirect support of the hypothesis. Direct support is limited but shows increasing PaO2 (at constant % Sat.) with decreasing Hb-O2 affinity due to species differences or increased temperature

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RELATIONSHIP OF PULMONARY MEMBRANE DIFFUSING CAPACITY (DMO_2) TO DLco IN THE TURTLE (P. scripta elegans). Barry Burns. MIEMSS, University of Maryland, Baltimore, Maryland 21201

Turtles (1 kg n=5) were anesthetized (Ketamine, 120 mg/kg, i.m.), tracheostomized and the rebreathing DLco measured at two levels of inspired O_2 (hematocrit = 15-25%)in the upright position at 23-25°C. Following this, the turtles were inverted, a 4 cm square hole cut in the plastron and the lungs perfused through the pulmonary artery with Na dithionite (DTT, 80 mM) solution (4 mg% albumin, 375 mOs) at 14-20 torr pulmonary artery pressure (25 °C). Rebreathing measurements of DMO_2 were made during DTT perfusion (JAP, 46 (1): 100, 1979). Results: The mean DLco (± S.E.M.) was 0.033 (± .0015) and 0.019 (± .0021) ml/min/torr STPD, at ca. 20% alveolar O_2 and 70% alveolar O_2, respectively. $DLco/V_L$ ratios were 0.00028 and 0.00017, respectively also. The DTT DMO_2 averaged 0.128 (± .0087) and the DMO_2/V_L ratio was 0.004 (± .00022). DMO_2 was only approximately 4 times larger than the normoxic DLco, indicating less "diffusion reserve" for gas exchange than in the mammalian lung, possibly reflecting the reduced aerobic metabolic requirements of poikilotherms and the increased thickness or diffusion resistance of the alveolar-capillary membrane.

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RESPIRATORY PROPERTIES OF BLOOD OF SKIN-BREATHING AMPHIBIANS. Robert Blake Reeves. Dept. of Physiology, School of Medicine, SUNY, Buffalo, N. Y. 14214.

Plethodontid salamanders lack lungs or gills; gas exchange occurs by diffusion across skin and buccopharyngeal surfaces. Exercise begets respiratory and metabolic acidosis. How is red cell Hb O2-carriage adapted to these conditions? Local specimens of Desmognathus ochrophaeus and Gyrinophilus porphyriticus, pithed after cooling, had blood samples withdrawn from the conus arteriosus. Normal acid-base conditions were presumed to be pH 7.75 at 25 degrees C. Complete dynamic oxygen equilibrium curves at 1, 2 and 4% CO2 were determined on thin (6 μm) whole blood films using a fiber optic dual-wavelength spectrophotometer (558/536 nm) and platinum electrode oximetry.

	#	BW(g)	P50(7.75)	Δlog P50/ΔpH	n
Gyrinophilus	7	6-21	25.6 ± 1.14	-0.23	2.24
Desmognathus	5	3-7	23.2 ± 1.52	-0.21	2.10

Isoelectric focusing disclosed distinctive Hbs. Gyrinophilus gave 4 peaks (pI & % total Hb:7.02, 61; 6.97, 27); Desmognathus IEF showed individual variation in Hbs present. Curve shapes were flattened providing a constant Beta ($\Delta S/\Delta P$) over saturation range .05 to .80. Uniform Beta and low Bohr effect assist O2 loading in activity even at low ambient PO2's. (Supported in part by NIH Grant PO1-HL-14414.)

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THE CO_2 AND FIXED ACID ROOT EFFECT IN BLOOD OF THE EEL, ANGUILLA ANGUILLA. M.P. Hlastala, C.R. Bridges, G. Riepl and P. Scheid. Max Planck Institut für exp. Med., Göttingen, Fed. Rep. of Germany and Univ. of Washington, Seattle, WA 98195.

The pH dependent desaturation of eel blood (Root effect) was separated into its fixed acid and CO_2 components. Pooled blood samples were divided into equal aliquots and acid-base status was adjusted either by equilibrating with varying P_{CO_2} (P_{CO_2} range - 0.0 torr to 74.0 torr) or by adding 0.15N ECl or 0.15N $NaHCO_3$ at a P_{CO_2} of 2.2 torr (pH range - 5.0 to 8.6). Equilibration P_{O_2} was held at either 148, 370, or 666 torr. Blood samples were analyzed for pH and oxygen content (Lex-O_2-Con). Analysis was performed at 15°C and 25°C.

Oxygen saturation decreased in a sigmoid shaped fashion as pH was reduced from 8.6 to 5.0. For 15°C, the reduction in oxygen content was to 45% of maximum HbO_2 content with ½ of the effect occurring at pH of 7.4. For 25°C, the reduction in oxygen content was to 26% of maximum HbO_2 content with ½ of the effect occurring at pH of 7.1. The decrease in oxygen saturation was independent of P_{O_2} between 148 and 666 torr. At pH>6.0, the effects of fixed acid and of CO_2 were indistinguishable. At pH<6.0, CO_2 had an independent effect further reducing oxygen content. The independent CO_2 effect was more important at 25°C than at 15°C.

We conclude that: 1) the Root effect is not an exaggerated Bohr effect, 2) there is an independent CO_2 Root effect at pH<6.0, 3) the Root effect is more important at 25°C than at 15°C.

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CHANGES IN EGGSHELL CONDUCTANCE AND PORE AREA AFTER TRANSFER OF HENS FROM AN ALTITUDE OF 3800 TO 1200 M. H. Rahn, T. Ledoux, C. V. Paganelli, and A. H. Smith. State University of New York at Buffalo, NY, White Mountain Research Station and University of California at Davis, CA.

Past evidence has shown that in birds incubating at altitude the total pore area of their eggshells is decreased in direct proportion to the barometric pressure, thus compensating for the increased diffusivity of gases at altitude and providing a normal shell conductance. Such adaptation would ensure a normal incubation water loss which appears to be mandatory for hatching success. Here we report shell conductance and pore dimensions of eggs of White Leghorn hens before and after they were transferred from 3800 to 1200 m. Within two months after their transfer the shell conductance and total pore area had increased in nearly direct proportion to the increased barometric pressure, from 480 to 657 torr. These observations of reacclimation provide additional evidence of an active structural adaptation to changes in altitude and the time required for this manifestation.

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INCUBATION OF CHICKEN EGGS UNDER HYPERBARIC CONDITIONS. Harold S. Weiss and Joseph F. Pitt*. Dept. of Physiology, The Ohio State University, Columbus, OH 43210

Fertilized chicken eggs incubated at 2 and 4 atmospheres pressure absolute (ATA) do not develop normally. At 2 ATA, hatch size was 40% and at 4 ATA only 4% of hatch size at 1 ATA (normal ground level controls). A common characteristic of eggs incubated at hyperbaric pressures was retention of fluid, as indicated by decreased weight loss during incubation. Eggs at 2 ATA lost ½ and those at 4 ATA ⅓ the weight of the 1 ATA eggs, which averaged 0.4 to 0.5% loss/day. The decreased weight losses in hyperbaria follow closely the prediction of the Chapman-Enskog equation for water vapor diffusion through gas filled pores of fixed area and length, as is presumed to exist in the eggshell. The problem of hatching in hyperbaria might therefore be alleviated by increasing shell pore area. An attempt was made to increase pore area by carefully grinding away parts of the calcified shell over the air cell, leaving the outer shell membrane intact. Progressive removal of shell resulted in progressive increase in weight loss during incubation, reaching as high as 3-4 times normal. For 1 ATA eggs, hatch decreased with increasing egg weight loss, as expected. For both 2 ATA and 4 ATA incubations, hatch tended to increase as egg weight loss increased, up to a loss approximately equivalent to that of intact 1 ATA eggs. Thereafter, continuing weight loss resulted in decreasing hatch. Peak hatch at 2 and 4 ATA remained low, however, at about 60% and 40% of controls, respectively.

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O_2 TRANSPORT IN REPTILIAN EMBRYOS. C.P. Black, G.F. Birchard, G.W. Schuett, and V.D. Black. Dept. of Biology, Univ. of Toledo, Toledo, OH 43606.

Our laboratory is undertaking a long-range project to describe O_2 transport from atmosphere to tissues in embryonic reptiles, both oviparous and viviparous. One feature which distinguishes oviparous and viviparous forms is a difference in the barriers to O_2 diffusion for the embryo. Thus, the O_2 transport characteristics of egg shells and chorioallantoic membranes versus those for the oviduct-placenta complex could become very influential in determining factors such as rates of embryonic O_2 consumption, development patterns and growth rates, and the respiratory characteristics of embryonic blood. Initial data from eggs of the Burmese Python show a shell structure which is highly porous (G_{H_2O} = 1040 mg H_2O/day·torr, 36X greater than predicted for a bird egg of similar mass), but which also has shell interstices filled with a layer of liquid water. Preliminary data suggest this layer may present a barrier to O_2 diffusion. Blood respiratory characteristics for python embryos just prior to hatch show P_{50} = 38 torr (pH = 7.4, T = 32°C), Bohr factor = -0.32, and Hct = 30.5. Comparative data from other oviparous and viviparous species will be presented.

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METABOLIC COST OF INCUBATION IN THE LAYSAN ALBATROSS AND BONIN PETREL. G. S. Grant, G. C. Whittow, and T. N. Pettit. University of Hawaii, Honolulu, HI 96822.

Whether birds increase their metabolism above resting level during incubation has been debated. In the present studies incubation and resting metabolism were compared in two species of Procellariiformes on their breeding grounds on Midway Atoll in the central Pacific Ocean. The Laysan Albatross (Diomedea immutabilis, ca. 3.0 Kg) nests on the ground and the Bonin Petrel (Pterodroma hypoleuca, ca. 0.18 Kg) nests in burrows. In both species incubation metabolism ($\dot{V}_{O_2}$) was 5 - 7% less than the resting value. Respiratory quotients during incubation were .68 and .73 in the albatross and petrel, respectively, suggesting ketogenesis and utilization of fat during the long fasts (24 days for the albatross and 7 days for the petrel) which are characteristic of the incubation bouts of these birds. Reduced energy expenditure during incubation is associated with a decrease in activity levels and a drop in body temperature of 1 - 2°C. (Supported by NSF Grant PCM 76-12353.)

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HEN EGG OUTER BARRIER GAS CONDUCTANCE IS MODIFIED BY ENVIRONMENTAL HUMIDITY. Amos Ar, Charles V. Paganelli, Gilbert S. Grant, Hermann Rahn and Johannes Piiper. Dept. Physiol., State Univ. of NY at Buffalo, NY 14214, and Dept. of Physiol., Max Planck Inst. Exp. Med., D-3400 Göttingen, W. Germany.

CO_2 and O_2 conductances in N_2 or He mixtures of eggshells with membranes were measured simultaneously in shell hemispheres, using CO_2 and O_2 electrodes. CO_2 diffused from the saturated interior outwards, and O_2 diffused inwards. Outer atmosphere was dry or humidified. Water content of the shell and its membranes was determined in different humidities. Pressure differences between air-cell and ambient atmospheres were determined with a differential pressure transducer. CO_2 and O_2 gas conductances were reduced by the water-saturated atmospheres to 0.72 ± 0.1 SE (n=5) and 0.77 ± 0.1 SE (n=5) and their dry atmospheric values respectively. CO_2/O_2 conductance ratios in dry atmospheres is 1.075 ± 0.025 SE (n=10) times that of saturated atmospheres. The shell and its membranes increase in water content by 0.6 mg/% RH ± 0.07 SD. Pressure in air-cells of 6 eggs was +6.5 Pa ± 1.5 SD and +25.0 Pa ± 7.8 SD in dry N_2 and He mixtures respectively. It was negative (-0.6 Pa ± 0.2 SD) in saturated atmospheres. Conductance reduction corresponds to reduction in gas spaces due to occupation by water. Changes in CO_2/O_2 conductance ratios correspond to the enhanced CO_2 and hindered O_2 diffusion in the convective flow that must have been generated by the pressure difference (Supported in part by NIH grants ROI-HL-18022 and POI-HL-14414, and the Minerva Foundation.

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PHYSIOLOGIC ADAPTATION TO HYPOXIA IN THE AVIAN EMBRYO: METABOLIC, RESPIRATORY, AND TISSUE. G.K. Snyder, C.P. Black, and G.F. Birchard. Dept. of EPO Biology, U of Colo. Boulder, CO.

In avaian embryos O_2 transport is a three-step process: 1) diffusion through shell and membranes from atmosphere to chorioallantoic capillary blood, 2) convective transport by blood to tissue capillaries, 3) diffusion from tissue capillaries to cells. Therefore, adaptation to hypoxia potentially may occur at any or all of these steps. Embryos from a seal-level species (canada goose-Branta canadensis) and a high-altitude species (bar-headed goose-Anser indicus) were incubated under either moderate (P_{O_2}=125 torr) or severe P_{O_2}=95 torr) hypoxia. Hypoxic tolerance was determined as critical P_{O_2}, and shell, blood and selected tissues were examined for evidence of hypoxic adaptation. Severe hypoxia incubation significantly improved hypoxic tolerance in canada embryos while no difference could be detected between treatments with bar-head embryos. Bar-head embryos had significantly greater tolerance than either group of canada embryo. Egg O_2 and H_2O conductance values were lower in bar-heads, but were unaffected by hypoxic treatment. Hematologic values were similar in all groups, but bar-head blood had higher Hb-O_2 affinity throughout development. Skeletal muscle capillary density was significantly higher in bar-head and severely hypoxic canada embryos, but myoglobin levels showed no difference. Adaptation to hypoxia in avian embryos therefore appears to occur at blood and tissue levels, but not within shell and shell membranes. (Supported by NSF)

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HIGH ALTITUDE INCUBATION OF CHICKEN EGGS. BASIC ASPECTS AND THEIR APPLICATION. A.H.J. Visschedijk. Vet. Physiol., Univ. of Utrecht, Netherlands.

Gas transport across gas filled pores of a bird egg shell is limited by diffusion. The transfer rate is determined by the partial pressure gradient and the effective egg shell conductance. The latter is inversely related to the barometric pressure and increases with altitude. Embryos in eggs, laid at sea level and incubated at altitude, thus show dehydration, hypoxia, hypocapnia, reduced gaseous exchange and poor hatchability. According to Fick's law of diffusion it can be shown that gaseous exchange at altitude is normalized when respiratory gas tensions on the air space are restored to sea level values and when, simultaneously, the partial pressure gradients of O_2, CO_2 and H_2O are reduced in accordance with the increase of the shell conductance. This condition is achieved by an increase of the ambient O_2 and CO_2 concentrations and of the relative humidity. Sea level incubators are ventilated with an air flow of at least 200 times the embryonic CO_2 production. Maintenance of the latter ventilation at altitude requires huge amounts of O_2 and CO_2. However, to economize on gas supply ventilation can be kept at the minimal value at which the embryos create their own optimal ambient CO_2 concentration. The gas mixture supplied should consist of air enriched with O_2 only.

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COMPENSATING PROCESSES FOR METABOLIC AND RESPIRATORY ACID-BASE DISTURBANCES IN THE CHICK EMBRYO. H. Tazawa. Dept. of Physiol. Yamagata Univ., Yamagata 990-23, Japan

The avian embryo is a unique experimental subject for study on compensation of acid-base disturbances, because it has no respiratory organ performing the convective ventilation. To produce metabolic disturbances, a hypertonic electrolyte solution must be infused through a catheter implanted in blood vessel. A volume of solution to be infused and of blood to be sampled is not negligible compared with the total blood volume (TBV) of the embryo. The preliminary experiment was designed in 16-day embryos to investigate the effect of electrolyte infusion and repetitive blood sampling on hemodilution which might influence the acid-base balance. The repetitive sampling which diminished the TBV to about 2/3 induced hemodilution without significant change in acid-base balance. The infusion of isotonic saline solution whose volume equaled about 5 % of TBV produced hemodilution causing dilution acidemia. The dilution acidemia was also induced by hypertonic infusion. The embryo was recovered from the acidemia in 6 hrs after infusion. On the basis of the preliminary study, the metabolic acid-base disturbances were made by administration of $NaHCO_3$ or NH_4Cl solution. The time course of the change in acid-base status shifted almost along the Pco_2 isopleth and returned to control level in 6 hrs. The respiratory acid-base disturbances which were made by exposing the egg to high CO_2 environment or to $He-O_2$ atmosphere were compensated after 3-6 hrs. The plasma $[HCO_3^-]$ seemed to be regulated by Pco_2 of blood.

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THE DYNAMICS OF THE DEVELOPMENT OF TISSUE OXYGEN IN THE EMBRYONIC NERVOUS SYSTEM. Bradford T. Stokes. Dept. of Physiology, Ohio State University, Columbus, OH 43210.

We have characterized and mapped the oxygen microenvironment of the embryonic spinal cord as it spontaneously changes during development and during manipulations designed to provoke changes in spinal cord blood flow. We have used an oxygen microelectrode system whose characteristics (tip diameter < 1.0 μm; oxygen consumption in room air < 1.0×10^{-14} amps) allow us to monitor tissue oxygen (T_{PO_2}) in small volumes and at low partial pressures. In spite of lower metabolic requirements (decreasing neuronal activity) and the relatively constant oxygen consumption of this tissue, tissue PO_2 fell by 70% from 15 to 19 days in ovo. Embryos who had pipped into the air space had a considerably greater T_{PO_2}. In a 10% oxygen environment, T_{PO_2} fell most rapidly in the 19 day embryos; the decline toward low PO_2 values was markedly prolonged (> 100 sec) at 15 days. Nineteen day embryos also had the greatest ability to increase their T_{PO_2} values above their own control values in the post-hypoxic period. The application of adenosine to the embryonic spinal cord usually provoked stage dependent increases in T_{PO_2}. Such reactions were most dramatic at day 15 and 19; at 17-18 days, such a response was absent. Changing modes of tissue metabolism coupled with blood flow dynamics may explain relative sensitivities to hypoxic insults during this period. (Supported by USPHS NS-10165 and NSF BNS-7905756.)

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EFFECTIVE DIFFUSIVITIES OF WATER VAPOR IN TERNARY MIXTURES CONTAINING N_2-O_2, $He-O_2$, and SF_6-O_2. C. V. Paganelli and H. K. Chang. State University of New York at Buffalo, Buffalo, NY, and McGill University, Montreal, Que., Canada.

We used the eggshell model to determine effective diffusivities of water vapor as a function of fractional composition in gas mixtures containing N_2-O_2, $He-O_2$, and SF_6-O_2. Water vapor fluxes at 25°C through the porous shells of intact, non-metabolizing hens' eggs were measured gravimetrically in gas mixtures whose fraction of O_2 was varied systematically from 0 to nearly 100% O_2, with either N_2, He, or SF_6 making up the balance. Effective diffusivity of water vapor was practically independent of fractional composition in N_2-O_2 mixtures, but varied significantly with fractional composition in both $He-O_2$ and SF_6-O_2. Experimentally determined values of effective diffusivities compare well in most cases with those calculated from the Wilke equation. If the data are viewed in another fashion, measured water vapor fluxes agree well with those predicted from multicomponent diffusion theory. (Supported in part by USPHS Grant 5-P01-HL 14414.)

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THE INITIATION OF PULMONARY RESPIRATION IN A BIRD EMBRYO: TIDAL VOLUME AND FREQUENCY. Ted N. Pettit and G. Causey Whittow. Dept. of Physiology, University of Hawaii, Honolulu, HI 96822

Pulmonary ventilation in paranatal embryos of the Wedge-tailed Shearwater (Puffinus pacificus), measured with a barometric plethysmograph, revealed a progressive rise in tidal volume (V_T) and minute volume ($\dot{V}_E$) during the paranatal period to achieve hatchling levels. V_T and $\dot{V}_E$ in internally pipped eggs (penetration of air cell) was 0.06 ml ± 0.03 (S.D.) and 3.11 ml·min^{-1} ± 1.80, respectively. Ventilation was significantly higher ($p < .05$) in eggs with pip-holes (V_T = 0.15 ml ± 0.04 and $\dot{V}_E$ = 7.09 ml·min^{-1} ± 2.76). A significant difference ($p < .05$) was also obtained for V_T and $\dot{V}_E$ between paranatal embryos and hatchling chicks. The respiratory frequency (f) was approximately 45 breaths·min^{-1} for both embryos and chicks. Acute changes in ventilation were examined in response to 2% CO_2, 5% CO_2, and 10% CO_2 in air. For paranatal embryos, V_T increased significantly ($p < .05$) only with 10% CO_2 and was accompanied by a significant decrease ($p < .05$) in f. Hatchling V_T increased significantly ($p < .05$) with each test gas and $\dot{V}_E$ increased significantly ($p < .05$) with acute exposure to 5% CO_2, from 16.5 ml·min^{-1} ± 2.0 in normoxic air to 53.9 ml·min^{-1} ± 8.6. The shearwater paranatal embryo is relatively insensitive to high levels of CO_2, suggesting a respiratory adaptation to naturally inspired air cell gas concentrations during internal rebreathing.

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TOLERANCE OF VARIATION IN EGGSHELL CONDUCTANCE AND DIFFUSIVE GAS EXCHANGE IN WILD AVIAN EMBRYOS. Cynthia Carey, Dept. of EPO Biology, University of Colorado, Boulder, CO 80309

Birds breeding at high elevations are confronted with a reduction in barometric pressure which enhances the diffusive flux of gases by increasing their diffusion coefficients. A reduction in eggshell conductance of eggs of wild birds breeding at high elevations relative to sea level controls has been interpreted as a necessary adjustment to offset the increased diffusivity of CO_2 and water vapor from the egg. Such adjustment has been assumed to be mandatory to prevent mortality, since chicken embryos exhibit high mortality if exposed to significant variation in rates of gaseous diffusion. This study tested the tolerance of embryos of red-winged blackbirds (Agelaius phoeniceus) to variation in gaseous diffusion. Eggshell conductances of birds breeding at 1600, 2400, and 2900 m were varied by poking 2 holes in the eggshell or by covering the aircell with wax on day 1 of incubation. Daily water loss, eggshell conductance, final water content on day 10, and hatching success were monitored. These manipulations significantly varied the rate of water loss from control values. Hatchability was very high except in some 2-holed shells, suggesting that embryos of wild birds are more tolerant of variation in eggshell conductance than previously appreciated.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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$30 lay public
Credits Available

Review of the natural history of HSV infections; neurological, ocular, and dermatological complications; management of the pregnant woman and neonate; chemotherapy; comfort measure; and trends in treatment.

Multidisciplinary Short Courses
Sept. 1981 - Jan. 1982
University of California, San francisco
Fees: $65
Credits Available

These short courses address issues of health care, health policy, and health care delivery.

Continuing Education in Health Sciences Certificate Programs:
Patient Education
Health of the Family
Health and Aging
Volunteer Management
Sept. 1981 - June 1983
University of California, San Francisco
Credits Available

Certificate programs designed to build on present skills and increase the knowledge base of practitioners in specific fields. In each certificate program eight two-day courses will be given over a two-year period. Courses must be taken sequentially on specified dates.

For Program Information:
University of California
Continuing Education in Health Sciences
24 Kirkham
San Francisco, CA 94143
(415) 666-3904

For Registration Information:
University of California
Continuing Education in Health Sciences
1308 Third Avenue
San Francisco, CA 94143
(415) 666-2894

USA NATIONAL COMMITTEE FOR THE INTERNATIONAL BRAIN RESEACH ORGANIZATION

ANNOUNCEMENT OF TRAVEL AWARDS

The USA National Committee for the International Brain Resarch Organization (IBRO) is sponsoring a travel grant program to benefit American scientists who could not attend the First World Congress of IBRO in Lausanne, Switzerland, April 1-6, 1982, without such assistance. A limited number of grants will be available. Those eligible to apply for awards are qualified scientists who are citizens or permanent residents of the United States of America, and who plan to participate fully in the Congress. Federal employees are not eligible for this award program. Each applicant will be judged on the merit of his contribution to the Congress in Lausanne, and also on his training, experience and potential. Priority will be given to young scientists. Grants will be in the range of $700-900 depending upon airport of departure and return.

Requests for application forms should be addressed to:

USA National Committee for IBRO
Attention: June S. Ewing, Staff Officer
Division of Medical Sciences
National Research Council
Washington, D.C. 20418

Deadline for postmark of completed application is November 6, 1981.

To the degree that it is possible, successful applicants will be notified by December 15, 1981.

1982 CLINICAL PHARMACOLOGY AWARD OF $200,000 OFFERED

The Burroughs Wellcome Fund is offering a Clinical Pharmacology Award for 1982 in the amount of $200,000, payable in annual installments of $40,000.

The Award is available to U.S. medical schools to support a clinical pharmacologist who will initiate and develop a new Division of Clinical Pharmacology; or, alternatively, to provide for the salary of a faculty member in an established Division. The program is designed to supply supporting funds for the discipline, needed even more today than when The Burroughs Wellcome Fund began its pioneering program over twenty years ago. A total of 34 Clinical Pharmacology Awards have been made.

Applications for the 1982 Award will be accepted until October 1, 1981

Selection of the Burroughs Wellcome Scholar in Clinical Pharmacology will be based upon the recommendation of the Advisory Committee, under the chairmanship of Dr. A. McGehee Harvey. The other members are: Sir Arnold Burgen, Dr. Alfred Gilman, Dr. Carl W. Gottschalk, Dr. Howard H. Hiatt, Dr. David M. Kipnis and Dr. John A. Oates.

The 1981 Clinical Pharmacology Award was made to the Mayo Medical School on behalf of Richard M. Weinshilboum, M.D.

The 1982 Award recipient will be announced in early spring 1982.

The Burroughs Wellcome Fund is a private nonprofit foundation, supported by Burroughs Wellcome Co., pharmaceutical manufacturers, and is located in Research Triangle Park, North Carolina.

SHORT COURSES AT WOODS HOLE

MARINE BIOLOGICAL LABORATORY, Woods Hole, Massachusetts, will conduct a series of residential laboratory courses in the fall of 1981 as follows:

October 18-23, 1981, *Liquid Scintillation Counting in Biology and Medicine,* Instructor in Chief, Yutaka Kobayashi, New England Nuclear Corp.; November 1-6, 1981, *Protein Analysis by Polyacrylamide Gel Electrophoresis,* Raymond E. Stephens, Marine Biological Laboratory and Boston University; November 15-20, 1981, *Biological Electron Microscopy for Technicians,* Morton D. Maser, Marine Biological Laboratory; November 29-December 4, 1981, *Quantitative Analysis of Electron Micrographs,* Lee Peachey, University of Pennsylvania; December 6-11, 1981, *Small Computers in Biomedical Research,* Larry Palmer, University of Pennsylvania; December 6-11, 1981, *Optical Microscopy and Imaging in the Biomedical Sciences,* Robert Day Allen, Dartmouth College.

GASTROENTEROLOGY RESEARCH GROUP SYMPOSIUM

Time & Place: November 6, 1981; 8:00-10:00 PM
Place: Hyatt Regency, Chicago
Title: Cellular Protein and Membrane Processing
Moderator: Dr. Robert Glickman, Chief of GI Unit, Columbia University College of Physicians & Surgeons
1st Speaker: Dr. Gunter Blobel, Professor of Cell Biology, Rockefeller University
Title: Translocation and Integration of Proteins Across & Into Membranes.
2nd Speaker: Dr. Marilyn Farquhar, Professor of Cell Biology & Pathology, Yale University School of Medicine
Title: Multiple Pathways of Intracellular Membrane Traffic.

COUNCIL OF ACADEMIC SOCIETIES BRIEF

ASSOCIATION OF AMERICAN MEDICAL COLLEGES • 1 DUPONT CIRCLE NW • WASHINGTON DC
(202) 828-0400 SPRING, 1981 VOL. 6., NO. 3

The CAS Brief is prepared by the staff of the AAMC Council of Academic Societies and is distributed through the auspices of your member society.

PROPOSED RESEARCH TRAINING CUTBACKS. In an unexpected move, the Reagan Administration has proposed to rescind $59.5 million from the NIH research training budget for the current year. Congress had approved, and NIH was operating on, a training budget of $194.4 million. Thus, Administration proposals, if accepted by Congress, would reduce the 1981 research training budget by 31%. OMB Director David Stockman said this reduction would be accomplished by removing all institutional allowances and the 8% indirect cost recovery rather than by reducing numbers of trainees.

Institutional allowances are used to pay for trainee travel and laboratory costs, to buy books, and to support partially the training program directors. They were instituted by NIH and Congress to enable institutions to provide a richer training environment than is possible on a program of fellowships alone. Veteran Hill staffers were amazed at the cleverness of the OMB move but not surprised given the implacable opposition of OMB to Federal support of biomedical research training.

In related actions, Congress prepares to review the research training authority (National Research Service Awards) which expires this year. It came as no surprise that the Republican-controlled Senate health Committee's NRSA bill (S. 800) provides a research training authorization of only $150 million--a level consistent with the OMB proposal to cut research training. It was very surprising, however, when Congressman Henry Waxman introduced a House NRSA bill that also accepts the Republican Administration's reduced funding ceiling for training.

FEDERAL BUDGET PROPOSALS FOR FY1981 AND FY1982. Budget and Appropriations Committees in both Houses of Congress are diligently working out details of Federal spending levels for the current fiscal year and for next year. The Senate Budget Committee adopted a budget resolution (Senate Concurrent Resolution 9) that was subsequently approved by the entire Senate. The Senate resolution directs the appropriating and authorizing committees to reduce spending this year by $14.7 billion and recommends extremely meager spending levels for the next two years. The passage of this bill in the Senate puts enormous pressure on the Senate Appropriations health subcommittee to approve the President's rescission requests for NIH and other programs of importance to the medical schools and to reduce drastically spending for controllable health programs next year.

In the House, there appears to be a higher degree of skepticism that health, education and other so-called people programs must be sacrificed in order to restore economic well-being in the country. On April 6, House Budget Committee Chairman Jones proposed an alternative Federal budget. Representative Jones indicated that his proposal supports "our national investments in human capital--in education and skills and health." When the House Budget Committee marked up its resolution, which will be voted on in the House shortly, it recommended partial restoration of many of the proposed rescissions and funding reductions for programs of interest to the medical schools. The House Appropriations health subcommittee just recently considered the FY1981 rescissions, and although the results have not yet been made public, it is understood that the Subcommittee did not approve all the rescissions requests, particularly in the research and research training areas.

1981 FALL MEETINGS—NOVEMBER 1-2—WASHINGTON, D.C.

SINGLE ROUTE TO LICENSURE CREATES CONTROVERSY. The proposal by the National Board of Medical Examiners and the Federation of State Medical Boards that there be a single route to licensure through a sequence of two examinations has generated discussion and controversy. The NBME has had a Comprehensive Qualifying Examination (CQE) under development for the past several years and the Federation has made a preliminary commitment to have the CQE be the first examination in the sequence (FLEX I).

At a presentation by the National Board at the 1981 CAS Interim Meeting, it was evident that the CQE cannot evaluate the technical skills, interpersonal skills and attitudes that faculties of accredited U.S. medical schools evaluate repeatedly by direct observation of a student's performance. The proposition that passing the FLEX I will assure that graduates are competent to care for patients in a graduate medical education programs is open to serious question.

Acting on the advice of the CAS Administrative Board, the AAMC's Executive Council has requested that the Federation and the National Board not proceed with the implementation of the proposed two examination sequence for licensure. An ad hoc Committee, chaired by Carmine D. Clemente, Ph.D., former chairman of the CAS, is developing an alternative proposal to ensure that graduates of schools not accredited by the Liaison Committee on Medical Education meet educational achievement and professional preparedness standards equivalent to those met by graduates of U.S. medical schools. For further information, call August G. Swanson, M.D., Director of the Department of Academic Affairs at 202-828-0430.

HOUSE AND SENATE MANPOWER BILLS INTRODUCED. In late February, Representative Henry Waxman (D-Ca), chairman of the health subcommittee, introduced H.R. 2004 which is essentially the same health manpower bill that passed the House last year by an overwhelming margin. One month later, Senator Orrin Hatch (R-Ut), chairman of the Senate health committee, introduced S. 799--a manpower bill that calls for a reduction in Federal support for medical education. The House and Senate proposals are markedly different: the House proposal is generally supportive in most areas of importance to medical schools and their students; the Senate proposal is very stringent and terminates or greatly reduces support for medical education programs.

H.R. 2004 reauthorizes with minor revisions the current health manpower law with the major exception that it phases out medical school capitation. The proposed phase out would mean that schools would receive approximately $400 per student in FY1982, $200 per student in FY1983, and no capitation support in FY1984. The House bill continues support for the existing special project grant program and includes generally favorable student aid provisions.

S. 799 terminates medical school capitation and greatly reduces support for several programs of importance to the medical schools: primary care residencies, area health education centers, departments of family medicine, and assistance for students from disadvantaged backgrounds. The Senate bill limits access and funds for student financial aid. If the Senate bill's student aid proposals were adopted and coupled with the Reagan Administration's plan to limit access to Guaranteed Student Loans, medical students would be forced to turn to the high-interest HEAL loan program, now running at 18%, and would not have the option currently available for some HEAL borrowers to consolidate their loans at a more reasonable interest rate.

GENERAL REQUIREMENTS FOR GRADUATE MEDICAL EDUCATION RATIFIED. After five years of debate, a revision of the General Requirements of the Essentials of Accredited Residencies has been ratified. The revision requires greater institutional accountability for the quality of sponsored graduate medical education programs than do the previous requirements. The ACGME has also provided the authority to determine the examination standards that are acceptable for graduates from foreign schools to be eligible to enter accredited graduate medical education programs. Copies of the revised General Requirements are available by writing to the Secretary of the Accreditation Council for Graduate Medical Education, 535 North Dearborn Street, Chicago, Illinois 60610.