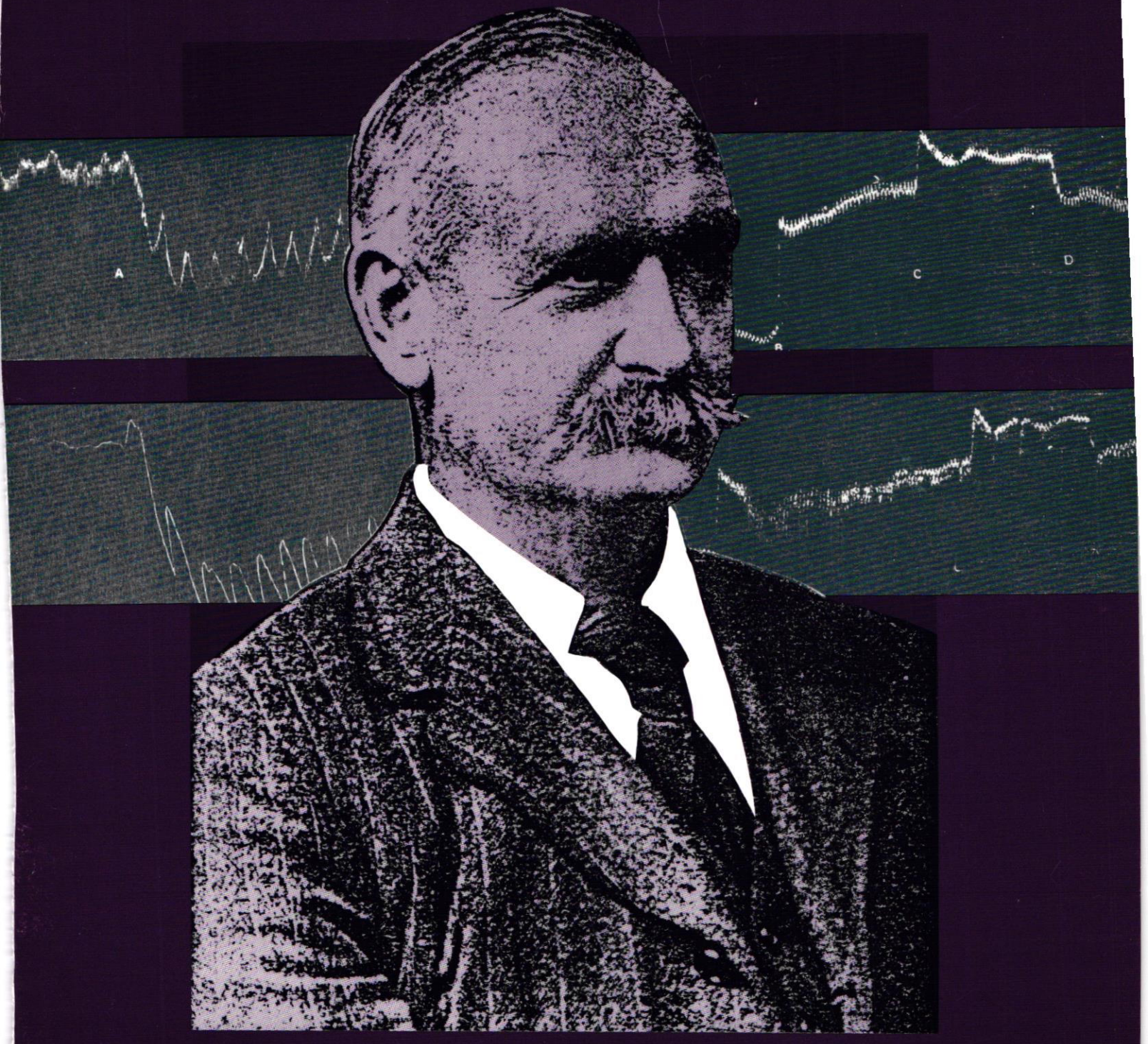
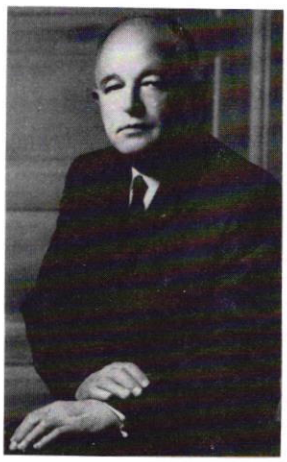
NASA

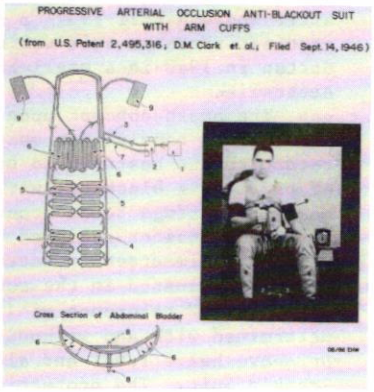
Proceedings of the Eighth Annual Meeting of the IUPS Commission on Gravitational Physiology

A Supplement to The Physiologist Volume 30, Number 1 February 1987

Published jointly by the American Physiological Society and the National Aeronautics and Space Administration







Figs. 2 and 3

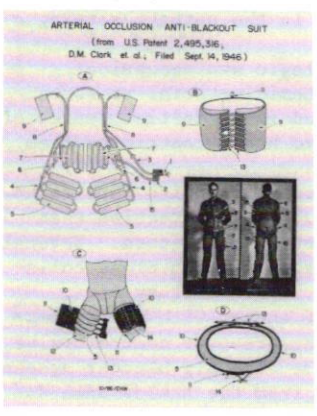
60 pounds per square inch pressure source. The resulting, very rapidly progressive high pressure inflation of the bladder system from the ankles to the abdomen was controlled by a pressure shut-off line from the top of the abdominal bladder, which regulated the final level of pressure according to the level of acceleration. This pressure was set to the presumed arterial occlusive level of 150 mm of Hg at 1.5G and increased automatically by 50 mm of Hg per G above this level--so, for example, at 5G the final suit pressure was about 325 mm Hg (9).

The average protection afforded by this suit of 2.1G was more than double the protection afforded by the Frank's suit. Addition of arterial occlusive arm cuffs in effect converted the subject to a heart-lung-head preparation and increased the average level of protection to 2.9G against visual systems and decrease in blood content of the ear (9).

The so-called simple arterial occlusion suit (Figure 4) which consisted of arterial occlusive cuffs on both thighs and arms, plus a highly effective abdominal bladder, was nearly as effective as the progressive arterial occlusion suit. A somewhat simpler version of this suit, without the arm cuffs, which could be worn over a conventional light-weight flying suit, was also fabricated and tested (Figure 5).

The effectiveness of the progressive arterial occlusion suit as well as the M-1 voluntary straining maneuver was documented in a series of restricted reports and acceleration physiology movies filmed on the Mayo human centrifuge and in a specially instrumented dive bomber during World War II.

Inflation of these suits to arterial occlusive pressures was accompanied by considerable



Figs. 4 and 5

discomfort. In spite of their high degrees of protection, pilots at that time did not consider blackout to be a sufficient problem to warrant use of such uncomfortable garments.

Consequently, these very high pressure anti-G suits were never used operationally. However, physiologic studies of the effects of separate inflation of the leg, abdominal and, in some suits, the arm cuff components of the pneumatic bladder system, and varying the size, location and pressures to which these individual components were inflated, provided the basis for fabrication by Mr. David M. Clark in 1943 of the so-called simple single pressure bladder system (Figure 6). This bladder system, or closely similar variants thereof, when incorporated into various coverall, trousers or externally worn skeleton-type garments, and its associated single pressure G activated valve has been the basis for all operationally used suits during World War II and up to the present (3,9,13).

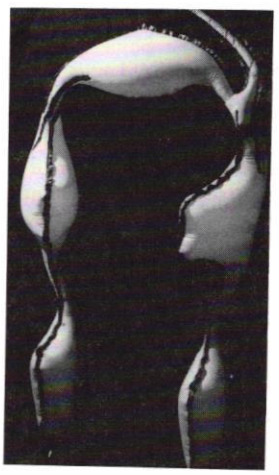


Fig. 6

Fig.7

Centrifuge tests demonstrated that increasing the area or the inflation pressure to which the bladder system was inflated and/or snugness of fit of the garment into which this bladder system was incorporated increased its effectiveness as an anti-G suit (13). Unfortunately, increasing any one or all of these factors also increased the discomfort associated with G-suit use. The relatively ineffective skeleton type suit (Figure 7) which is still used today (4,9) was the result of a compromise between these factors during World War II (16).

The most effective of these simplified suits, the so-called Model 21, incorporated the single pressure bladder system into a closely fitting inelastic trousers. In multiple bioassay-type tests (17) in the centrifuge and in flight, the average protection afforded by this suit was 1.9G (18,19).

Direct recordings of arterial pressures in 1945 (Figure 8) obtained simultaneously at heart

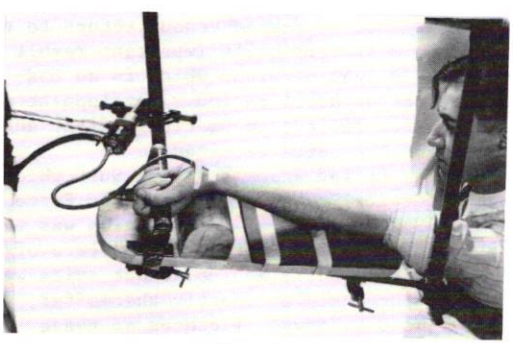


Fig. 8

DEVELOPMENT OF METHODS FOR PREVENTION OF ACCELERATION INDUCED BLACKOUT AND UNCONSCIOUSNESS IN WORLD WAR II FIGHTER PILOTS. LIMITATIONS: PRESENT AND FUTURE

Earl H. Wood
Department of Physiology and Biophysics
Mayo Medical School
Rochester, Minnesota

During World War II and up to the relatively recent past, use by fighter pilots of an anti-G suit combined with voluntary straining maneuvers were considered to provide adequate protection against acceleration induced losses of vision (blackout) and the much more serious (but thought to be relatively rare) losses of consciousness (1-3).

However, multiple recent crashes of current high speed, very maneuverable fighter planes, due to pilot $+G_z$ induced losses of consciousnesss (GLOC) during sustained high acceleration simulated combat maneuvers indicate that the physiologic capabilities of the pilot and his supporting anti-G suit are being exceeded and will be increasingly so in future, ever higher performance fighter planes (4,5).

Consequently, if sustained very high G maneuvering capability fighter planes provide important tactical advantages, more effective methods for prevention of black-out and GLOC in the pilots of these planes are urgently needed.

In the conventional sitting position, a fighter pilot's primary defense against blackout is his anti-G suit which he can supplement by voluntary straining maneuvers up to the limit of his physiologic capabilities (2).

Although the ultimate effectiveness of the combined use of a G suit and voluntary straining maneuvers are subject to the limitations of human cardiovascular and pulmonary physiology, the currently used U.S. Air Force anti-G suit does not approach this limit. This is remarkable since more effective anti-G suits and associated automatic inertial suit pressure control valves were fabricated and tested during World War II (6,7).

However, in spite of its known relatively low protective value, the current externally worn Air Force anti-G suit was adopted over 40 years ago mainly because of pilot acceptance. This acceptance resulted from its convenient donning and doffing characteristics, the minor degree of discomfort associated with its inflation during exposure to acceleration, and more importantly that GLOC was not considered, or at least not admitted by pilots to be a tactically important problem in the relatively low speed fighter planes of that era. The current urgency of the GLOC problem dictates, among other things, an in-depth review of what is known concerning the physiology and limitations of anti-blackout suits.

Initially developed anti-G suits were based on the belief that decreased venous return to the heart was the most critically important result of the increased weight of blood which is an unavoidable effect of acceleration. Development of cumbersome water filled, pneumatic gradient and pulsatile pressure suits resulted.

The water filled Frank's Flying Suit which was used successfully by the British Air Force during the 1942 invasion of North Africa was the foremost anti-G suit during the early years of World War II (8). Early anti-blackout suits were developed concurrently or shortly thereafter, chiefly by the U.S. Navy. Pictures of these suits, including an anti-G abdominal bladder, a pulsatile pressure suit, and a gradient pressure suit, are included in a review published shortly after World War II (9). A somewhat more cumbersome gradient pressure suit was designed and tested by Cotton in 1940 in a small human centrifuge in Australia.

The basic concept upon which these early suits were based, namely that maintenance of venous return to the heart would be a very effective means of preventing blackout, was tested when the Mayo human centrifuge became operational in late 1942. A steel container designed to allow a seated subject to be immersed in water up to base of heart level was mounted in the cockpit of the centrifuge (10). The G tolerance of 15 healthy young men was determined with and without water immersion up to or above heart level and also while wearing the Frank's Suit. The protection against subjective losses of vision and objective decreases in blood content of the ear provided by the Frank's suit and actual immersion in water to an equivalent level was determined to be about 1G (11). This was less than hoped for and stimulated search for more effective means of prevention of blackout.

Following the lead of the Canadian human centrifuge group, the duration of exposures to given levels of acceleration on the Mayo human centrifuge was initially restricted to five seconds. This restriction was based on the fact that aircraft at that time had insufficient power to sustain accelerations greater than several G for more than five seconds and also on the belief that circulatory collapse, due to cessation of venous return, would occur if high levels of acceleration were maintained for longer periods.

This concept was tested in 1942; and, somewhat unexpectedly, as illustrated in Figure 1 the progressive loss of blood content and arterial pulsation in the ear, which occurred during the first seven seconds of the exposure, were, if the exposure was prolonged to more than ten seconds, interrupted by a rapid recovery of both of these objective parameters, and a concomitant restoration of vision occurred (12).

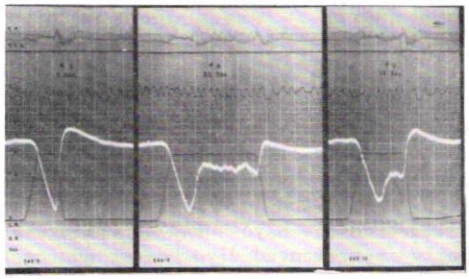


Fig. 1

These findings along with water immersion studies strengthened belief that arterial pressure rather than venous return is the major determinant of human G tolerance when in the upright sitting position.

Consequently, physiologic and mechanical methods of increasing systemic arterial pressure were considered and studied in an initial series of intensive tests on the Mayo human centrifuge from 1942 through 1943 (13-15).

So-called arterial occlusion suits were found to provide much higher levels of protection than devices designed to support venous return. Several types were designed and fabricated in close collaboration with Mr. David M. Clark (Figure 2).

The most effective of these, with its automatic, very rapidly inflating pressure control valve, is illustrated in Figure 3. The air bladder system was inflated very rapidly from the ankles upwards to the abdomen via a valve, which at 1.5G opened the bilateral air inlet lines at the ankles to a

18 Epperson, W.L., R.R. Burton and E.M. Bernauer. 1982. The influence of differential physical conditioning regimes on simulated aerial combat maneuvering tolerance. Aviat. Space Environ. Med. 53:1091-1097.

19 Tesch, P.A., H. Hjort and U.I. Balldin. 1983. Effects on strength training on G-tolerance. Aviat. Space Environ. Med. 54:691-695.

20 Space, D.W., M.J. Parnell and R.R. Burton. 1981. Abdominal muscle conditioning as a means of increasing tolerance to Gz stress. Preprint. Aerospace Medical Association Meeting. 148-149.

21 Parnell, M.J. and J.E. Whinnery. 1982. The effects of long-term aerobic conditioning on tolerance to Gz stress. Preprint. Aerospace Medical Association Meeting. 22-23.

22 Shubrooks, S.J. Jr. 1973. Positive-pressure breathing as a protective technique during Gz acceleration. J. Appl. Physiol. 35: 294-298.

23 Balldin, U.I. 1982. Positive pressure breathing and a faster filling ready pressure ant-G-suit: effects on Gz tolerance. Preprint. Aerospace Medical Association Meeting. 16-17.

24 Haswell, M.S., W.A. Tacker, Jr., U.I. Balldin and R.R. Burton. 1986. Influence of inspired oxygen concentration on acceleration atelectasis. Aviat. Space Environ. Med. 57:432-437.

25 Noddeland, H., K. Myhre, U.I. Balldin and H.T. Andersen. 1986. Proteinuria in fighter pilots after high Gz exposure. Aviat. Space Environ. Med. 57:122-125.

26 Burton, R.R. and W.F. MacKenzie. 1975. Heart pathology associated with exposure to high sustained Gz. Aviat. Space Environ. Med. 46: 1251-1253.

27 Gillingham, K.K. 1978. Absence of high-G stress cardiopathy in a human centrifuge rider. USAF School of Aerospace Medicine. Report from Brooks AFB. Tx. U.S.A. SAM-TR-78-17.

28 Laughlin, M.H. 1982. An analysis of the risk of human cardiac damage during Gz stress: a review. Aviat Space Environ. Med. 53:423-431.

Flying with future high performance aircraft also means that colour displays may be used to present flight and weapon information. Colour vision may be disturbed during high G-loads, in the same way as peripheral vision is disturbed by the blood pressure drop accompanied by hypoxia in the retina. This gray-out during high G-loads may sometimes proceed to black-out, where all vision is lost. Similar phenomenona might happen to the hearing as well as to the other senses.

The use of joy-stick mediated CRT-pointing as command in the aircraft instead of the pressing of buttons or the movements of switches may also cause problems due to motoric difficulties during high G-loads. The control and strength of the muscles to move the hand with the very high precision required must be sufficient in the high G-situation, otherwise the commands may become inaccurate.

Speech commands may also be used in high performance aircraft. The automatic interpretation of such speech commands at 1 G has now reached a very remarkable level of correct responses. During high G-loads, however, the speech is distorted as it is during vibrations. During the time the pilot has to perform the straining maneuvers with closed or semiclosed glottis, the speech is either impossible or very difficult and highly distorted. If positive pressure breathing is going to be used in future high performance aircraft to improve G-tolerance, the use of speech commands might also be difficult during the high G-loads.

In conclusion, the high performance aircraft of today and in the near future may expose the pilot to rapid onset high sustained G-loads. This implies that the physiological limitations of the human tolerance to G acceleration sometimes are reached and might even be exceeded. In some respects the psychological and physiological requirements on the pilot are much more pronounced in the high performance aircraft, while in other respects, the modern technology facilitates the tasks for the pilot. The psychomotor performance may be decremented with the high G-loads as well as the vision and speech. The high physical demands in the high sustained G environment with repeated straining maneuvers may cause general as well as local muscle fatigue. The kidneys as well as other internal organs of the body are influenced by the high G loads and their performance may be affected. A decreased oxygen saturation of the blood in combination with a rapid cerebral blood pressure drop during high G loads, might result in a G-induced loss of consciousness with disastrous consequences to the pilot. Such a loss of consciousness may require an autopilot system to temporarily take-over the controls of the aircraft. In that case the aircraft definitely has caused the pilot to exceed the physiological limitation of human tolerance to Gz acceleration.

REFERENCES

1 Burton, R.R. and J.E. Whinnery. 1985. Operational G-induced loss of consciousness: something old, something new. Aviat. Space Environ. Med. 56:812-817.

2 Pluta, J.C. 1984. LOC survey. Flying Safety, (Jan.) 25-28.

3 Whinnery, J.E. and R.M. Shaffstall. 1979. Concurrent loss of consciousness and sino-atrial block during Gz stress. Aviat. Space Environ. Med. 50:635-639.

4 Whinnery, J.E. and D.R. Jones. 1986. Psychologic aspects of Gz-induced loss of consciousness. Aviat. Space Environ. Med. 57:498.

5 Bloodwell, R.D. and J.E. Whinnery. 1982. Acceleration exposure during competitive civilian aerobatics. Preprint. Aerospace Medical Associaton Meeting. 167-168.

6 Kirkham, W.R., S.M. Wicks and D.L. Lowery. 1982. G incapacitation in aerobatic pilots: a flight hazard. US Federal Aviation Administration report No. FAA-AM-82-13, 1-33.

7 Balldin, U.I., K. Myhre, P.A. Tesch, U. Wilhelmsen and H.T. Andersen. 1985. Isometric abdominal muscle training and G-tolerance. Aviat Space Environ. Med. 56:120-124.

8 Burton, R.R. and R.M. Shaffstall. 1980. Human tolerance to aerial combat maneuvers. Aviat. Space Environ. Med. 51:641-648.

9 Burns, J.W. and U.I. Balldin. 1983. Gz protection with assisted positive pressure breathing (PPB). Preprint. Aerospace Medical Association Meeting. 36-37.

10 Burton, R.R., S.D. Leverett, Jr. and E.D. Michaelson. 1974. Man at high sustained Gz acceleration: a review. Aerspace Med. 45: 1115-1136.

11 Balldin, U.I. 1984. Acceleration stress training and G-tolerance in aviation. Abstract. Aerospace Medical Association Meeting. Aviat. Space Environ. Med. 55:475.

12 Tesch, P.A. and U.I. Balldin. 1984. Muscle fiber type composition and G-tolerance. Aviat. Space Environ. Med. 55:1000-1003.

13 Sporrong, A., R. Baer, U. Balldin and L. Nurmi. 1986. ACM G-tolerance and cardiovascular responsiveness to task-induced emotional stress at 1 G. Aviat. Space Environ. Med. 57:499.

14 Tesch, P.A., A. Sporrong and U.I. Balldin 1986. Physical performance and G-tolerance. Aviat. Space Environ. Med. 57:496.

15 Balldin, U.I., A. Sporrong, and P.A. Tesch. 1984. Rehydration and G-tolerance, psychomotor performance and muscle function. Aviat. Space Environ. Med. 55:467.

16 Forster, E.M. and J.E. Whinnery. 1986. Effects of G-onset rate on cardiovascular response. Aviat. Space Environ. Med. 57:498.

17 Gillingham, K.K. 1984. Centrifuge training of USAF fighter pilots. Aviat. Space Environ. Med. 55:467.

reached. An indication of the adaptation of the circulatory system may be given by the passive slow onset rate G-tolerance measurements. The more active G-tolerance measurements will, on the other hand, give an indication of the circulatory system as well as of the correct technique, the muscle force and endurance required to perform the straining maneuvers.

The endurance G-tolerance may be measured by the aerial combat maneuver (ACM) G-profile with repeated 15 s periods of, for instance, 3.5 and 5.5 G without anti-G-suit (7), 4.5 and 7 G with anti-G-suit (8) or 10 s periods of alternating 5 and 9 G (9) until volitional exhaustion. Here the general physical endurance as well as local muscle fatigue are important factors.

The ability to recover after repeated periods of high G-loads is still another type of G-tolerance, giving an indication of the readiness for new G-exposures during a 24 h period.

To measure G-tolerance in a human centrifuge the subjects have to be familiar to the G-loads and the vestibular effects in the centrifuge. Fighter pilots are of that reason often chosen. Naive subjects have to be trained for weeks in the centrifuge to be able to be used in G-tolerance measurements.

The variability in different subjects exposed to high G-loads is very great (10, 11). Some may tolerate only 7 G for less than 15 s, while others may tolerate 9 G for 45 s with anti-G-suit. During unsuccessful circumstances even an experienced fighter pilot may encounter a G-induced loss of consciousness at such a low G-load as 3.5 G, indicating a great G-tolerance variability in the same day as well as on a daily basis. Selection procedures should be more important in the future, at least to eliminate those with low G-tolerance, who could be a flight hazard when flying high performance aircraft. It is not only a question of such constitutional factors as blood column distance from heart to brain and baroreceptor reactivity, but also of physical ability and endurance to perform the necessary straining maneuvers during high G loads. Among other constitutional factors than height, weight, age etc., which are investigated so far, no evidence exists that muscle fiber composition and muscle capillary density can be a good predictor of high G-tolerance (12). If other muscle function tests, anaerobic tests or psychomotor stress reaction tests might be used in the selection of pilots with high G-tolerance remains to be investigated (13, 14). It appears, however, to be very difficult to predict a good future G-tolerance in a subject.

Many environmental and physiological factors may interfere with a good G-tolerance. Such limitations may be caused by heat stress, dehydration, hypoglycemia, fatigue, hyperventilation, hypoxia, alcohol and hangover etc., but also by a minor illness and by medication. A dehydration of 3 % of the body weight without raised body temperature may, for instance, reduce the ACM G-tolerance without anti-G-suit by about 40% (15). A dehydration of this magnitude is not inconceivable in a fighter pilot operation. If it is combined with raised body temperature, which could be the result of using a chemical defence protection equipment, the effect should be still more pronounced. Even small decrements in G-tolerance, however, may have a major impact on the operation of a high performance aircraft at high G-loads. All these negative factors should, therefore, be still more important now. The negative factors may not only increase the risk of G-induced loss of consciousness, but they may also induce a further impaired psychomotor performance during the high G-loads.

The very rapid onset high sustained G-load in air combat maneuvering with high performance aircraft may cause inadequate cardiovascular response. The immediate heart rate response may be only a fourth of the final heart rate reached with very rapid onset rate (16). The tendency to rapid cerebral blood pressure drop during this situation may also require immediate respiratory and muscle straining maneuvers (M-1 or L-1) as a countermeasure. The adequate performance of the straining maneuvers implies a correct technique to execute them as well as a sufficient muscle endurance. A correct technique may best be trained in a human centrifuge and the muscle endurance is best obtained by strength training. Consequently, centrifuge training (17) as well as strength training (18, 19) has been shown to increase ACM G-tolerance substantially. The strength training requires, however, that many muscle groups are trained to obtain an improved G-tolerance, and not only, for instance, abdominal muscles (7, 20). Aerobic training, on the other hand, has not been shown to increase G-tolerance (18). Endurance training might even imply proneness to cardiac dysrhythmias, G-induced loss of consciousness and motion sickness (21).

The very high sustained G-loads requires a good muscle endurance to be able to execute repeated straining maneuvers. A muscle strength training program is, therefore, beneficial for that reason, but to recover from missions with many strenous high G-loads a combined strength and moderate aerobic training could be of value (21).

Another way to push the physiological limitations of human tolerance to Gz acceleration appears to be the use of positive pressure breathing in combination with an effective anti-G-suit, and especially assisted positive pressure breathing (22, 23, 9).

The high sustained G-loads may imply functional physiological disturbances such as shunting of the blood in lungs and G-induced pulmonary atelectases (24) with deteriorated blood oxygen saturation as well as strain on the kidneys with proteinuria (25). It may also imply injury to some structures of the human body, as for instance the petechial hemorrhages in the skin (so called G-measles) that may be found in unprotected external areas of the body. If other internal organs of the human body will be injured by the high G-loads, such as some time ago was suggested in the hearts of pigs (26), remains to be investigated. So far no such findings have been found in humans (27, 28).

PHYSIOLOGICAL LIMITATIONS OF HUMAN TOLERANCE TO Gz ACCELERATION

Ulf I. Balldin

Department of Aerospace Medicine
Karolinska Institute and National Defence,
Research Institute, Stockholm, Sweden

The advances in aircraft technology with higher engine thrust, higher wing loading and computer assisted electronic "fly by wire" flight controls of a highly unstable and extremely maneuvrable fighter aircraft may expose the pilot to very high G-loads of up to or even exceeding 9 G. The onset-rate of the G-load may also be very rapid in these high performance aircraft, but is usually restricted by the computer of the aircraft to 6 G/s. This restriction is mainly due to a presumed physiological limitation of the pilot with a risk of G-induced loss of consciousness. The high performance aircraft also allows the execution of steep turns for extended periods of time, thus exposing the pilot to sustained high G-loads. This sustained high G-load is very fatiguing as it continuously requires maximal respiratory and muscular straining maneuvers (M-1 or L-1 maneuvers) of the pilot to avoid a cerebral blood pressure drop with a following risk of G-induced loss of consciousness.

The presentation of important flight and weapon data with head-up and head-down displays, CRT-techniques and better ergonomics of the cockpit facilitate the pilot´s operation of the aircraft. The interpretation of the great amount of information given, the requirements for very rapid decision making and the necessity for simultaneous looking out through the cockpit in these very fast flying aircraft exert, however, an extreme high stress on the pilot. If the stress of the high sustained G-load, requiring repeated very tiresome straining maneuvers, is added to that, it is apparent that the pilot may have a deteriorated mental performance and may be the limiting factor for the fully operation of the high performance aircraft in high G environments (1).

The development of chemical warfare has forced the introduction of protective devices for the pilots that will interfere with their performance. These devices will induce heat stress, which is lowering the G-tolerance of the pilot and are adding further stress to the pilot.

Reports of G-induced loss of consciuousness during flying with high G-loads of high performance aircraft with sometimes disastrous consequences have appeared (2). The occurrence of these can be looked upon as a failure of the ability to protect the pilot against the high G-loads and a transgression of the limit of the pilot´s maximal performance. Other measures have to be taken to avoid the disastrous consequences, when the G-induced loss of consciousness already has occurred. It may imply the development of equipment to detect the G-induced loss of consciousness in order to let the computer of the aircraft with help of the advanced ground proximity warning device and the autopilot system take command of the aircraft for a low G climb to safe altitude. During this maneuver the pilot may have a chance to recover and to resume the control of the aircraft again.

The mean incapacitation time of a G-induced loss of consciousness appears to be about 15 s (3). During the final stages of the unconsciousness clonic convulsions may appear, before the consciousness is regained. As this unconsciousness is accompanied by a retrograd amnesia, confusion and deteriorated mental performance (4), the ability to properly handle the aircraft may be impaired for long periods afterwards. A G-induced loss of consciousness may therefore, for safety reasons, be considered as a cause of aborting a sortie.

Rapid onset G-loads may also be found in civilian competitive and aerobatic flying with very maneuvrable small aircraft. Most dangerous seem the rapid transitions from, for instance, 5 negative G to more than 5 positive G to be (5). The baroreceptor response during the rapid transitions from negative to positive G-loads appears to be too slow, which may result in rapid drop in cerebral blood pressure. Reports of G-induced loss of consciousness of that reason have also appeared (6).

Negative G-loads provoking occasional premature atrial and ventricular contractions and bradycardia to the extent of asystole may also impose a risk to pilots (6).

During the acceleration phase of a space shuttle launched into space or during the re-entry, the astronauts are only exposed to G-loads not exceeding about 3 G. Orthostatic reactions may, however, be seen during the re-entry and the immediate time thereafter, as a result of a deconditioning of the circulatory system during the microgravity in extended sojourns in space.

G-tolerance in human subjects may be measured in many ways. Orthostatic tests on tilt tables seem not to be a very effective tool to estimate G-tolerance during high G exposure. Instead, human centrifuges are used to measure G-tolerance usually relaying on subjective end-points. Motivation and subjective experience of the effort level may influence the results in endurance type G-tolerance measurements to volitional exhaustion. The tolerance to withstand rapid onset and high sustained G-loads, where tiresome straining maneuvres continuously are required, is one way of defining G-tolerance. Another way may be the passive G-tolerance measurements, when subjects are exposed to slow onset rate but gradually increasing G-loads without the use of straining maneuvers until peripheral light loss end-point criteria is

Although Coermann (2) years ago developed a two-degrees-of-freedom model to measure the response of his eight seated, human subjects to vibration, his two-mass model did not account for any of the peaks beyond the primary one and assigned a small percentage of the total mass to the upper torso.

In evaluating the new model further, the model or calculated mass ($m_1 + m_2$) was compared to the actual mass (test weight) of each primate. The results are shown in Table 2. The agreement between the two masses was very good in the case of all seven test animals. It also strongly supports the previous observations (7-9) that both the monkeys and baboons vibrate out of phase rather than rigidly with the seat over most of the frequency range tested.

Table 2. Comparison of measured and model mass values*

Animal	Test weight	Model values ($m_1 + m_2$)
Rhesus monkey:		
#058	21.0 (9.53)	17.76 (8.06)
#314	20.3 (9.21)	20.31 (9.21)
#A360	16.8 (7.62)	16.79 (7.62)
#318	28.0 (12.70)	25.87 (11.73)
Mean	21.3 (9.66)	19.30 (8.75)
Baboon:		
#F96	26.0 (11.79)	25.98 (11.78)
#F26	37.5 (17.01)	36.76 (16.67)
#F88	31.0 (14.06)	27.99 (12.70)
Mean	31.5 (14.29)	28.49 (12.92)

*All values in pound (lb) units (kg units in parentheses)

Interspecies Scaling. Based on the insignificant difference in impedance and transmissibility between the Rhesus monkeys and baboons, the question was raised in the previous report (9) concerning the selection of the baboon as a better biodynamic model than the Rhesus monkey and also the phylogenicity of the two subhuman primate species. Moreover, in a study by Little and coworkers (4), it was found that in evaluating the viscoelastic properties (e.g., max. strain rates) of the major spinal ligaments of Rhesus, baboon and chimpanzee, the Rhesus was closer to the chimpanzee in many cases than was the baboon. Thus, in combining the results of both programs, it appears that the baboon may not be in the same lineage with the Rhesus and chimpanzee but on another converging line. In view of the cost and availability of both animals, the Rhesus appears to be a good research model to extrapolate data to humans (9).

Acknowledgments

The author is indebted to the many individuals of the Veterinary Sciences Division, AMRL, and the University of Dayton Research Institute, Dayton, Ohio, who collaborated on the experiments and to Dr. Ints Kaleps, AMRL, who directed the modeling efforts throughout this program.

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council, Washington, D.C.

REFERENCES

1. Broderson, A.B., and H.E. von Gierke. Mechanical impedance and its variation in the restrained primate during prolonged vibration. ASME Publ. No. 71-WA/BHF-8, 1971.
2. Coermann, R.R. The mechanical impedance of the human body in sitting and standing position at low frequencies. Human Factors 4: 227-253, 1962.
3. Edwards, R.G., J.F. Lafferty, and C.F. Knapp. Experimental and analytical determinations of the mechanical impedance response of animals to vertical vibration. J. Biomech. 9: 55-61, 1976.
4. Little, R.W., R.P. Hubbard, D.L. Hyler, and A.R. Slonim. Mechanical properties of spinal ligaments for Rhesus monkey, baboon and chimpanzee. AFAMRL-TR-81-40, Wright-Patterson AFB, Ohio, 1981.
5. Quandieu, P., and L. Pellieux. Study in situ et in vivo of the acceleration of lumbar vertebrae of a primate exposed to vibration in the Z-axis. J. Biomech. 15: 985-1006, 1982.
6. Quandieu, P., L. Pellieux, and F. Lienhard. The role of nucleus pulposus in the propagation of vibration along the lumbar spine of the primates. Preprints of Aerosp. Med. Assn. Mtg., May 1983, p. 10-11.
7. Slonim, A.R. Some vibration data on primates implanted with accelerometers on the upper and lower spine: Methodology and results in Rhesus monkeys. AFAMRL-TR-81-153, Wright-Patterson AFB, Ohio, 1983.
8. Slonim, A.R. Some vibration data on primates implanted with accelerometers on the upper thoracic and lower lumbar spine: Results in baboons. AFAMRL-TR-83-091, Wright-Patterson AFB, Ohio, 1984.
9. Slonim, A.R. Comparative biodynamic response of two primate species to the same vibrational environment. Aviat. Space Environ. Med. 56: 945-955, 1985.

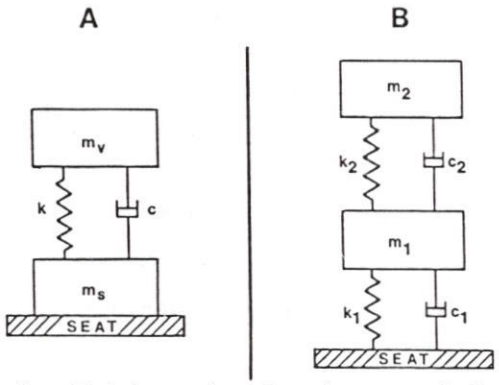


Fig. 5. Models. A. One-degree-of-freedom model where m_s = mass of lower half of body, m_v = mass of upper half of body, c = damping factor, and k = spring factor [modified slightly after (1)]. B. Two-degrees-of freedom (TDOF) model where m_1 = mass of pelvis and upper leg, m_2 = mass of upper body and head, c_1 and c_2 = damping coefficients for respective masses, and k_1 and k_2 = elastic coefficients for respective masses.

secondary peaks seen in some of the animals, (e.g., Baboon #F96) as well as provides a good fit of impedance magnitude for both species (Figs. 6 and 7).

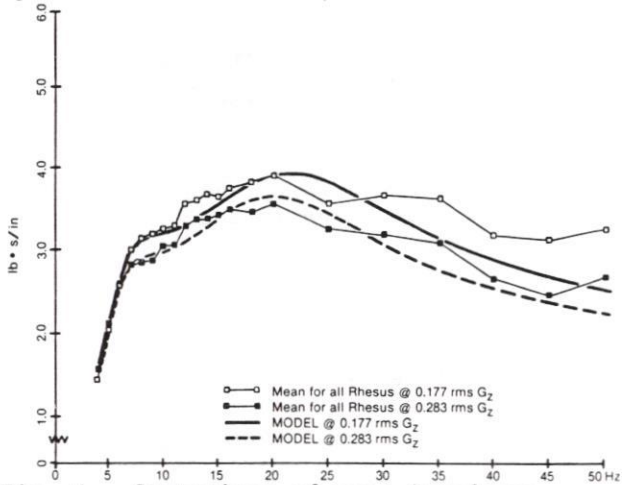


Fig. 6. Comparison of mean impedance magnitude of four Rhesus monkeys and TDOF model at both G levels.

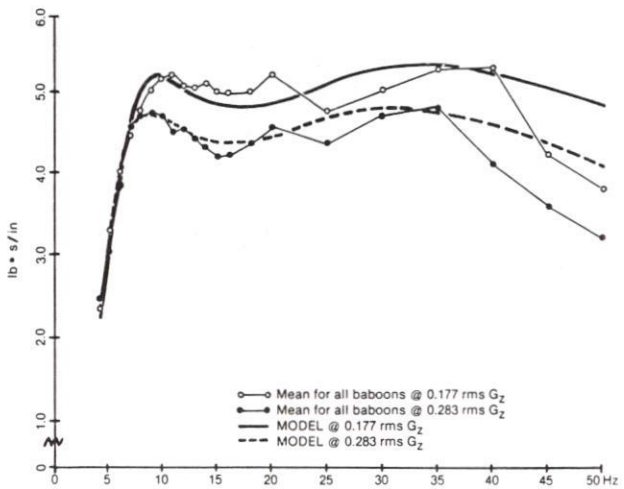


Fig. 7. Comparison of mean impedance magnitude of three baboons and TDOF model at both G levels

Table 1. Model parameters for impedance data at two acceleration levels

Animal		m_1*	c_1†	k_1‡	m_2	c_2	k_2
Rhesus monkey:							
#058	L§	0.0260	1.81	350	0.0200	0.96	35
	H	0.0260	1.68	300	0.0200	0.85	30
#314	L	0.0280	2.13	450	0.0246	1.08	37
	H	0.0280	1.96	380	0.0246	0.95	29
#A360	L	0.0075	1.41	735	0.0360	2.20	105
	H	0.0075	1.23	560	0.0360	1.85	74
#318	L	0.0200	2.36	775	0.0470	2.12	75
	H	0.0200	2.08	600	0.0470	2.01	67
Mean	L	0.0230	1.90	435	0.0270	1.35	53
	H	0.0230	1.76	375	0.0270	1.25	45
Baboon:							
#F96	L	0.0190	3.09	1400	0.0483	2.79	126
	H	0.0190	2 87	1200	0.0483	2.81	128
#F26	L	0.0360	3.32	850	0.0592	2.54	85
	H	0.0360	2.90	650	0.0592	2.46	80
#F88	L	0.0135	2.20	1000	0.0590	3.32	146
	H	0.0135	2.06	875	0.0590	2.91	112
Mean	L	0.0202	2.83	1100	0.0536	3.02	133
	H	0.0202	2.58	900	0.0536	2.76	111

*m_1, m_2 = masses in $lb \cdot sec^2/in$

†c_1, c_2 = damping coefficients in lb·sec/in

‡k_1, k_2 = elastic coefficients in lb/in

§L and H refer to 0.177 and 0.283 rms G_z acceleration levels, respectively

Note: By multiplying the tabulated data by 174.98, the model would be expressed in the following SI units: "m" in $N \cdot s^2/m$, "c" in N·s/m and "k" in N/m.

The model matched also the phase angle data but not as well as impedance magnitude; this is detailed elsewhere (Kaleps, Yackiel and Slonim: Ms to be published). An estimate of the modeling parameters derived from the TDOF model for both primate species at both G levels is presented in Table 1. When the mean impedance magnitude curve for each species was compared with the TDOF model, the fit was very close, as shown in Fig. 8.

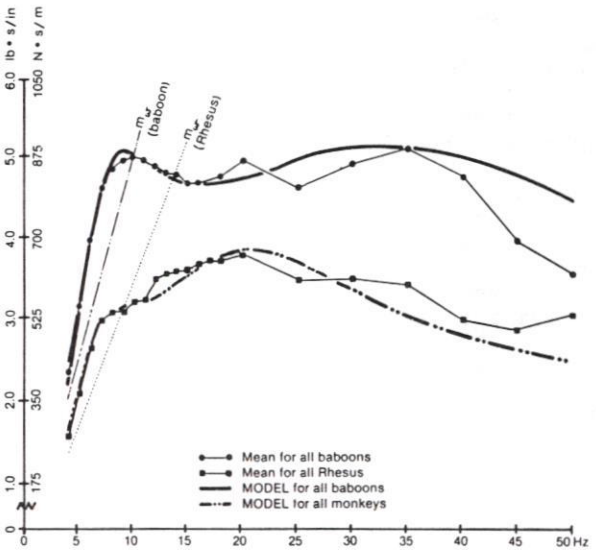


Fig. 8. Comparison of mean impedance magnitude of all Rhesus monkeys, all baboons and TDOF model within the 0.18-0.28 rms G_z range. A pure mass line (m_ω) for each species is included.

Impedance Phase. The impedance phase, which was measured starting with the last monkey and in all three baboons, showed a phase angle minima at the low frequency region, 10-20 Hz, and at an amplitude from 20 to 40 degrees. As showed in Fig. 3, there was no significant difference in phase between G levels, reflecting a linear response here also. At the higher frequencies, 35-50 Hz, the response varied; one baboon (#F88) showed a sharp rise in phase angle, whereas another (#F26) tapered off. The former exhibited "mass-like" characteristics as reported for Rhesus by Broderson and von Gierke (1), and the latter was "damper-like" as described for Rhesus also by Edwards et al. (3). The third baboon (#F96) was intermediate in response between the other two. Thus, the results (Fig. 3) showed that impedance phase can vary from mass-like to damper-like in character. When the mean phase angle curve of one Rhesus monkey was compared to that of the three baboons, there was no significant difference between the two species (9).

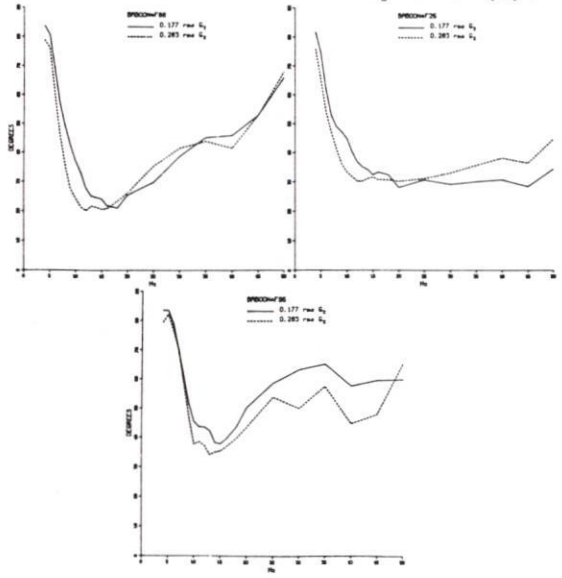


Fig. 3. Impedance phase vs. G level for each of the three baboons. (8)

Transmissibility. The transmissibility from seat pan to the top spinal accelerometer in all seven primates showed the greatest amplification at low frequency, 5-12 Hz. Transmission at the bottom accelerometer, which was near the vibration source, was close to unity over most of the frequency spectrum tested, with a slight peak in the 6-9 Hz area. There was no significant difference between G levels in any of the three transmissibility ratios, indicating a linear response. The small difference between G levels reflected a tendency towards non-linearity but not to the extent observed with the impedance data. When the mean curve of the Rhesus monkeys was compared to that of the baboons, there was no significant difference between species in any of the three transmissibility ratios; see, e.g., Fig. 4 comparing transmission from the seat to the top spinal accelerometer (TOP/TAB) between both species.

In a similar but somewhat complementary study, which began also in the late 1970s, another group of workers sought to

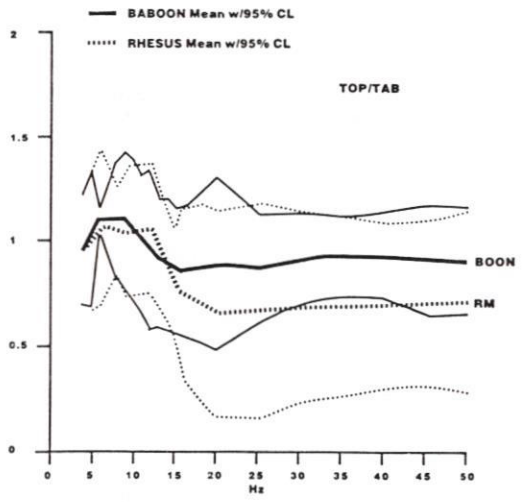


Fig. 4. Mean TOP/TAB transmissibility curves compared between baboon (solid lines) and Rhesus monkey (dashed lines).

directly measure transmissibility in primates. Quandieu et al. (5,6) in France implanted 3-5 accelerometers on the ventral surface of the lower lumbar centra of Rhesus monkeys and very small baboons and exposed them to sinusoidal and/or random vibrations ranging from 0 to 100 Hz at either 0.1 or 0.25 rms G_z. Quandieu reported differences in response between his animals in terms of both transfer and coherent functions upon which he based his results; he reported also on a lack of non-linearity over the 0-80 Hz range at low acceleration levels (below 0.5 rms G_z). The latter observation corroborates the results found in this study.

One explanation for the lack of non-linearity observed throughout this study may be that the range of excitation was too narrow, i.e., 0.25 and 0.40 peak G_z rather than one farther apart. This should be considered in future efforts.

Modeling. A one-degree-of-freedom model developed by Broderson and von Gierke (1), as shown in Fig. 5A, had been applied to these data, and the results were satisfactory (7-9). This model considers the restrained, seated animal as having a two-mass response: one reactive ("sprung") and the other inert (or moving with the seat). The lower half of the body is assumed to respond like a pure mass, m_s, and only the upper torso, m_v, is free to move relative to the chair. The modeling results indicated that there was a tendency to be less rigid (more decoupling from the seat) at the higher G level (9). However, this simple model, which assumes "ischial stiffness" and no lower body response, did not account for the secondary peaks in the 25-50 Hz range exhibited by many of the seven primates. Therefore, other models were evaluated, and a two-degree-of-freedom (TDOF) model was selected and applied to the same data as before. In the new model, which is shown in Fig. 5B, the lower torso characteristics are incorporated. This model, developed this year by Kaleps et al., not only fit well the individual primates, but also the mean response of each species. The model clearly accounts for the large

BIODYNAMIC RESPONSE OF SUBHUMAN PRIMATES TO VIBRATION

Arnold R. Slonim*

Aerospace Medical Research Laboratory
Wright-Patterson Air Force Base, Ohio

A program was initiated in this laboratory eight years ago to develop a method to directly measure transmissibility up the spinal column and determine the impedance of subhuman primates to vertical sinusoidal vibration. Accelerometers were implanted on the spinous process at the upper and lower region of the spine of Rhesus monkeys and later baboons. This report will present the results obtained on the impedance and transmissibility characteristics of both species of primates as well as on the application of a recently developed model to the data to obtain a better approximation of the biodynamic response and, to a small extent, on an effort towards interspecies scaling to humans.

METHODS

The methodology for implanting two miniaturized, damped, heat-compensated accelerometers on the spinous processes of the upper thoracic and lower lumbar spine, respectively, and the procedures used for measuring impedance magnitude, phase angle, and transmissibility from the load plate (seat pan) up the spinal column have been described previously (7-9). Four 7-8 year-old Rhesus monkeys (Macaca mulatta) and three 4-5 year-old baboons (Papio papio), all males of similar size (8-17 kg), were tested four days after accelerometer implantation on an electrodynamic vibration machine for a period of one hour (mean 53 min) per day up to four consecutive days. They were exposed to vibrations from 4 to 50 Hz at 0.177 rms G_z then at 0.283 rms G_z (0.25 and 0.40 peak G_z, respectively). The frequency spectrum was as follows: 4-16, 18, 20, 25, 30, 35, 40, 45 and 50 Hz; the exposure period per frequency per G level was approximately 30 seconds, which was similar to that of other workers (1,3).

The biomechanical response to vibration was measured by impedance magnitude, phase angle, and three transmissibility ratios; the latter were the ratios of rms accelerations between the top spinal accelerometer (TOP), bottom spinal accelerometer (BOT) and table or seat pan accelerometer (TAB). The modeling parameters, comprising mainly the damping and elastic coefficients and mass values, were calculated from the impedance data.

*Present address: 5282 Greencroft Drive, Dayton, Ohio 45426.

RESULTS AND DISCUSSION

Impedance Magnitude. The impedance magnitude of the four Rhesus monkeys and three baboons showed a resonant peak at low frequencies, 7-20 Hz, with some primates showing one or two other peaks from 25 to 50 Hz. Impedance magnitude was generally less at the high G level than at the lower G level over most of the frequency spectrum tested, as seen in Fig. 1. The difference between the two G levels was not significant, thus the response was linear although the tendency towards non-linearity existed for all seven primates. A plot of the mean impedance magnitude per G level of each species showed that the largest resonant peak for both species occurred at 20 Hz. When the mean impedance magnitude curves (±95% CL) of both species were plotted and compared, the results showed no significant difference between species, except in one small area, 8-9 Hz (Fig. 2).

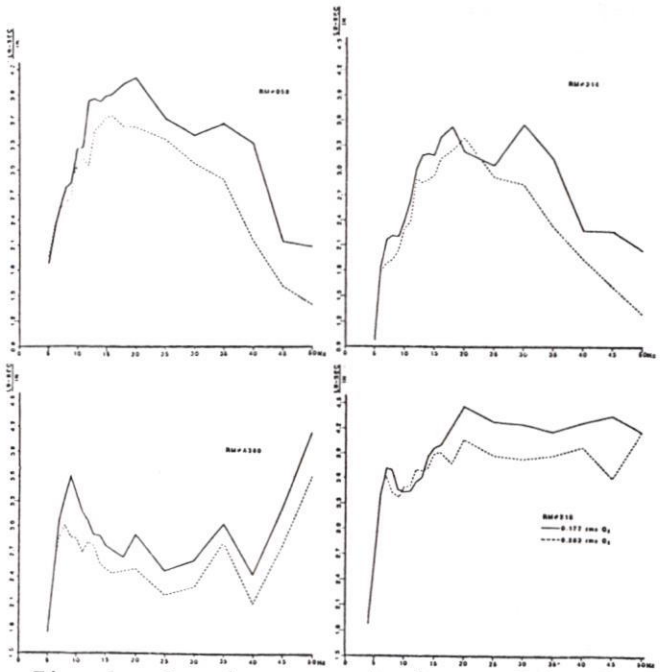


Fig. 1. Impedance magnitude vs. G level for each of the four Rhesus monkeys. (7)

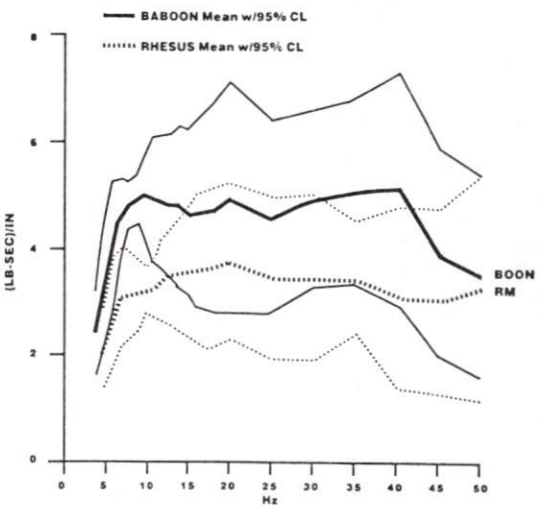


Fig. 2. Mean impedance magnitude curves compared between baboon (solid lines) and Rhesus monkeys (dashed lines).

5. Hargens, A.R., R.W. Millard, K. Pettersson and K. Johansen. Gravitational hemodynamics and oedema prevention in the giraffe. **Nature,** submitted 1986.

6. Hargens, A.R., R.W. Millard, K. Pettersson, W. van Hoven, D.H. Gershuni, and K. Johansen. Transcapillary fluid balance in the giraffe. In: **Interstitial-Lymphatic Liqued and Solute Exchange, Advances in Microcirculation,** edited by N.C. Staub, J.C. Hogg, and A.R. Hargens. Basel: S. Karger, in press, 1987.

7. Henriksen, O. Local sympathetic reflex mechanism in regulation of blood flow in human subcutaneous adipose tissue. **Acta Physiol. Scand. Suppl.** 450:1-48, 1977.

8. Lillywhite, H.B. Postural edema and blood pooling in snakes. **Physiol. Zool.** 58:759-766, 1985.

9. Patterson, J.L., Jr., R.H. Goetz, J.T. Doyle, J.V. Warren, O.H. Gauer, D.K. Detweiler, S.I. Said, H. Hoernicke, M. McGregor, E.N. Keen, M.H. Smith, Jr., E.L. Hardie, M. Reynolds, W.P. Flatt and D.R. Waldo. Cardiorespiratory dynamics in the ox and giraffe, with comparative observations on man and other mammals. **Ann. NY Acad. Sci.** 127:393-413, 1975.

10. Pettersson, K., A.R. Hargens, R.W. Millard, K. Johansen, D.H. Gershuni, R. Burroughs, D.G.A. Meltzer, and W. van Hoven. Dependent hypertension and arterial wall hypertrophy without interstitial edema in the giraffe. **Proc., XXX Congress, I.U.P.S.** XVI: P 414.16 (abstract), 1986.

11. Sejersted, O.M., A.R. Hargens, K.R. Kardel, P. Blom, O. Jensen and L. Hermansen. Intramuscular fluid pressure during isometric contraction of human skeletal muscle. **J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.** 56:287-295, 1984.

12. Starling, E.H. On the absorption of fluids from connective tissue spaces. **J. Physiol. (Lond.)** 19:312-326, 1986.

13. Van Citters, R.L., S. Kemper, and D.L. Franklin. Blood flow and pressure in the giraffe carotid artery. **Comp. Biochem. Physiol.** 24:1035-1042, 1968.

14. Warren, J.V. The physiology of the giraffe. **Scient. Amer.** 231(5):96-105, 1974.

15. Williamson, J.R., N.J. Vogler, and C. Kilo. Regional variations in the width of the basement membrane of muscle capillaries in man and giraffe. **Am. J. Pathol.** 63:359-370, 1971.

DISCUSSION

In terms of adaptation to high gravitational pressures in its cardiovascular system, the giraffe is certainly unique. The edema-preventing mechanisms that were detected in giraffe legs included: 1) variable and sometimes negative P_vs and P_ts, 2) impermeable capillary membranes to retain intravascular proteins, 3) arterial wall hypertrophy and vasoconstriction to reduce dependent blood flow, 4) a prominent lymphatic system, and 5) skin and fascial "g-suit" combined with one way valves in the veins and lymphatics to reduce venous capacitance and to propel blood and peripheral lymph upwards against a gravitational pressure gradient. This study demonstrates that intravascular and interstitial fluid pressures are highly variable during normal exercise and that studies of recumbent and upright-stationary animals may give misleading information about transcapillary fluid balance. For example, it is known that sick giraffes soon die after assuming the recumbent position. Also, our static, upright results provide an incomplete picture. Therefore, normal exercise activities with concomitant pumping of veins, interstitial fluids and peripheral lymph are important for edema prevention in dependent tissues. In this context, it is noteworthy that taller mammals (e.g. giraffes and humans) have tight fascial layers around their lower extremities whereas shorter mammals (e.g. rats and rabbits) do not. Apparently the cyclical compression and decompression associated with muscular activity and tight fascial enclosures (11) explain the highly variable P_a, P_v, and P_t that were observed.

The existence of impermeable capillaries in the giraffe tends to raise π_c and lower π_t but also, this relative impermeability may importantly reduce fluid conductivity Lp through the capillary membrane, allowing the lymphatic system to carry away any excess interstitial fluid that forms. In addition, based on our Xe-133 washout results, it is apparent that precapillary vasoconstriction normalizes blood flow and reduces capillary filtration area A in dependent tissues.

Some anatomical adaptations of the giraffe and human obviously represent developmental adjustments to high and variable gravitational pressures. For example, the important work of Williamson and colleagues document that capillary basement membrane thickness increases two fold from neck muscle to leg muscle of adult giraffes and humans (15). On the other hand, such membranes in the human fetus are uniform and considerably thinner than those in children and adult humans. A thicker capillary membrane in dependent tissues of the adult provides anatomical evidence for lower permeability to plasma ultrafiltration across the capillary. In this context, it would be interesting to investigate alterations of edema-preventing parameters in human legs during long-term exposure to microgravity and subsequent readjustment to Earth's 1 g or to hypergravity conditions on a larger planet. It is possible that the smooth muscle tone of precapillary arterioles and lymphatic vessels in dependent tissues is lost during long-term space flight in the absence of countermeasures. Long-term bed rest studies of edema-preventing mechanisms in humans may elucidate the time course of this postulated vascular deconditioning. The effect of long-term microgravity on fascia and other connective tissue structures needs careful assessment as well. Such studies should provide knowledge about mechanisms and rates of deconditioning and reconditioning in space travelers as well as in patients exposed to long-term bed rest.

The venous and arterial pressure data indicate that a siphoning phenomenon is probably not important to maintenance of blood perfusion in the giraffe brain (5). The existence of dense valves in the head and distal neck as compared to sparse valves in the proximal neck indicates their importance for preventing retrograde venous flow, for example, during short periods when the giraffe's head is lowered below heart level during drinking.

The results obtained in these initial studies of the giraffe suggest avenues of future gravitational physiology research in giraffes, other animals, as well as humans. For example, adaptations to head-down drinking in the giraffe requires further study to determine if intracranial hypertension is a problem in this posture. Cerebral spinal fluid pressures should be measured in various positions and activities. Lymphatic flow and pressures deserve detailed studies in giraffes and in patients exposed to long-term bed rest. More complete histomorphometric studies would provide greater anatomical understanding of the physiological mechanisms involved in edema prevention. Sleep patterns in the giraffe should be studied because of the lack of recumbency. Fascia and skin compliance should be studied in legs of various animals. Studies of other gravity sensitive animals [e.g. snakes (8) and ostriches] are indicated. Finally, better and more complete studies of venous pressures from the head into the thoracic cavity and right ventricle are needed.

ACKNOWLEDGEMENTS

This research was supported by grants from NIH (HL-32703), NSF (DCB-8409253), National Geographic Society (3072-85) and by a travel award from NASA through the American Physiological Society.

REFERENCES

1. Aukland, K. and H.M. Johnson. A colloid osmometer for small fluid samples. **Acta Physiol. Scand.** 90:485-490, 1974.

2. Goetz, R.H., J.V. Warren, O.H. Gauer, J.L. Patterson, Jr., J.T. Doyle, E.N. Keen, and M. McGregor. Circulation of the giraffe. **Circ. Res.** 8:1049-1058, 1960.

3. Hargens, A.R. Interstitial Fluid Pressure and Lymph Flow. In: **Handbook of Bioengineering,** edited by R. Skalak and S. Chien. New York: McGraw-Hill, Chapter 19, p. 1-25, 1986.

4. Hargens, A.R., J.B. Cologne, F.J. Menninger, J.S. Hogan, B.J. Tucker and R.M. Peters. Normal transcapillary pressures in human skeletal muscle and subcutaneous tissues. **Microvasc. Res.** 22:177-189, 1981.

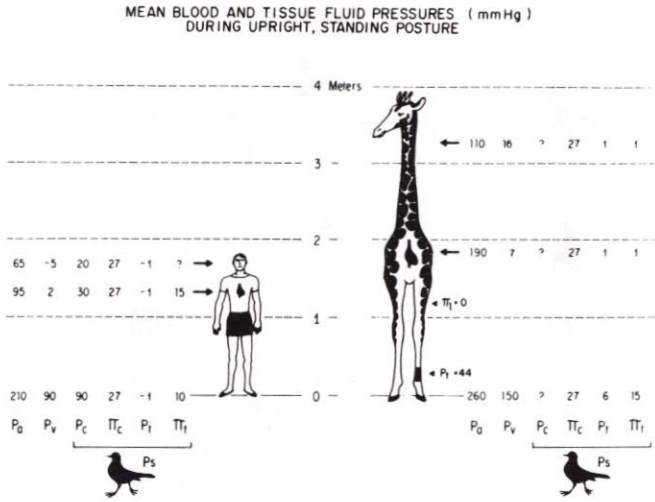


Figure 2. Mean arterial P_a, venous P_v and Starling pressures (P_c, π_c, P_t, and π_t) in giraffe (right) as compared to human (left) at hydrostatic levels between the head and feet. Lymph samples obtained from the leg had only trace amounts of protein and π_l = 0. Foot samples for π_t were often contaminated by blood and therefore, were less reliable. It's noteworthy that P_t beneath the tight skin and fascia of the legs ranged between 40-50 mmHg, indicating the presence of a "natural g-suit" in the giraffe. Data for human pressures are obtained from several sources besides our previous studies [From Hargens et al. (6)].

Although P_c was not measured directly in the giraffe, it's probably near P_v in the feet (150 mmHg) and near 10-20 mmHg at the top of the giraffe's neck (5). Surprisingly π_c was identical in the giraffe and human and therefore, π_c in the giraffe foot offers no unusual resorptive pressure for preventing dependent edema. Although some P_ts in the neck were negative, average bodily P_t ranged between 1 and 6 mmHg, except under the tight skin and fascia of the extremities where mean P_t was 44 mmHg. Interestingly, π_t was very low (1 mmHg), except in foot samples that were often contaminated by blood. This finding provided evidence that giraffe capillaries are highly impermeable to plasma proteins and that σ_p approximated unity. This conclusion was supported by studies of peripheral lymph that indicated only trace amounts of protein were present and π_l equalled zero.

Blood flows in skeletal muscle of the neck and the leg both averaged 4 $ml \cdot min^{-1} \cdot 100g^{-1}$. Therefore, it was apparent that arteriolar smooth muscle was effective in normalizing blood flow in the leg despite significantly higher arterial perfusion pressures. Precapillary sphincter activity combined with pronounced arterial and arteriolar wall hypertrophy in dependent tissues were prominent features of our giraffe histomorphometric studies (10).

Plugging our values for the Starling pressures into Equation 1 yielded a net resorptive pressure of -7 mmHg in the giraffe neck and net filtration pressures of +88 to +152 mmHg for tissues of the leg. These calculations suggested that giraffes were susceptible to dependent edema in an upright, stationary posture. However, our radiotelemetry data for the giraffe foot indicate that P_a (ranging between 70 to 380 mmHg), P_v (-250 to +240 mmHg) and P_t (-120 to +80 mmHg) were highly variable during normal ambulation. Consequently, it appeared there was an effective pumping mechanism in the vascular and interstitial spaces for removing blood and interstitial fluid against gravity. The tight skin and fascial layers of the giraffe leg provided a functional "g-suit" to prevent pooling of blood and interstitial fluid in dependent tissues.

The pressure gradient down the jugular vein was about one-tenth that expected for a continuous column of blood (Fig. 3).

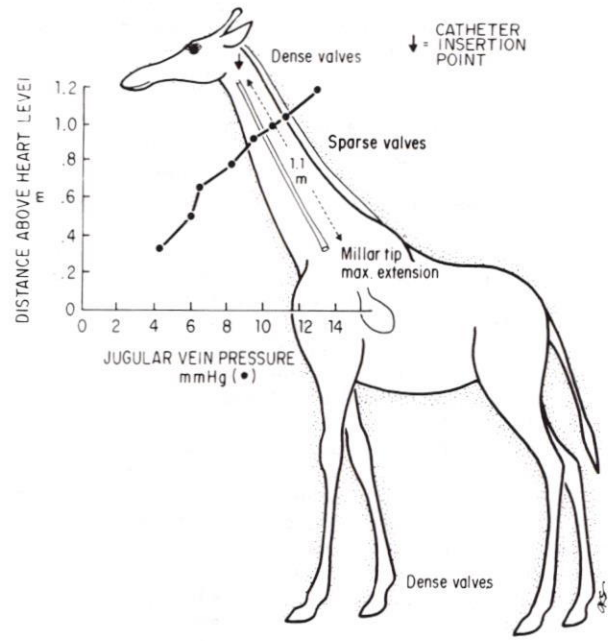


Figure 3. Pressure as a function of hydrostatic height in the jugular vein and intervalve distances in the giraffe neck and leg. In one giraffe the jugular vein pressure gradient was approximately 0.14 cm H_2O per cm of vertical distance. Intervalve distances were short in the head, distal neck, and proximal legs but long in the proximal neck [From Hargens et al. (5)].

GRAVITATIONAL CARDIOVASCULAR ADAPTATION IN THE GIRAFFE

Alan R. Hargens

Division of Orthopaedics
and Rehabilitation (V-151)
University of California
and VA Medical Center
San Diego, California 92161

INTRODUCTION

This paper reviews our recent results (5,6) concerning hemodynamics and fluid balance in the giraffe as it pertains to gravitational physiology. By virtue of its tallness, the giraffe provides a sensitive animal model for investigating adaptive mechanisms to terrestrial life in a normal gravitational field (1 g). Compared to other mammals, adult giraffes are unique because they reach five to six meters and walk around most of the day and night in an upright posture. Previous physiological studies of the giraffe have focused upon arterial blood pressures at levels of the head and neck (2,9,13,14). Briefly, these investigations demonstrated that arterial pressure near the giraffe heart is about twice that in humans so as to provide more normal blood pressure and perfusion to the brain. It is also known that giraffes faint when exposed to relatively small increases in g forces while they are transported by plane. However, another important question to gravitational adaptations of tall animals is how giraffes avoid pooling of blood and tissue fluid (edema) in dependent tissues of their extremities. Assuming a 5 1/2 meter giraffe has a mean arterial pressure of 200 mmHg at heart level, one may roughly calculate the mean arterial pressure in the foot may exceed 400 mmHg. The famous Danish physiologist August Krogh speculated that colloid osmotic pressure must be very high in blood of giraffe feet in order to prevent edema formation (14). Previous to our experiments last year, however, no one had measured colloid osmotic or hydrostatic pressures in blood or tissue of giraffe feet.

METHODS

The forces that regulate transcapillary fluid balance were first identified by the pioneering British physiologist Ernest Starling (12). These fluid pressures are commonly called "Starling pressures" and are represented as P_c, P_t, π_c, and π_t (Fig. 1) in the present formulation of transcapillary fluid flow J_c:

$$J_c = L_p A[(P_c - P_t) - \sigma_p (\pi_c - \pi_t)] \qquad \text{Eqn. 1}$$

where L_p is fluid conductivity, A is capillary membrane surface area, and σ_p is the protein reflection coefficient for the capillary membrane (3).

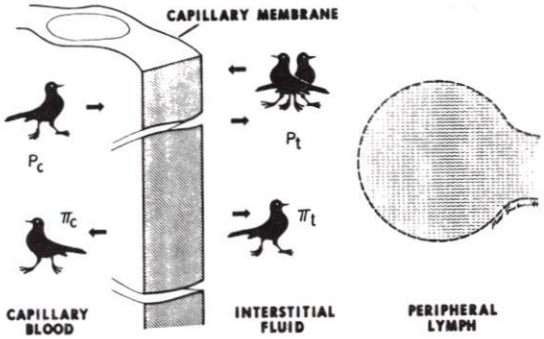


Figure 1. Starling pressures that govern fluid exchange across the capillary membrane are filtration pressures (capillary blood pressure P_c and interstitial fluid colloid osmotic pressure π_t) and resorptive pressure (blood colloid osmotic pressure π_c). Interstitial fluid pressure P_t is sometimes positive (favoring resorption) and sometimes negative (favoring filtration). Usually, fluid is filtered across the capillary membrane into the interstitium and drained by the peripheral lymphatic system.

During the 1985 Giraffe Physiology Expedition to South Africa, eight 3-4 meter male and female giraffes were studied in terms of their "Starling pressures", regional blood flow, and histomorphology. Because of culling programs unique to South Africa, two giraffes were killed by a local butcher who allowed harvesting of multiple tissue samples from various regions of the giraffes' bodies. Separately, arterial and venous blood pressures were determined by saline-filled, polyethylene tubing connected to pressure transducers kept level with each catheter tip. This also allowed periodic sampling of arterial and venous blood for determination of colloid osmotic pressure (1). Concurrently, interstitial fluid pressure P_t was measured by the wick catheter technique (4), maintaining the pressure transducer level with the catheter tip. Empty wick catheters were employed to collect 5 µl samples of interstitial fluid for determination of colloid osmotic pressure (4). Jugular vein pressures were measured as a function of hydrostatic height in three giraffes using the Millar Mikrotip transducer. Thus, venous pressures were determined without saline-filled catheters because the pressure-sensing surface was at the catheter's tip. These measurements were correlated with venous valve spacing studies in dissected veins. Local blood flows in neck and leg tissues were measured by the Xe-133 washout procedure (7). These initial studies of the giraffes in a stationary upright posture were possible using a mixture of detomidine and azaparone to sedate the giraffes during all catheterizations and blood flow measurements. Subsequently, a radiotelemetry system was mounted in a backpack at the base of each giraffe's neck. This allowed continous monitoring of blood and interstitial fluid pressures while the giraffe was free to move during normal day and night activities.

RESULTS

Mean values for arterial and venous pressures qualitatively matched the expected gravitation pressure gradients using the heart as a reference for fluid discontinuity between the head and foot (Fig. 2).

power spectra between HUT and HDT during MA increased substantially, especially for the higher frequency activities. The powers of 15-17 Hz and 40 Hz activities during HDT-MA were significantly less than those during HUT-MA at O_1-P_3-T_5 and O_2-P_4-T_6, especially at O_2-P_4-T_6.

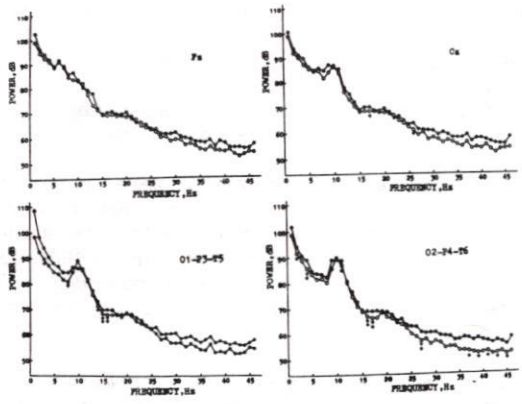


Figure 2. The mean EEG power spectra of 15 subjects at different electrode positions during HUT-MA (·) and HDT-MA (∘).

Comparison of EEG Responses to MA during HUT and HDT

In Table 1, the statistical results of comparison between the EEG power responses to MA were summarized for HUT and HDT respectively. Two major features were revealed: compared with R, the power of 40 Hz activity was significantly increased during HUT-MA but not during HDT-MA so that the power of 40 Hz during HDT-MA was significantly less than that during HUT-MA at O_2-P_4-T_6 ; however, the power of 8-10Hz and 15-17Hz activities were decreased significantly during HDT-MA but not during HUT-MA.

Table 1. Summary of EEG responses to MA during HUT and HDT

	FREQUENCY (Hz)																					
	7	8	9	10	12	15	16	17	19	20	21	23	25	27	34	40	41	43	44	45	46
HUT																					
Fz									•	-•							•			•	
Cz								•								•	•			•	
01-P3-T5				-•								•				•	•		•	•	•
02-P4-T6				-•					•							•	•	•	•		
HDT																					
Fz			-•	-•	-•	-•					-•	-•			•						
Cz		-•••	-•	-•••		-••	-•	-•							•						
01-P3-T5	-•	-•			-••	-•	-•	-•	-•				•-••								
02-P4-T6		-•	-•	-••				-•							•			•	•		

*: P<0.05; **: P<0.01; ***: P<0.001

DISCUSSION

Reliable EEG responses to MA were derived from present study by using the triggered MA and a time-locked delayed sampling method. Taking the EEG samples from 0.3 to 1.3 seconds after each number displayed could basically eliminate the effect of visual perception and could just cover the period during which MA was taking place.

The most interesting finding was that the increase of 40 Hz EEG activity during MA was significantly declined during HDT, especially in the posterior right brain. It is known that the 40 Hz activity is related to the focused attention (2) and the right brain is probably more envolved in the attention process (1). Therefore, it is reasonable to suppose that in the simulated WLC the responsibility of the brain is declined as far as the attention is concerned. As mentioned before, one of the reasons of the EEG response change to MA may be the increased activity of baroreceptors resulted from the body fluid shift during simulated WLC. This point is supported by Walker's data (3) that the amplitude of P_1 in the VEP at systolic pressure phase recorded from right brain is significantly less than that at diastolic phase. The supposed suppression of brain's activity is also supported by another finding in present study, i.e., the great reduction of 8-10 Hz and 15-17 Hz ativities during HDT-MA. As it is evidenced that the low frequency (below 13 Hz) and the high frequency (above 26 Hz) EEG activities are more related to the activities of subcortical structures (4), the results of present study, i.e., the decrease of 1-7 Hz activities during HDT (Fig.1 and 2) and the response change of 40 Hz and 8-10 Hz activities during HDT-MA, suggest that HDT may has more profound effects on the function of subcortical structures.

In summary, the results of present study provides the evidence to show that the BFS is substantially changed in the simulated WLC, so that investigating the BFS change during space flight is by no means unimportant.

ACKNOWLEDGMENTS

The authors are grateful to Ms. Wang Aihua for patient preparation of the manuscript.

REFERENCES

1. Geschwind, N. Disorders of attention: a frontier in neuropsychology. Phil. Trans. R. Soc. Lond. B298:173-185, 1982.
2. Sheer, D.E., Focused arousal, 40Hz EEG and dysfunction. In: Th. Elbert, B. Rockstroh, W. Lutzenberger and N. Birbaumer (Eds.), Self-Regulation of the Brain and Behavior. Springer-Verlag, Berlin, New York, 1984, pp.64-84.
3. Walker, B.B., Visual evoked potentials change as heart rate and carotid pressure change. Psychophysiology 19:520-527, 1982.
4. Itil, T.M. and Saletu, B., Digital computer-analysed resting and sleep EEGs (sleep prints) after hemispherectomy in man. Electroenceph. Clin. Neurophysiol., 30:457-461, 1971.

THE EFFECT OF HEAD-DOWN TILT ON THE EEG RESPONSE TO MENTAL ARITHMETIC (MA)

Wei Jinhe, Yan Gongdong,
Guan Zhiqiang, Shen Xianyun

Institute of Space Medico-Engineering
Beijing, China

ABSTRACT

To investigate the possible change of brain function state (BFS) in the weightless condition (WLC), 15 normal subjects' EEG responses to MA during 45° head-up tilt (HUT) and -10° head-down tilt (HDT) were compared. The major finding was that the increase of 40 Hz EEG activity during MA was significantly less during HDT than during HUT, especially at the scalp area corresponding to right associate cortex. It was suggested that the responsibility of brain was declined and the BFS was readjusted, especially in the posterior right brain in the simulated WLC.

The hypothesis of present study is that, as the BFS is determined by the interactions among the subsystems of brain, the following physiological changes in human resulted from the microgravity environment during space flight may affect the BFS: (a) a great portion of body fluid shifts to the head and chest from lower body which may cause changes in the brain circulation and the activity of baroreceptors in the cardiovascular system; (b) the abruptly change of the function state of vestibular system; (c) the disturbance to the weight-supporting and posture-maintaining system and it's adaptation process. To see if there is any change of BFS in the simulated WLC, the EEG responses to MA during HUT and HDT have been compared. This is one part of a series studies on the effects of simulated weightlessness on the reponse property of central nervous system.

METHODS

15 right handed healthy volunteers (male, 18-50 yr) were studied. The subjects were lying on a comfortable tilt table in a sound attenuated and electrical isolated room. A triggered MA method was used. Twenty one-digit numbers were displayed to the subjects successively, once per 3 seconds, through a Sharp-pc-1500 computer which was fixed at the front of the subjects with a 30cm-distance away from their eyes. The subjects were asked to add or substract the displayed numbers to or from the preceeding result according to it's sign.

Four EEG electrodes were placed at F_z , C_z, O_1 - P_3 - T_5 and O_2-P_4-T_6 of the International 10-20 system with linked ears as reference. The vertical EOG of right eye was also recorded. The EEG and EOG signals were amplified with a pass band of 0.05-100Hz, and recorded an analog tape (Sony A-69 tape recorder) for off-line analysis.

The procedures of experiment were as follows: after practising MA and preliminary EEG recording at supine position on the tilt table, the subject was turned to 45° HUT, on the 30 min of HUT, EEGs at rest (R) and during MA were recorded; then set the subject to -10° HDT, taking the same recordings.

EEGs were analysed on pathfinder II (Nicolet), all the programs were written in FORTRAN by the authors. The powers of 1-46 Hz EEG activities were calculated in terms of a time-locked and delayed sampling method and FFT, the sampled data were tapered first by a cosine window. For both the rest and MA condition, twenty 1-sec samples were used to get the mean power spectra of each subject. To reduce the effect of visual perception on the EEG response, the samples were started 0.3 sec after each number was displayed, The power differences in each of the 1-46 Hz EEG activities in 15 subjects were compared between MA and R as well as between HDT and HUT, respectively, in terms of paired-data t-test.

RESULTS

Comparison of EEG Power Spectra between HUT and HDT at rest

The mean EEG power spectra of 15 subjects during HUT and HDT at R were shown in Fig.1. There were only a few frequencies at which the power differences between HDT and HUT were significant. The decrease of 1-7 Hz activities at O_1-P_3-T_5 and O_2-P_4-T_6, and the decrease of 34 Hz activity at C_z and O -P -T during HDT were prominent.

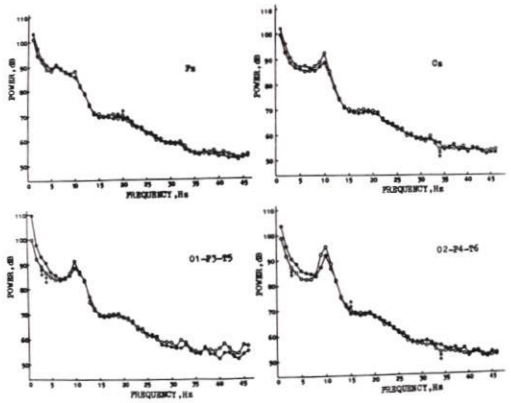


Figure 1. The mean EEG power spectra of 15 subjects at different electrode positions during HUT (·) and HDT (∘) at rest.

Comparison of EEG Power Spectra between HUT and HDT during MA

As seen in Fig.2, the differences of EEG

Integration of preparations, experiments and postflight evaluation

An informal coordination of research proposals was initiated at an early stage among several potential investigators in the Anthrorack project. An effort was made to encourage proposals which would be synergistic rather than competing. The subsequent peer review and accommodation study also aimed at identifying experiments which could be coordinated. Within each physiological subdiscipline (e.g. pulmonary physiology) a coordinating principal investigator has been appointed.

The ground-based development and validation of experimental methods must be performed by each participating investigator, who must provide national funding for that work. ESA on the other hand provides the Anthrorack facility with its service elements and access to common facilities for the training of astronaut scientists. Last but not least ESA provides the space transportation in collaboration with US and German agencies.

The time-lining of the experiments is performed by the project management and represents a compromise between investigator requests, availability of crew time and constraints dictated by other activities in the Spacelab. As an example one important consideration must be whether vigorous physical activity such as during ergometry generates disturbances of the microgravity environment necessary for certain experiments in material science. Other important considerations concern the contamination of the Spacelab atmosphere with certain breathing gases used in pulmonary studies. A similar time-lining will be made for the various ground control studies, that the astronauts must undergo before and after the space mission.

In comparison to traditional ground-based physiology, space research must be based on observations made on a very limited population. Extreme care must therefore be taken to avoid overinterpretation of chance findings. By careful experimental design this risk can be minimized, i.a. by observing similar (but not identical) phenomena with several different methods. A coordinated post-flight analysis of data is also necessary. Efforts will be spent to facilitate exchange of data and conclusions between the various investigators. The ultimate aim of the Anthrorack study is to perform a systems analysis of human physiology in microgravity rather than the mere compilation of results from mutually independent investigators.

- Pourcelot, L. (F-11): Cardiovascular system: regulation and adaptation to weightlessness

ENDOCRINE RESPONSES. The blood and fluid shifts resulting from the absence of gravity elicit and are modified by concomitant endocrine responses. In particular the investigations in this area have focused their interest on endocrine mechanisms of the pituitary and the kidneys:

- Norsk, P. (DK-22): The influence of microgravity on endocrine and renal elements of volume homeostatis in man

- Riondino, G. (I-40): Effect of spaceflight on pituitary activity, reproductive function and some retinal parameters related to cephalic circulation

- Roecker, L. (D-52): The role of volume regulating hormones and plasma proteins in man for the adaptation to micro-g, and for the readaptation to terrestrial conditions

PULMONARY FUNCTION. On the earth, gravity is generally considered to be the single most important determinant of the distribution of both alveolar ventilation ($\dot{V}A$) and blood perfusion ($\dot{Q}$) of the lungs. However, this remains to be proven, and it could not be excluded that other important mechanisms for the $\dot{V}A/\dot{Q}$ distribution can be detected in the absence of gravity. The following studies employ i.a. rebreathing and wash-out techniques to study these scientific issues. The possibilities of fluid accumulation in the lungs during microgravity will also be considered:

- Linnarsson, D. (S-21): Pulmonary perfusion and ventilation in microgravity, during rest and exercise

- Maelskaer, P. (DK-35): Pulmonary stratification and compartment analysis with special references to microgravity

- Paiva, M. (B-55): Ventilation distribution in microgravity

METABOLISM. A multitude of influences will give rise to metabolic changes in microgravity. Among such influences can be mentioned muscular unloading, which is likely to affect both long-term protein metabolism and the energy cost of during short-lasting muscular exercise. Studies in this area are:

- Fern, E.B. (CH-49): Changes in the rate of whole- body nitrogen turnover, protein synthesis and protein breakdown under conditions of microgravity

- Linnarsson, D. (S-20): Overall gas exchange during rest and exercise in microgravity

GERMAN AND US STUDIES. The Anthrorack facility will be shared with a number of German and US investigators. The selection of these non-ESA experiments is not finalized at the time of this review (October 1986). However, a high degree of scientific and operational synergism is anticipated between these experiments and the above ESA experiments.

The hardware

The Anthrorack hardware is under construction and consists of a double rack designed to fit into the Spacelab, which provides power, cooling etc. The rack will provide recording and computing facilities of more general type. In addition, there will be a number of service elements, i.e. equipment for specific experimental purposes in areas where a number of different investigators have specified the use of similar instrumentation. Among the service elements the following can be mentioned:

- Amplifiers for surface potentials such as ECG

- Blood pressure device for non-invasive intermittent determinations during rest and exercise

- Blood sampling kits

- Centrifuge for blood samples

- Ergometer for studies of dynamic leg exercise

- Facility computer for on-line display and computations

- Freezer/Cooler for sample preservation

- Limb volume measurement device

- Lower body negative pressure device with a controlled internal environment in terms of pressure and termal exchange

- Respiratory monitoring system including gas flow meters, mass spectrometer and facilities for rebreathing

- Ultrasonic monitoring system including a two-dimensional echocardiograph and doppler facility for blood flow studies.

Several contractors are now in the process of determining the final design of the Anthrorack hardware, and the construction of certain elements is already completed. The progress of this work is monitored by technical and scientific experts from ESA and participating research institutions.

Experiment-specific equipment is to be provided by the investigator, who must qualify the equipment against the same rigorous standards as ESA-developed equipment. Examples of such equipment are:

- Tonometer for intraocular pressure

- Body fluid densitometer

- Shell tissue thickness meter

- Electrical impedance device for segmental fluid volume

- Demand valve for pulmonary wash-out studies

THE ESA ANTHRORACK PROJECT: INTEGRATED RESEARCH IN HUMAN PHYSIOLOGY

D. Linnarsson

Department of Baromedicine
Karolinska Institute
S-104 01 Stockholm, Sweden

The evolution of terrestial life has taken place under the constant influence of gravity, but in all fields of life sciences there is a lack of knowledge about the importance and nature of the influence of gravity on life processes. This is true also for the area of human physiology. A new exciting tool for experimentation became available with the onset of the manned exploration of space. The men and women who were exposed to microgravity could be observed as experimental subjects. Areas where new insights could be gained were e.g. in the control of balance and locomotion, in cardiovascular dynamics, in fluid balance and in bone mineralization.

In the European Space Agency, the preparation for a life science programme was started in the early 70´s, with the aim to offer European life scientist the possibility of using microgravity as a tool for basic research. A "Life sciences working group" was established as an advisory organ within the agency. Announcements of opportunities were distributed to the scientific community as a call for ideas in 1975 and a call for proposals in 1976. On the basis of this iterative dialogue with the scientific community the concept of a facility for studies in human physiology was formulated and was given the working name "Anthrorack". The facility was to be flown as a double rack in the European-built Spacelab. The Anthrorack project has come to be used not only to designate a certain set of hardware but also for the set of experiments to be performed with it.

During the early 80´s the parallel processes of defining the scientific experiments to be performed and the corresponding hardware were initiated with calls for proposals and for tender respectively. The final selection of experiments was made during the fall of 1986, and was based first on a scientific peer review process and then on a technical and scientific accommodation study. The first flight opportunity for Anthrorack experiments will be with the Spacelab flight D-2 in the early 90´s.

The experiments

Provisions were made to accommodate all types of physiological experiments. However, previous space experimentation in the US and in the USSR, and the iterative communication with the scientific community has shown that especially the following areas could profit scientifically from experiments in microgravity: control of balance and locomotion, cardiovascular dynamics, endocrine responses to fluid and blood shifts, pulmonary function and metabolism. Due to constraints of experimental time in particular it was decided to put the emphasis on the latter four areas during the first mission with Anthrorack. This, however, does not reflect any scientific priority between the various subdisciplines.

The proposed and selected experiments deal with overlapping areas, so that any subdivision of the experiments into subdisciplines will not be entirely consistent. However, for the purpose of simplicity an attempt has been made to group the experiments as they are listed below: Within each group principal investigators are listed in alphabetical order.

FLUID BALANCE. Earlier space flights have revealed the presence of a previously unknown fluid distribution mechanism causing a headward shift of fluid and edema in the cephalad areas of the body. The studies in this area employ a variety of methods to quantify and to follow the time course of these fluid shifts during a 7-10 day exposure to microgravity:

- Draeger, J. (D-47): Tonometry: measurement of intraocular pressure in microgravity
- Hinghofer-Szalkay, H. (A-41): Body fluid densitometry: investigation of volume and protein shifts
- Kirsch, K. (D-51): Fluid volume distribution within superficial shell tissues and the tissue compliance along body axis in man
- Linnarsson, D. (S-19): Total body fluid and segmental fluid distribution in microgravity.

CARDIOVASCULAR DYNAMICS AND BLOOD. Blood shifts in the cephalad direction go along with the fluid shifts mentioned above. Net reductions of blood volume are known to follow together with a reduced orthostatic tolerance. So far only sparse and indirect data exist on cardiac performance during rest and exercise (stroke volume, cardiac dimensions) and central and peripheral vascular control during tests with simulated gravity (lower body negative pressure, LBNP). The activity of certain form elements of the blood is also altered. In the following studies an integrated study of these changes can be made:

- Bonde-Petersen, F. (DK-44): Peripheral and central hemodynamic adaptation to weightlessness during rest, exercise and lower body negative pressure in humans
- Cherrier, M. (F-34): Study of the incidence of hemorheologie diseases found in individuals subjected to weightlessness or space motion sickness, thanks to new biologic and pharmacologic techniques (Erythrometer and Troxerutine CAS)
- Foldager, N. (DK-17): The central venous Pressure during weightlessness

ACKNOWLEDGEMENTS

The authors thank Susan Brand and Alan Nordheim of G.E./MATSCO, Sharon Jackson of Technology Incorporated, and Dr. Jane Krauhs of Northrop Services, Inc. for their help in preparation of the manuscript.

REFERENCES

1. Anonymous. Life Sciences Flight Experiments Program Life Sciences Laboratory Equipment (LSLE) Description, JSC-16254I. Houston, TX: NASA/Johnson Space Center, 1986.

2. Froehlich, W. Spacelab: an International Short-Stay Orbiting Laboratory, NASA EP-165. Washington, D.C.: National Aeronautics and Space Administration, 1983.

3. Johnston, R. S., and L. F. Dietlein (Eds.) Biomedical Results from Skylab, NASA SP-377. Washington, D.C.: National Aeronautics and Space Administration, 1977.

4. Johnston, R. S., L. F. Dietlein, and C. A. Berry (Eds.) Biomedical Results of Apollo, NASA SP-368. Washington, D.C.: National Aeronautics and Space Administration, 1975.

5. Leach, C. S. Metabolic experiments on Spacelab-4. Society of Automotive Engineers Technical Paper Series, #820831, 1982.

6. Leach, C. S., J. P. Chen, W. Crosby, P. C. Johnson, R. D. Lange, E. Larkin, and M. Tavassoli. Spacelab 1 Hematology Experiment (1NS103): Influence of Space Flight on Erythrokinetics in Man, NASA Technical Memorandum 58268. Houston, TX: Johnson Space Center, 1985.

7. Nicogossian, A. E., and J. F. Parker, Jr. Space Physiology and Medicine, NASA SP-447. Washington, D.C.: National Aeronautics and Space Administration, 1982.

8. Perry, T. W., L. D. Griffiths, R. J. White, J. A. Rummel, and J. I. Leonard. The first dedicated life sciences Spacelab mission. International Astronautical Federation Symposium on Life Sciences, Lausanne, Switzerland, October 12, 1984, IAF Paper 84-170.

9. Perry, T. W., and D. H. Reid. Spacelab mission 4--The first dedicated life sciences mission. Aviat. Space Environ. Med. 54: 1123-1128, 1983.

10. Sisakyan, N. M. (Ed.) The Second Group Space Flight and Results of Soviet Missions Onboard the Spacecraft Vostok. Moscow: USSR Academy of Science, 1965.

TABLE 1. Spacelab Life Sciences Experiment Complement

Discipline/Investigator	Mission
Renal/Endocrine	
C. S. Leach	1,2
M. C. Moore-Ede	2,3
Cardiovascular/Cardiopulmonary	
C. G. Blomqvist	1,2
D. L. Eckberg	1,2
L. E. Farhi	1,2
P. M. Hutchins	1,2
V. P. Popovic	1,2
J. B. West	1,2
Hematology	
P. C. Johnson, Jr. (2 experiments)	1,2
R. D. Lange	1,2
Immunology	
A. Cogoli	1
Muscle	
K. M. Baldwin	1,2
J. F. K. Hoh	1,2
D. Riley	1,2
T. P. Stein	1,2
Calcium/Bone	
C. D. Arnaud	1,2
E. R. Morey-Holton	1,2
Vestibular	
M. D. Ross	1,2
L. R. Young	1,2
General Biology	
C. A. Fuller	2,3

inflight period and others will be centrifuged to expose them to as many as 4 times the force of gravity. Information from other experiments will be provided to the principal investigator of this experiment for comparison of the actual environment of in vivo lymphocytes during spaceflight with that of the cultured cells.

Muscle Discipline

Four experiments will investigate the origin of the muscle atrophy and negative nitrogen balance that were documented in the Skylab missions. One will deal with the question: Is protein synthesis decreased or is protein breakdown increased, or do both occur during spaceflight (8,9)? The rate of synthesis of several proteins, including fibrinogen, albumin, immunoglobulin G and hemoglobin, will be calculated from the rate of urinary excretion of a radiolabeled amino acid. The rate of breakdown of collagen and muscle protein will be determined by measuring the rate of excretion of amino acids that are characteristically produced by catabolism of those proteins (5).

Since the breakdown of muscle cells puts quantities of electrolytes and nitrogenous substances into the blood, and the excess must be eliminated by the kidneys, results of this protein metabolism experiment and the fluid/electrolyte metabolism experiment are related. Measurements of fluid compartments will be used in determining how the fluid environment around muscle cells may change, and body mass data can be compared to protein synthesis and degradation rates. Circulating levels of hormones involved in metabolism, such as cortisol and catecholamines, will also be useful for interpretation of the protein metabolism experiment.

Three experiments are concerned with the effects of spaceflight on skeletal muscle (8, 9). Investigators will attempt to detect any early signs of atrophy and impaired muscle function and determine which muscles are affected.

Calcium/Bone Discipline

Studies of mineral loss during spaceflight will be concerned with factors that control calcium metabolism (5,8). Circulating levels of the calciotropic hormones calcitonin, vitamin D, and parathyroid hormone will be determined; a calcium tracer will be used to study calcium turnover, and bone growth will be measured. Data from the fluid/electrolyte experiment (circulating and urinary levels of calcium, phosphorus, sodium, and hormones regulating fluid and electrolyte metabolism) will be provided to the principal investigator of the mineral loss experiment.

Vestibular Discipline

The objective of two experiments is to document effects of spaceflight on the vestibular system (8). In one experiment the gravity receptors (otolith apparatus) will be examined. In the other, the sensory conflict theory of space motion sickness will be investigated by measuring a number of the manifestations of perception by the vestibular system. These will include eye deviation during rotation, and leg electromyographic activity. Signs and symptoms of space motion sickness will be measured and compared with hormone and fluid metabolism data from the fluid/electrolyte experiment.

General Biology Discipline

A thermoregulation experiment will be performed (8,9) in which body temperature will be monitored continuously. Changes in circadian rhythms during spaceflight might alter normal control of body temperature. To date, little information is available concerning circadian rhythms during flight.

Conclusion

The experiment complement for SLS-1, SLS-2, and SLS-3 was selected to enhance the basic understanding of physiological adaptation during spaceflight. Although the results of previous studies confirm that suspected changes are occurring, causal relationships cannot yet be defined. The integrated experiments to be conducted on the SLS-1, SLS-2, and SLS-3 missions should bring us closer to defining such relationships. These missions will contribute to the progressive improvement of man's performance in space, both in the short term for Shuttle operations and in the projected long-term Space Station missions.

The dedicated Spacelab life sciences mission was designed to provide the first opportunity to study the acute effects of microgravity exposure in a comprehensive, interrelated fashion. Primary emphasis was placed on gathering more data related to previously observed physiologic effects of weightlessness. The immediate, major effects of the absence of gravity are reduction of the load on weight-bearing tissues such as bone and muscle, reduction of hydrostatic gradients of body fluids, and alteration of vestibular system function.

Twenty-one experiments are being developed as the scientific payload of the Spacelab life sciences mission. These experiments can be arranged into eight disciplines: renal/endocrine, cardiovascular/cardiopulmonary, hematology, immunology, muscle, calcium/bone, vestibular, and general biology (8) (Table 1). Although the original research flight plan was conceived as that of a single mission, payload development and maturation have resulted in division of the original payload into three dedicated missions. These missions are identified as Spacelab Life Sciences 1 (SLS-1), Spacelab Life Sciences 2 (SLS-2) and Spacelab Life Sciences 3 (SLS-3).

A data sharing plan was formulated to maximize the amount of information to be obtained from each mission and to minimize redundancy. Although each experiment concentrates on a particular problem of space medicine, the problems are interrelated and must be solved by using information from several different research areas. Investigators will also share information at group meetings and through publications. The synergistic effect of payload integration is expected to result in a scientific yield that far exceeds that of its component experiments conducted independently.

Renal/Endocrine Discipline

Two experiments investigating fluid and electrolyte metabolism provide a good example for demonstrating interrelationships between experiments on a mission. These experiments will focus on the headward fluid redistribution resulting from spaceflight, and its effects on fluid and electrolyte metabolism. The volume of fluid in various compartments of the body will be measured before, during, and after flight. The compartments to be measured are blood plasma, intracellular and extracellular fluid, interstitial fluid and total body water. Body mass will be determined on every inflight day, and volume of all urine voids will be recorded. Subjects' food and water intake will also be recorded throughout the flight, and the amounts of sodium, potassium, calcium and protein ingested will be calculated.

A radioactive tracer will be used to measure the secretory rate of aldosterone, which plays a major role in regulation of fluid and electrolyte metabolism. Additional hormones to be measured in blood plasma include antidiuretic hormone, angiotensin I, prostaglandins, cortisol, adrenocorticotropin, aldosterone, atrial natriuretic factor, and catecholamines. All of these hormones are involved in the regulation of fluid and electrolyte levels in the body. Renal function tests will be conducted during spaceflight: glomerular filtration rate and effective renal plasma flow will be determined early and late in the mission. Blood urea nitrogen, sodium, potassium, calcium, phosphorus, creatinine, chloride, and osmolality will also be measured. Most of the same variables will be assayed in urine if volume is sufficient.

Cardiovascular/Cardiopulmonary Discipline

Six cardiovascular/cardiopulmonary experiments are concerned with the effects of acute fluid shifts on the cardiovascular and pulmonary systems, adaptation of the cardiovascular system to weightlessness, and postflight cardiovascular and pulmonary readaptation to terrestrial gravity (8,9). The data to be collected include blood pressure and heart rate, electro- and echocardiograms, cardiac output measurements, pulmonary blood volume and blood flow distribution, central venous pressure, leg blood flow and venous compliance, and static leg volume. Echocardiography and early measurement of central venous pressure during the first 12 hours of flight should make it possible to determine the time course of the buildup of fluid in the head and chest during weightlessness. This information as well as data pertaining to fluid volume in the leg will complement the fluid volume measurements to be made for the fluid/electrolyte experiment. Aspects of central and peripheral circulation, including arterial/venous pressure, microcirculation, and aortic blood flow, will be measured before launch and after landing. The decreased blood volume expected to develop during spaceflight may cause changes in these hemodynamic variables. One of the experiments will provide detailed information about pulmonary function in microgravity, an integral part of the picture of cardiovascular/cardiopulmonary system physiology in spaceflight.

Hematology Discipline

Three hematology experiments will focus on erythrokinetics (8,9). The body's "correction" of a perceived increase in fluid volume is thought to be the cause of the decrease in plasma volume that has consistently been observed after spaceflight. The decreased plasma volume, in turn, is thought to result in an increased proportion of cell volume in the blood, which is eventually reduced by a decrease in red cell mass (6). Determination of the times at which the alterations occur would help to confirm or refute this hypothesis. The results of renal function tests should aid interpretation of the hematology experiments because they should show how fast the kidney is eliminating fluid. Plasma volume, total body water, and body mass are other variables that will be measured in the fluid/electrolyte experiment but are important in understanding blood cell production during flight. Blood levels of electrolytes, minerals, creatinine, urea nitrogen, and most of the hormones will also be furnished to the principal investigators of the erythrokinetics experiments. Hematocrit and serum protein data collected for the erythrokinetics experiments will be used in interpretation of the fluid/electrolyte experiment because these variables indicate how concentrated the blood is with respect to red blood cells and proteins.

Immunology Discipline

An immunology experiment (8,9) will be directed toward answering the question of whether spaceflight effects on lymphocytes are caused by weightlessness itself or by other spaceflight-related stresses. Lymphocyte cultures prepared on the ground, as well as cultures prepared during flight, will be used for studies of lymphocyte ultrastructure, proliferation, and protein synthesis during spaceflight. Some of the cells will be exposed to microgravity throughout the

SPACELAB LIFE SCIENCES 1 AND 2 SCIENTIFIC RESEARCH OBJECTIVES

Carolyn S. Leach and Howard J. Schneider
NASA/Johnson Space Center
Mail Code SD4
Houston, Texas 77058

The pressurized Spacelab module was designed and built to allow investigators to conduct research in space in an environment approximating that of a ground-based laboratory. It is configured to allow multiple investigations employing both human and non-human subjects. This flexibility is exemplified by the SLS-1, SLS-2, and SLS-3 experiment complement. Twenty-one experiments will be performed on these missions; the areas to be investigated are renal/endocrine function, cardiovascular/cardiopulmonary function, hematology, immunology, metabolic activity of muscle, calcium metabolism, the vestibular system, and general biology. A plan for integration of measurements will allow each investigator to use data from other experiments. The experiments make up a scientifically balanced payload that addresses fundamental biomedical problems associated with space flight and provides the first opportunity to study the acute effects of weightlessness in a comprehensive, interrelated fashion.

The Life Sciences Flight Experiment Program of the National Aeronautics and Space Administration is developing a dedicated Spacelab Life Sciences mission (9). The concept of a life sciences dedicated mission evolved from a desire to fully utilize life sciences research opportunities afforded by the Space Shuttle/Spacelab system toward the fulfillment of program goals. These goals are to promote the safety, well-being, and productivity of man in space, as well as to use the space environment to further man's understanding of fundamental problems in gravitational biology.

Early Research in Space Medicine

Examination of human physiological effects of spaceflight began with limited preflight and postflight measurements during the Mercury, Gemini, and Apollo programs (4) in the United States and the Vostok program (10) in the Soviet Union. Observed effects included degradation of cardiovascular performance, hemoconcentration, loss of red cell mass, loss of exercise capability, loss of bone density and calcium, loss of muscle nitrogen, vestibular disturbances, and disturbances in fluid and electrolyte metabolism.

The Skylab missions provided the first opportunity to conduct a comprehensive program of biomedical investigations in the microgravity environment (3). Unlike the previous programs, in which few inflight tests were performed, Skylab had equipment onboard for inflight physiologic testing. A great deal of biomedical information was obtained, which confirmed and added to the results from earlier spaceflight investigations. However, as in many research efforts, data from the Skylab studies generated more questions than answers. They showed that the many physiologic systems involved in the response to weightlessness have different response times. The body is normally in a steady state: blood pressure, fluid content of the body, red blood cell mass, and other physiologic conditions are stabilized at particular set points. Results from Skylab and other missions have indicated that after a few days the body begins to adapt to weightlessness and new homeostatic set points are established (7).

In these early periods of research in space medicine, emphasis was placed on identifying and characterizing disturbances in a number of physiologic systems. The limitations of spaceflight research at that time precluded the rigorous, systematic study necessary to explain the underlying mechanisms, but it was recognized that many of the important issues of space medicine could be addressed on short missions if proper facilities and techniques were available (8). The Spacelab facility, which can carry sensitive equipment normally unavailable for flight, provided the opportunity to document the integrated human response to spaceflight while attempting to understand the role of each major physiologic component.

Advantages of Spacelab

The Spacelab, built by the European Space Agency, is carried in the payload bay of the Space Shuttle. The pressurized Spacelab module is a versatile inflight laboratory that can be configured to meet the hardware requirements of an experiment payload (2,9). A set of laboratory core equipment designated as Life Sciences Laboratory Equipment is available for a wide variety of life sciences investigations (1). Experiments can be conducted in a comfortable shirt-sleeve environment with a controlled atmosphere.

Spacelab Life Sciences Missions

In response to an Announcement of Opportunity, approximately 400 investigators submitted proposals for experiments to be conducted on a Spacelab Life Sciences mission (9). Each proposal underwent peer review by scientists from the academic and industrial communities. Approximately 100 proposals were further evaluated for their ability to meet engineering requirements for flight (2) and objectives set forth in the Announcement of Opportunity (9). Requirements for experiment selection included the need to perform the experiment in space and a relatively high probability that the experiment objectives could be attained under the conditions imposed by payload integration and the laboratory itself. Reviewers gave preference to studies that dealt with issues important for manned spaceflight and to studies that could be combined to make efficient use of Spacelab resources.

primary, acute and secondary adaptive reactions in different subjects vary widely, then the measurements performed at specific or standardized time intervals are not actually standard because they describe changes that correspond to different stages of adaptation. This statement, which is correct with respect to ground-based simulation studies, seems to be obligatory in relation to space studies where nonuniformity associated with the reacting systems is aggravated by the nonuniformity of the situations and operational functions.

References

1. Aslanova I.F. et al. Proceedings of II Gagarin's conf., p.34, M., 1981.

2. Gazenko O.G. et al. In: Influence of dynamic factors of space flight on animals body, pp.28-37, M., 1979.

3. Gevlich G.M. Phd thesis, M., 1984.

4. Grigoriev A.I. et al. Space biol.med., 3, pp.21-27, 1985.

5. Gurovsky N.N. et al. Space biol. med., 2, pp.48-53, 1975.

6. Gurfinkel V.S. et al. In: Problems of Space biology, 13, pp.148-161, M., 1969.

7. Kozlovskaya I.B. et al. Proceed. of VI Conf. on space biol. med., 1, pp. 18-19, Kaluga, 1979.

8. Kozlovskaya I.B. et al. Physiologist, 25, 6, pp.49-52, 1982.

9. Noskoff V.B. et al. Physiology of man, 12, 5, pp.810-816, 1986.

10. Person R.S. In: Neural mechanisms of motor activity, M., 1969.

11. Tcherepakhin M.A., Pervushin V.I. Space biol.med., 4, 6, pp.46-49, 1970.

12. Berry C.A. Weightlessness in Bioastronautic, datebook NASA SP-3100 Washington, DC, 8, 349415, 1973.

13. Granit R. In: The basis of motor control. London, Acad. Press, 1970, 346 p.

14. Grigoriev A.I. et al. Ann. Aerospace association, Miami, USA, 1982.

15. Kozlovskaya et al. Physiology, 24, 6, 59-62, 1981.

16. Kvetnansky R. et al. Space biol. med., 4, 64-65, 1981.

17. Leach C. et al. Aerospace environment med., 47, 4, 402-408, 1976.

mechanical tension, decrease of the load upon the musculo-skeletal system, etc. The ensuing muscle atrophy and bone resorption facilitate the excretion of nitrogen, potassium and calcium. These changes are enhanced by variations in hormonal regulation, viz. increased secretion of parathyroid hormone, glucocorticoids, aldosterone, decreased production of calcitonin and thyroxine. After provocative tests with calcium lactate and potassium chloride the excretion of calcium and potassium grew (Figs. 6, 7). This can be induced by a smaller amount of the electrolytes and consequently by a lower capacity of muscles and bones to retain them.

The data obtained allowed the conclusion that exercises may act as an effective countermeasure against adverse changes developing in weightlessness. The earlier hypothesis that electrolyte deficiency developing in microgravity can be compensated by salt supplementation has not been confirmed (12). However, in simulation studies in which the test subjects received potassium and calcium supplements and exercised regularly and actively the beneficial effect was evident (14).

Comparison of the data obtained d during and after flights gives evidence that transition and long-term exposure to microgravity produce a milder stress on the hormonal regulation systems than the subsequent period of readaptation to Earth gravity. The stimulation effect of the normal gravitational field acts as a specific stress-agent that triggers various adaptive reactions.

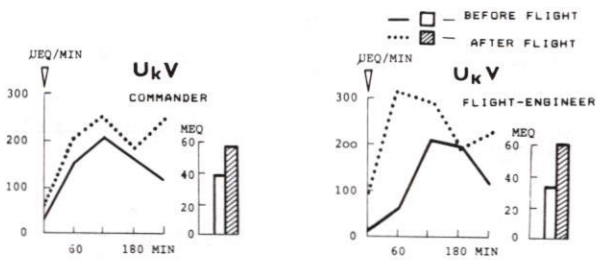


Figure 6. Potassium excretion during KCl loading before and after 175-day flight.

After short-term flights biochemical changes show features of the adaptation syndrome of a moderate degree: stimulation of the sympatho-adrenal system, transfer of the stimulation effect to the pituitary-adrenal system and adequate involvement of mechanisms that can rapidly restore the homeostatic level. By contrast, after long-term flights biochemical changes become more dramatic and involve changes in carbohydrate and lipid metabolism, energy exchange, amino acid and vitamin balance. In this situation the sympatho-adrenal system develops distinct shifts involving its activation (in which the hormonal component predominates during the first days and the transmitter component afterwards) and rearrangement of steroidogenesis which may modify the proportion of gluco- and mineralocorticoids, reduce prostaglandins and stimulate the kallicrein-kinine system at different stages of readaptation. The specific feature of homeostasis after a prolonged exposure to microgravity is a mismatch between a significant stimulation of the sympatho-adrenal system and an inadequate manifestation of biological effects of catecholamines.

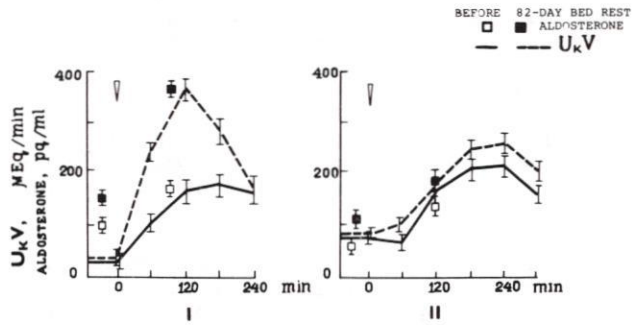


Figure 7. Changes in the rate of potassium renal excretion and concentrations of aldosterone in blood flow. Potassium chloride load before and during bed rest in control (I) and exercising (II) test subjects.

The data summarized in this presentation that describe very clearly significant differences in the mechanisms of acute and delayed adaptive responses to microgravity, are obviously at variance with the concept mentioned at the beginning of the report that views the processes of adaptation as a sequence of events triggered by the same agent, i.e. microgravity and developing at a different rate. In the light of the data reviewed preference should be given to the hypothesis according to which these processes occur as independent reactions controlled by different systems and induced by different triggers: by microgravity that manifests in immediate, acute reactions and by microgravity-induced variations in the inner medium that manifest in delayed reactions. It seems therefore justifiable to term those latter as secondary reactions.

If this hypothesis is true, then the probability of a very wide variability of the data obtained in microgravity is very high and the probability of a close similarity of such data is very low. Since the pattern and rate of development of

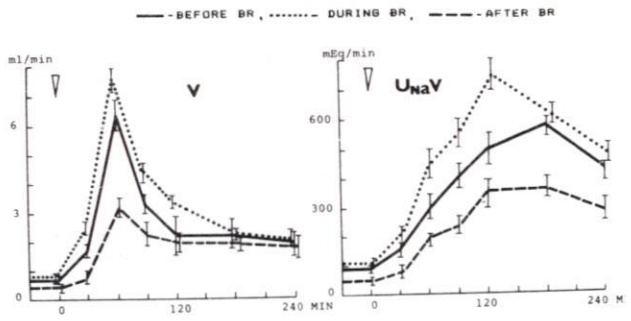


Figure 4. Diuresis and sodium excretion rate before, during and after 49-day head down tilt in response to 0.9% NaCl load.

se in the excitation of the motoneuronal pool and a decrease of the segmentary inhibition rate (1). The increase in the excitability of motoneurons together with the decrease of inhibitory processes seems to be the most plausible cause of the drastic increase of the variability of III of motor units. As it is known one of the major factors responsible for the stabilization of the rhythmic activity of motoneurons is recurrent inhibition (13).

After 30 days of head-down tilt the signs of hypersensitivity of all parameters under study disappeared; the distribution of alterations, i.e. increase in the frequency of motor unit discharges, appearance of paired discharges when reproducing and maintaining of efforts of small amplitude - pointed to a change in the predominant mechanism of adaptation: the mechanism of recruitment of additional motor units sufficient to make up for a relatively mild contraction deficiency of the acute stage was replaced with the mechanism of enhanced excitation of each motor unit. The latter is less favorable energetically but is capable to support motor activity under the conditions of increasing muscle hypotrophy.

Systems of neuro-humoral regulation. During 25 years of manned space flights a large body of factual data was accumulated that concerned metabolic processes and neuro-humoral and hormonal regulation at different stages of adaptation to usual flight factors and subsequent readaptation to Earth's gravity. They showed metabolic changes typical of different stages of adaptation to the flight effects.

The stage of primary (acute) adaptive metabolic reactions (of 1 or 2 days in duration) is associated with the neuroemotional stress during launch and insertion into orbit as well as with blood redistribution to the upper body during orbital flight. The stress situation is also responsible for the tension of the hypothalamic-pituitary-adrenal system recorded during the first hours of exposure to immersion and head-down tilt. Blood and interstitial fluid shifts in the cranial direction occur due to the absence of the hydrostatic pressure and lead to increases in venous return, blood central volume, vascular distension in the cardiopulmonary area and reflex responses that produce changes in the cardiovascular function and fluid-electrolyte metabolism. The decline in the antidiuretic and antinatriuretic activity causes a decrease in the production of ADH, renin, aldosterone, an increase in the secretion of prostaglandins and renal excretion of water, sodium, potassium and chlorine (4). The above changes in volumoregulation are transient and hormone secretion grows by the end of the first day of exposure when the blood volume diminishes. This process is physiologically favorable and the reduced circulating blood volume is adequate to the specific conditions; this seems to explain why the level of water and electrolyte excretion after administration of NaCl isotonic solution on immersion day 2 was higher than the pretest value (Fig. 4).

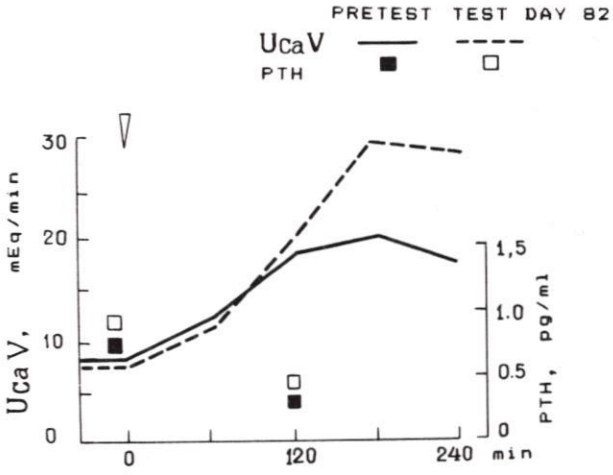


Figure 5. Calcium lactate loading during prolonged bed rest.

The next stage of adaptation is characterized by the development of compensatory reactions that prevent further enhancement of the above metabolic variations and abolish to a certain extent the changes recorded at the acute stage. The decrease of plasma ACTH detected in the Skylab crewmembers (17) and the reduction of catecholamine metabolites in urine with blood epinephrine and norepinephrine remaining unchanged during the 237-day mission (4,9) are indicative of the lack of stimulation of the sympatho-adrenal system in long-term flights. Measurement of the norepinephrine concentration and activity of catecholamine-synthesizing enzymes in the hypothalamus of rats after 20-day space flights did not reveal a distinct stress-reaction (16).

However, as the time in microgravity increases it produces a direct effect related to the abolition of deformation and

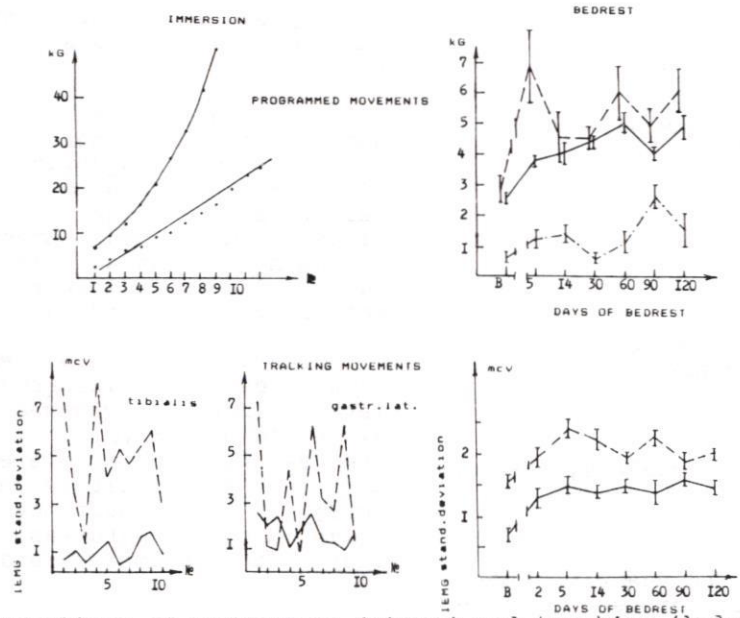


Figure 1. Alterations of programmed (above) and tracking (below) movements parameters during immersion (on the left) and bed rest (on the right). Upper part. On the left-average values of the tension, developed in subsequent movements; on the right - average value of increase in tension in subsequent movements. Lower part. Variability of EMG level shown by SD. Solid line - control, dashed line - hypokinesia; SD is shown by vertical lines.

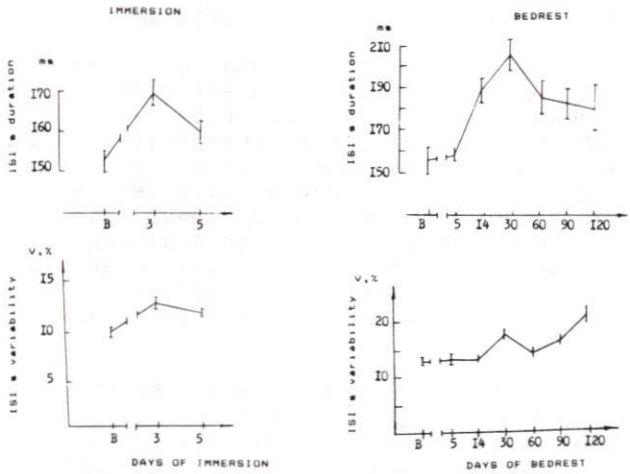


Figure 2. Alterations of motor units characteristics, namely interspike intervals (ISI, above) and their variability (below) during immersion (on the left) and bed rest (on the right).

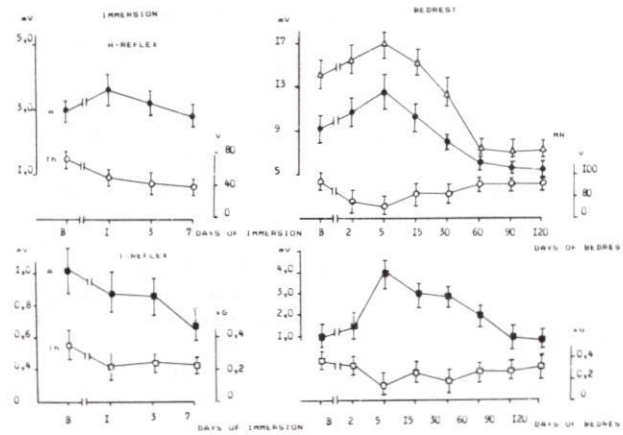


Figure 3. Alterations of characteristics of H-reflex (above) and T-reflex (below) during immersion (on the left) and bed rest (on the right).

Amplitudes of H- and T-responses are shown by black signs, thresholds by open signs; the triangles show the amplitude of M-wave.

Similar variations were seen in other components of the motor system. It has been previously demonstrated that microgravity results in a noticeable (40% and over) decline of the tone of the leg back muscles. In immersion this decline reached a maximum on day 2-3 while in bed rest it developed at a slower rate: it was detected on day 2 and continued to increase progressively by days 14-30 (3).

Considering possible mechanisms of the effect of the simulation studies on the motor unit function, the appearance of low frequency motor units we would like to notice during immersion and bed rest phase 1. It is known that low frequency of motor units discharges when muscle tension is not high, is characteristic of high threshold motor units - the decline in the recruitment threshold in this group of motor neurones could be a consequence of increased excitation of the motoneuronal pool. This increase excitation was also indicated by synchronization of motor unit activity and by enhancement of the tendon (Achilles) reflex and its receptor-free analog H-reflex (Fig. 3) which during immersion and the first 30 days of head-down tilt displayed changes pointing out to an increa-

MECHANISMS OF ACUTE AND CHRONIC EFFECTS OF MICROGRAVITY

O.G. Gazenko, A.I. Grigoriev, I.B. Kozlovskaya

Institute of Biomedical Problems, Moscow, USSR

Direct (primary) and adaptive (immediate and delayed) responses of different systems of the human body to microgravity were and still are in the focus of space physiology investigations. The results can be well illustrated by schemes and tables from (2,4). The importance of this problem is beyond any doubt. It is clear that discrimination in the mosaic picture of the microgravity syndrome of the reactions that maintain or disturb homeostasis, correct description of the trend and time-course of development of adaptation changes at different stages of exposure to microgravity, and identification of the factors that may inhibit or stimulate them are necessary for both practical and theoretical purposes. Extended biomedical investigations carried out in manned space flights of varying duration onboard the Salyut stations, on the one hand, and in ground-based simulation studies, on the other, have furnished a large body of data that have helped a better understanding of the intrinsic mechanisms of adaptation processes responsible for homeostasis in altered gravity fields. The complexity of these mechanisms, their heterogeneous and sometimes opposite action at different stages of exposure to microgravity are discussed with respect to specific adaptation processes in certain physiological systems.

Motor system. Coordination disorders have been regularly observed after exposures to microgravity. Kinematic changes of locomotor acts, decrease of vertical posture tolerance, increase of motor reaction time have been consistently recorded after both short- and long-term exposures to actual and simulated microgravity (5,6,11). The microgravity-induced syndrome involves alterations in every component of the motor system: activity of the main proprioceptive inputs, state of muscle periphery, spinal reflex mechanisms and central systems of motor control (7,15,8). It is obvious that any of the above factors may play a leading role in the origin of coordination disorders; however, the mechanisms of their development at different stages of exposure have remained obscure until recently.

With the purpose of clarifying these mechanisms during short- and long-term exposures to microgravity, we investigated the motor apparatus in simulated weightlessness using a standard battery of tests and methods. Emphasis was placed on the motor unit activity which is known to be a direct indicator of the spinal motoneuron function (10).

Our investigations demonstrated that exposure to microgravity caused dysmetria. In the programmed movements this dysmetria was shown up by a decrease in the gradations of muscle efforts, an increase of the amplitude and number of errors; in the pursuit movements this involved a drastic increase of the variability of the parameters under study (Fig. 1).

The above changes were reliably detected in various experimental situations: immersion per se and combined with bed rest and head-down tilt, when performing a task at rest or along with the other motor tasks simultaneously. The universal and consistent pattern of these changes indicated their close association with simulation effects.

Characteristics of the changes of movements parameters in different simulation studies were dissimilar: in the 7-day immersion study they were monophasic, rapid and reached a maximum by test day 3. During the 120-day head-down tilt test the variations developed at a slower rate and went through two stages that can be distinguished in all parameters measured: the 1st stage covered the first 14-30 days and the 2nd stage developed thereafter.

During exposure to immersion and head-down tilt the activity of motor units of agonist muscles, i.e. soleus and gastrocnemius muscles, varied distinctly. The pattern and time-course of these changes were also different: during head-down tilt the above two phases were very distinct. During immersion and the first 30 bed rest days the mean duration of interimpulse intervals (ISI) increased due to the appearance of units with unusually low frequency, the variability of this parameter also increased drastically and synchronization of motor unit activity was clear (Fig. 2).

After 30 days of head-down tilt the mean duration of III in the soleus and gastrocnemius muscles decreased consistently, reaching a minimum by day 120 ; the variability of this parameter slightly diminished by test day 30-60 and increased significantly thereafter; there was no synchronization of motor unit activity.

Permit me to extend the Commission's great appreciation and gratitude to the distinguished members of the local Organizing Committee and its Chairman, Professor Saiki, as well as the Advisory Board of this Committee, for all the efforts expended in the preparations for this meeting, and especially for arranging the excellent meeting facilities in the renowned Nihon University, making possible for many of us to enjoy a unique experience in a fascinating environment. Let me also express our appreciation to all speakers and their colleagues for sharing with us the results of their endeavors in many areas of gravitational physiology, expended in many parts of the world, far and near. The Commission is especially pleased and impressed by the fact that so many colleagues from our host country have responded to our invitation by submitting many excellent papers.

We hope that this meeting will be enjoyable also for those who are here as representatives of sponsoring and supporting organizations, which have played a decisive role in the realization of this meeting. In conclusion, I wish to introduce Professor Masao Ito, President of the Physiological Society of Japan. The Society has graciously accepted to act as host for this annual meeting of our Commission. Professor Ito is Dean of the Faculty of Medicine of the University of Tokyo and a Member of the IUPS Council. He is famous to all physiologists involved in research on the functions of the brain.

H. Bjurstedt
Chairman, Commission on Gravitational Physiology
International Union of Physiological Sciences

Department of Environmental Physiology
Karolinska Institutet, Stockholm, Sweden

PRELIMINARY ANNOUNCEMENT

IUPS Commission on Gravitational Physiology—Ninth Annual Meeting 28 September–2 October 1987 Nitra, Czechoslovakia

The Ninth Annual Meeting of the Commission on Gravitational Physiology of the International Union of Physiological Sciences is being planned for Nitra (1-h drive from Bratislava), Czechoslovakia in September 1987.

The Commission Meeting will comprise open sessions for slide presentations of voluntary papers dealing with the effects on physiological systems of humans, animals, and plants of changes in magnitude or direction of the force environment. Included are the effects of the weightlessness during spaceflight, acute and chronic acceleration, vibration, and the various forms of simulated weightlessness. Also included is consideration of the evolutionary consequences of gravity and the role of gravity in the manifestations of scale effects in animals and plants. The Commission Meeting will also include symposia by invited speakers on several topics in gravitational physiology.

It is planned to publish the Proceedings of the Ninth Annual Meeting as a Supplement to *The Physiologist*. As previously, the Proceedings will contain the voluntary papers and symposium papers presented at the Meeting.

Your participation in the Commission Meeting is welcomed. If you are interested in the particulars, please contact Dr. Orr E. Reynolds, Commission Business Officer, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, USA.

It is a great pleasure for me, as Chairman of the IUPS International Commission on Gravitational Physiology, to welcome you all to another of the Commission's Annual Meetings, the eighth of its kind. Although gravitational physiology can be regarded as a very young branch of the physiological sciences, the Commission is pleased to note that it has rapidly attracted increased interest from the international scientific community. Our latest meeting was held in Niagara Falls in 1985 and was organized in conjunction with the Fall Meeting that year of the American Physiological Society. At this joint meeting the number of papers in gravitational physiology represented no less than a fifth of the total number of papers in all the physiological areas taken together. The contributions to the programs of our annual meeting have shown a steady increase in scientific content, and we are pleased to note that the present meeting is no exception. It is the first time that a Commission meeting is held in the Orient. This certainly contributes to making this meeting a most stimulating experience for participants who have not previously visited this part of the world.

Our Commission has as its ultimate aim to understand the physiological significance of gravity, the enigmatic and, at the same time, probably the most familiar of all forces in our environment. Gravitational physiology encompasses the functions of living matter in response to the full range of gravitational forces both above and below the norm force of gravity exerted on stationary objects on the surface of the earth. The advent of aviation, and particularly the more recent developments in this area, have necessitated inquiry into the deleterious physiological effects produced by increased force environments. To find the answers, research started about a half century ago with the aid of human centrifuges capable of producing high gravitoinertial conditions. However, in order to fully understand the physiological significance of normal gravity, the device of studying the effects of removal of the acting force is both informative and necessary. But this is not possible in earth-bound laboratories for more than a few seconds. It was not until the birth of the space age that a weightless environment could be created and maintained for long periods of time. In this way, the arrival of the space age opened the opportunity for experimentation over the full spectrum of G forces.

One can look at gravitational physiology in terms of problems belonging to three interconnected areas, viz. those dealing with man's health and survival in space, the use of weightlessness in space flight as a tool for studying fundamental issues in biology and medicine, and ground-based research aimed at simulating the effects of gravitational forces greater or smaller than the norm of earth gravity.

Ever since the beginning of the space age there has been a continuing need to know the nature of the adverse physiological effects resulting from exposure to the weightless state in long-term space missions. It is important to find out about possible obstacles to space habitation, both in terms of ill effects during the exposure itself and following the return to the normal force environment on the earth. These problems have to do with the nature of space-related adverse effects and the possibilities of treatment or prevention. We now have a wealth of information from a considerable number of man-years in space. This area is in many aspects of an applied nature but also has proven of great interest in the case of problems of a more basic nature.

The "pure science" area of research in gravitational physiology is that in which the G factor, or rather imposed changes in the strength and direction of the effective G vector, including its reduction down to zero, is used as a tool primarily for research to understand the physiology of living organisms on earth, and thus to look into problems of intrinsic scientific interest. As the G factor is increasingly utilized as a biological tool, it will more and more attract interest from researchers in the basic biological and medical sciences.

Ground-based experimentation in gravitational physiology has already given extremely valuable insight into the physiology of gravireception, changes in the distribution of blood volume and their secondary effects on cardiovascular and endocrine functions, as well as other functions that have been shown to be especially susceptible to influences from the gravitational environment. Such ground-based research is of great importance also because it yields results and ideas that can be verified and tested using space experimentation for validation and refinement.

This meeting will deal with several problem areas concerned with effects of the force environments on living matter at various levels of organization. There will be four symposia with invited papers. The first special symposium will be held today and will be devoted to the general topic of current concepts in gravitational physiology. The second symposium will be held tomorrow and will be entirely devoted to reports and discussions of results in gravitational physiology obtained in recent space flights. Into this symposium we have fitted a special NASA Life Session with invited papers. The third symposium, on Friday, is concerned with problems related to the mechanisms of gravireception in mammals and associated functions of the brain. Here we have the opportunity to hear about and discuss results from experiments performed both on the ground and in the space environment. The fourth symposium will be held on Saturday and will deal with the possibilities of simulating various effects of weightlessness and studying them in ground-based laboratories, in other words, the design and use of different kinds of animal and human models of weightlessness.

We are certainly happy that so many colleagues have responded to our call for voluntary papers. During the course of this week, 47 such papers, in addition to the 36 invited papers, have been submitted for presentation in four open sessions. These voluntary papers will highlight results from many diverse areas of gravitational physiology, including results from experimentation in space, effects of changes in body position in the normal force environment, simulation of gravity, models of weightlessness, fluid shifts and electrolytes, gravireception, and high G environments.

Human and Animal Models of Weightlessness Symposium

Physiological Comparison of Rat Muscle in Body Suspension and Weightlessness. X. J. Musacchia, J. M. Steffen, R. D. Fell, and J. Dombrowski S–102

Neurophysiological Responses in Suspended Animal Models. Y. Oomura and T. Katafuchi S–106

Effects of Gravity on Rhythmic Activities in the Phrenic and Sympathetic Nerve Discharges. T. Hukuhara, N. Kimura, K. Takano, and F. Kato S–109

Comparative Aspects of Hematological Responses in Animal and Human Models in Simulations of Weightlessness and Space Flight. R. D. Lange, J. B. Jones, and P. C. Johnson, Jr. S–113

Local Fluid Shifts in Humans and Rats: Comparison of Simulation Models with Actual Weightlessness. C. M. Tipton, J. M. Overton, M. J. Joyner, and A. R. Hargens S–117

Metabolic Adaptation in Hypokinesia in Humans. H. Saiki, J. Nakajima, M. Nakaya, Y. Sugita, M. Sudoh, K. Shioda, and Y. Saiki S–121

Controlled Water Immersion as a Model of Weightlessness. I. D. Pestov and A. V. Pokrovsky S–125

Hypogravity and Gravireception

Directional Difference in Effects of Long-Term Hyper-Gravity Upon the Cardiac System of the Hamsters. H. Satake, Y. Mizuno, S. Watanabe, and K. Matsunami S–129

Chronic Acceleration and Organ Size in Domestic Fowl. A. H. Smith S–131

Changes of Cardiac Systems of Decerebellated Hamsters in Hypergravity Conditions. S. Ueki, T. Kawashima, H. Satake, M. Nakashima, and K. Matsunami S–133

Cardiopulmonary Response of Rats to Centrifugal Accelerations. M. Sudoh, K. Shioda, M. Kohno, S. Ikawa, K. Kawakami, and H. Saiki S–135

The Response of Skeletal Muscle Mass to Changes in Acceleration. G. C. Pitts S–137

Receptor Mechanism and Neuronal Circuit Subserving Gravitational Responses in Crayfish. M. Hisada, M. Takahata, T. Nagayama, and M. Yoshina S–139

Physiological Roles of Calcium in Light-Induced Gravitropism in *ZEA* Primary Roots. A. Miyazaki and T. Fugii S–141

Gravitational Physiology

(Presented at the XXXth International Congress of Physiological Sciences, Vancouver, B. C., Canada, July 13–18, 1986)

Cardiovascular Responses to Central Hypovolaemia in Man: Physiology and Pathophysiology. T. Bennett S–143

The Effects of Exercise Training on Factors Affecting Orthostatic Tolerance. P. R. Raven, M. L. Smith, D. L. Hudson, and H. M. Graitzer S–147

Index S–151

Table of Contents

Introductory Remarks
H. Bjurstedt S–vii

Current Concepts of Gravitational Physiology Symposium

Mechanism of Acute and Chronic Effects of Microgravity. O. G. Gazenko, A. I. Grigoriev, and I. B. Kozlovskaya S–1

Spacelab Life Sciences 1 and 2: Scientific Research Objectives. C. S. Leach and H. J. Schneider S–6

The ESA Anthrorack Project: Integrated Research in Human Physiology. D. Linnarsson S–10

The Effect of Head-Down Tilt on the EEG Response to Mental Arithmetic (MA). W. Jinhe, Y. Gongdong, G. Zhiqiang, and S. Xianyun S–13

Gravitational Cardiovascular Adaptation in the Giraffe. A. R. Hargens S–15

Biodynamic Response of Subhuman Primates to Vibration. A. R. Slonim S–19

Physiological Limitations of Human Tolerance to Gz Acceleration. U. I. Balldin S–23

Development of Methods for Prevention of Acceleration Induced Blackout and Unconsciousness in World War II Fighter Pilots. Limitations: Present and Future. E. H. Wood S–27

Recent Space Flight Results in Gravitational Physiology Symposium

Physiological Investigations of Primates Onboard Biosatellites Cosmos-1514 and Cosmos-1667. O. G. Gazenko and E. A. Ilyin S–31

Central Circulation During Exposure to 7-Day Microgravity (Head-Down Tilt, Immersion, Space Flight). V. E. Katkov, L. I. Kakurin, V. V. Chestukhin, and K. Kirsch S–36

Hormonal Regulation in Space Flights of Varying Duration. I. A. Popova, B. V. Afonin, N. A. Davydova, and A. I. Grigoriev S–42

Space Flight Results and Topics in Terrestrial Environment

Effects of 7-Day Space Flight on Weight-Bearing and Non-Weight-Bearing Bones in Rats (Cosmos 1667). L. Vico, D. Chappard, A. B. Bakulin, V. E. Novikov, and C. Alexandre S–45

Body Impedance Measurement During Space Mission D1. F. Baisch and L. Beck S–47

Magnetic Effect on Cardiopulmonary Function in Man. O. Okai S–49

A Unique Relationship Between Economs' Theory on the Largest Land Mammal and Our Dynamic Theory of Growth, Maturation and Ageing. S. Tatsunami, N. Yago, and N. Fukuda S–51

Study of the Initial Period of Adaptation to Microgravity in the Rat Experiment On-Board COSMOS-1667. O. B. Gazenko, E. A. Ilyin, E. A. Savina, L. V. Serova, A. S. Kaplansky, I. A. Popova, V. S. Oganov, K. V. Smirnov, and I. V. Konstantinova S–53

Body Position and Simulation of Gravity

Cardiovascular Responses During 70° Head-Up Tilt: The Effect of Elevated Body Temperature and High Alcohol Blood Levels. I. B. Mekjavic, C. A. Gaul, M. D. White, and K. D. Mittleman S–56

Changes of Arterial and Venous Blood Flow During Orthostasis and the Effect of Atropine. W. K. Park and E. U. Chae S–58

The Effect of Body Position on Ventilation and Perfusion in the Lung. E. Moriya, E. Kawakami, M. Sudoh, and S. Ikawa S–60

Effects of Graded Head-Up Tilting on Muscle Sympathetic Activities in Man. S. Iwase, T. Mano, and M. Saito S–62

Cardiovascular Effects of Head-Up Tilt As Affected by a Vasopressin Analogue. R. Baer, O. Eiken, and U. Balldin S–64

10° Head-Down and -Up Tilting on the Water Intake and Cardiovascular Responses During Mild Exercise in Woman. K. Yokozawa, S. Torikoshi, M. Inazawa, K. Itoh, Y. Fukase, J. Nagano, and Y. Suzuki S–66

Cardiovascular Responses of Aged Men to Orthostatism During Heat Exposure. K. Shiraki, S. Sagawa, M. K. Yousef, N. Konda, and K. Miki S–68

Cardiorespiratory Responses to Supine Leg Exercise During Lower Body Negative Pressure (LBNP). O. Eiken and H. Bjurstedt S–70

Effects of LBPP Stocking on Cardiovascular Responses During Rest and Exercise in LBNP and Upright Position in Woman. J. Nagano, S. Torikoshi, K. Yokozawa, M. Inazawa, K. Itoh, Y. Fukase, and Y. Suzuki S–72

Increased Cholinergic Activity During Graviation-Induced Pre-Syncope in Man. K. Sander-Jensen, J. Mehlsen, C. Stadeager, N. J. Christensen, T. W. Schwartz, J. Warberg, and P. Bie S–74

Effects of Lean Body Mass and Aerobic Power on LBNP Tolerance in Woman. S. Torikoshi, K. Yokozawa, M. Inazawa, K. Itoh, Y. Fukase, J. Nagano, and Y. Suzuki S–75

Mammalian Gravireception and Brain Function

Organization of Maculo-Ocular Pathways Via Y-Group Nucleus and Its Relevance to Cerebellar Flocculus in Cats. Y. Sato and T. Kawasaki S–77

Cerebellar Adaptive Function in Altered Vestibular and Visual Environments. M. Ito S–81

Characteristics of Vestibular Reactions to Canal and Otolith Stimulation at an Early Stage of Exposure to Microgravity. M. G. Sirota, B. M. Babayev, I. B. Beloozerova, A. N. Nyrova, S. B. Yakushin, and I. B. Kozlovskaya S–82

Sensory Interaction in Weightlessness. L. N. Kornilova, G. Bodo, and R. R. Kaspransky S–85

Implications of Otoconial Changes in Microgravity. M. D. Ross S–90

Models of Weightlessness, Fluid Shifts and Electrolytes

Physiological Responses During Whole Body Suspension of Adult Rats. J. M. Steffen, R. D. Fell, and X. J. Musacchia S–94

Influence of Simulated Weightlessness on Maximal $\dot{V}O_2$ of Untrained Rats. J. M. Overton and C. M. Tipton S–96

Continuous Determination of Blood Volume and Blood Sodium Concentration on Conscious Rats: A Potential Tool for the Analysis of Water Balance During Weightlessness. T. Morimoto, E. Sugimoto, H. Nose, T. Okuno, T. Natsuyama, and M. Morita S–98

Mechanism of the Increase in Plasma Volume During Head-Out Water Immersion (WI) in Dogs. K. Miki, S. K. Hong, and J. A. Krasney S–100

breathing at rest is controlled so as to keep the alveolar pressure of carbon dioxide regulated with narrow limits even under the influence of relatively large variations in the ambient atmospheric pressure. By exposing human subjects to a barometric pressure of 6 atmospheres, Hill obtained most valuable confirmation of this conclusion; although the percentage by volume of carbon dioxide was found to be less than 1.0 instead of about 5.5 found at normal atmospheric pressure, the calculated alveolar carbon dioxide was the same in both cases. Hill was the first proponent, in one of his papers in 1908, for the use of a mixture of air, or preferably oxygen with some 5 percent of carbon dioxide, in the resuscitation of cases of carbon monoxide poisoning—a treatment widely used today in order to induce hyperpnea and an increased rate of removal of the noxious gas.

During the latter part of his professional life, after accepting the position as Director of Applied Physiology at the Medical Research Institute, which he was to keep until his retirement in 1930, Hill was able to give free scope to his gift for research into more practical aspects of human physiology and medicine. Much of Hill's research during this period gives away his continued curiosity in basic physiological mechanisms. From a more formal point of view, however, his area of responsibility was often expressed in the term "physical medicine" (a more modern and descriptive designation for this area might be "environmental medicine"). He devoted his attention very largely to the influence of environmental temperature and to the humidity and movement of the air as well as solar radiation on human comfort, health, and capacity for work.

With the outbreak of the First World War, one of Hill's first assignments was concerned with the medical aspects of gas warfare, and he also contributed reports on the ventilation of dugouts. Hill went on to investigate the influence of varying atmospheric conditions on heat loss from the body by convection, radiation, and the evaporation of water, and for assessing these environmental factors he developed the "kata-thermometer," by which the rate of heat loss from the instrument by convection, radiation, and evaporation could be calculated.

Hill and his co-workers proved, largely with the use of the kata-thermometer, that what causes the stuffiness of badly ventilated rooms is not lack of oxygen, or excess of carbon dioxide, or the presence of any mysterious exhalations; what chiefly matters in the ventilation of "closed" spaces is the maintenance of suitable humidity, temperature, and movement of the air. Hill's investigations on factors determining subjective sensations of comfort or discomfort both indoors and outdoors, in a variety of climates, including tropical as well as temperate, were summarized by him in two books, *Health and Environment* and *Sunshine and Open Air. Their Influence on Health, with Special Reference to Alpine Climates*, both published in 1925. A noteworthy fact is that Hill was the first to design a bed-tent for the clinical administration of oxygen (1921). He described the physiological basis for the limits of high-altitude flying with oxygen and the role of oxygen breathing in the 1933 Mt. Everest expedition.

Hill had many other interests besides his scientific work. He had a remarkable talent for painting and was equally adept with oils and with watercolors. Indeed, at one time it was touch and go whether he became a professional artist or a physiologist. He held private exhibitions of his paintings and animal studies and these were very favorably received by the critics. An example of his gift as an artist is the self-portrait hanging in the Physiology Theatre at the London Hospital Medical School.

In the present context, it is particularly appropriate to note that a friendship with a distinguished Japanese artist led to Hill's meeting many Japanese visitors to London; Hill's artistic production was specially admired by these visitors, and this resulted in three very successful exhibitions of his paintings in Japan. In Britain he became the first president of a Medical Art Society.

Another gift that Hill had was for writing fairy tales for children, of which he published two books, one illustrated with his own drawings. These tales showed an intuitive understanding of the child mind. A friend writes (cited in *The Lancet*, April 12, 1952): "The artistic and scientific temperaments are often incompatible, but in Leonard Hill they attained an almost uniquely happy synthesis which, combined with his humanitarianism, was the secret of his outstanding contribution to medicine . . ." and continues: "Hill's last published contribution was a letter to *The Listener* (March 27, 1952), in which the final paragraph aptly sums up his own philosophy: 'There is no lack of mystery in the universe as shown by the physicist, the astronomer and the biologist, and the brain is capable of investigating the mystery and of spreading poetry and delight.' In his book *Philosophy of a Biologist*, published in 1930, Hill had given his reflections on what life and his studies had taught him. Renouncing all religious doctrines, he declared that modern science has brought mankind to recognize the existence of "a power equivalent to the purest conception of God stripped of all dogma and superstition."

Leonard Hill's scientific standing was early recognized, and he was elected a Fellow of the Royal Society in 1900. He was knighted on his retirement in 1930. Hill died at Corton, near Lowestoft, on March 30, 1952, in his 86th year.

Biographical notes on Sir Leonard Hill generously provided by Professor Henry Barcroft, F.R.S., London, Dr. James P. Henry, Los Angeles, and Professor Eric Neil, London, are gratefully acknowledged.

H.B.

Dedication

The *Proceedings* of the 8th Annual Meeting of the IUPS International Commission on Gravitational Physiology are dedicated to Sir Leonard Hill in recognition of his fundamental and insightful discoveries concerning the influence of gravity on the circulation in man and animals. These discoveries contributed importantly to present knowledge of factors of mechanical and reflex nature that maintain circulatory homeostasis when challenged by changes in the gravitational vector.

Leonard Hill was born in Tottenham, England, on 2 June 1866, third son of G.B.N. Hill, and a grandnephew of Sir Rowland Hill of penny-postage fame. Family abilities are well reflected in Hill's own generation, with his elder brother, Sir Norman Hill, being a leading legal authority on shipping and another brother, Sir Maurice Hill, being a High Court judge; Lord Justice Scott was his cousin. Hill entered University College, London, duly qualifying in medicine in 1889 and becoming M.B. (London) in 1890. After a year as house surgeon at University College Hospital, he entered upon an academic career in physiology, returning to University College where he worked as an assistant professor in the physiology department, and then continued his research as lecturer at the London Hospital Medical School. Here he was to become professor of physiology when the chair was instituted in 1912. Hill accepted in 1914 the appointment as Director of Applied Physiology at the National Institute for Medical Research, then situated at Mt. Vernon, Hampstead.

It was not until the nineteenth century that the first notions of a connection between certain severe circulatory disturbances, sometimes fatal, and body position began to appear in the literature. Notable examples were the observations of Piorry in France, who communicated case reports and recognized the pooling effect of gravity in dependent blood vessels, and Wagner in Germany, who measured the blood pressure of animals in different body positions to determine the location of the "hydrostatic indifference point."

In his first paper on the influence of gravity on the circulation in 1895, Hill stated in the introductory sentence that this question is "of very obvious importance, yet it is one curiously neglected by physiologists." Hill had examined a clinical case in which the skull had been trephined and noticed that a negative intracranial pressure developed when the patient stood up. This observation led to his extensive research on the hemodynamic effects of changes in body position. For his experimental work he constructed an animal holder, which could be swung round a horizontal axis with the animal's limbs fully extended and in the same direction as the long axis of the body. The pressures in the vessels under observation were recorded with manometers and a smoked-drum kymograph. The research was carried out on anesthetized rabbits, cats, dogs, and monkeys, and the same general results were obtained from all. From the results of his experiments, Hill concluded that, in the head-up position, as the blood drains into the abdominal veins, the heart empties and the perfusion of the brain ceases. He was the first to recognize the perfection of the vasomotor and other compensatory mechanisms that make it possible for man and monkeys to withstand the effects of gravity produced in the upright position in which they are destined to exist. In a paper published a few years later, Hill used the sphygmomanometer devised by himself and H. Barnard to demonstrate in human subjects the variations in arterial pressure that depend on the hydrostatic component (they lost precedence over Riva Rocci for the armlet method by only a few months). They were the first to recognize the decrease in effective circulating blood volume caused by gravity-induced sequestration of blood in dependent veins and, by inference, the protection afforded by the leg muscle pump.

Most of Hill's observations and conclusions on the influence of gravity on the circulation are contained in several papers published by him and his co-workers in the *Journal of Physiology (London)* during the period 1895–1899; they are summed up and supplemented by additional findings and interpretations in some of his books from the same period and in his chapter on the circulation in the large *Textbook of Physiology* (Ed. E. A. Schäfer, 1900).

If the physiology of the cardiovascular system was Hill's "first love," his continued research at the London Hospital Medical School increasingly came to focus on integrative aspects of circulatory and respiratory function, especially with regard to influences of various environmental stresses. During the opening years of this century, much of Hill's research was devoted to hyperbaric physiology and medicine. At the time such work was of great practical importance in view of the high incidence of serious illness and loss of life among deep-sea divers and caisson workers. Hill and his colleagues confirmed and extended Paul Bert's observations about the cause of the symptoms of decompression sickness and could demonstrate the movements of nitrogen into the blood and urine during compression; they could also demonstrate the immediate appearance of bubbles of gas in the capillaries of a frog's foot on rapid decompression as well as their disappearance on recompression. Hill successfully decompressed himself after exposure to an excess pressure of 6 atmospheres using his own method of slow decompression with a ramp-shaded profile. Subsequently, J. S. Haldane devised the quicker method of stage-decompression. From his book, *Caisson Sickness and the Physiology of Work in Compressed Air*, published in 1912, it appears that Hill accepted the method of stage-decompression; he was later to make further contributions to this subject. Hill considered Haldane's decompression tables for compressed air too close to the limit of safety—he favored a reduction of the permissible pressure drop between steps in stage-decompression from the ratio of 2:1, adopted by Haldane, to 1.75:1, a contribution of fundamental importance, and more in accord with present-day procedures for safe deep-sea diving on compressed air.

Hill used the hyperbaric environment as as tool for basic research into the chemical control of respiration. Haldane and Priestly showed in 1905 that normal

Proceedings of the Eighth Annual Meeting of the IUPS Commission on Gravitational Physiology

4–8 November 1986
Toyko, Japan

Orr E. Reynolds, Guest Editor

International Union of Physiological Sciences
Commission on Gravitational Physiology

CARDIORESPIRATORY RESPONSES TO SUPINE LEG EXERCISE DURING LOWER BODY NEGATIVE PRESSURE (LBNP)

O. Eiken and H. Bjurstedt

Department of Environmental Medicine
Karolinska Institutet
104 01 Stockholm, Sweden

It is well known that suction applied over the lower portion of the human, supine body (LBNP) induces physiological responses that are in many respects similar to those caused by gravitational loading in the upright position. In this way, changes in hydrostatic pressure components at various reflexogenic zones in the circulatory system can be avoided. LBNP may therefore be used to isolate and study those responses to gravity which are due solely to the caudad displacement of blood volume in the low pressure system.

This study is concerned with the dynamics of cardiac and respiratory responses to leg exercise as influenced by LBNP-induced translocations of the blood volume. Three questions were posed. 1) How do heart rate and stroke volume respond to the onset of dynamic leg exercise? 2) Is there a rapid phase in the exercise hyperpnea at the onset of exercise? 3) How is the magnitude of exercise hyperpnea affected?

Methods

The experiments were carried out with the subjects positioned supine in an opening to an altitude chamber with the lower portion of the body positioned inside the chamber. Hermetic sealing at the level of the iliac crest (in the experiments on ventilation, slightly below this level) was accomplished by a rubber diaphragm. Graded leg exercise was performed on an electrically braked cycle ergometer, with the axis of the pedals at the level of the heart. A shoulder support was used to avoid work with the arms during pedalling. Heart rate (HR) was recorded by a linear cardiotachometer, stroke volume (SV) by an impedance cardiograph. Breath-by-breath inspiratory minute volume ($\dot{V}_I$) and mouth-occlusion pressure ($P_{0.1}$) were recorded by a computer-assisted assembley.

The protocol in the experiments on cardiac responses was as follows. Following a period of rest, exercise was performed at 0, 50 and 100 W for 4 min at each workload. In the experiments on ventilatory responses, a period of rest was followed by two 5 min bouts of exercise (0 and 100 W) separated by 5 min of rest. The chamber pressure was maintained at atmospheric level (control) and at -50 Torr (LBNP), respectively.

Results

As is evident from Fig. 1, resting values for SV and HR were lower and higher, respectively, during LBNP than in the control condition. Initiation of exercise in the control condition caused an abrupt initial increase in HR, which subsequently continued to increase with the work intensity; stroke volume, on the other hand, remained essentially at resting values throughout the exercise periods. During exposure to LBNP, onset of exercise induced a prompt and considerable rise in SV, with a further slight increase as work intensity was raised, whereas HR showed a small but significant drop during loadless pedalling.

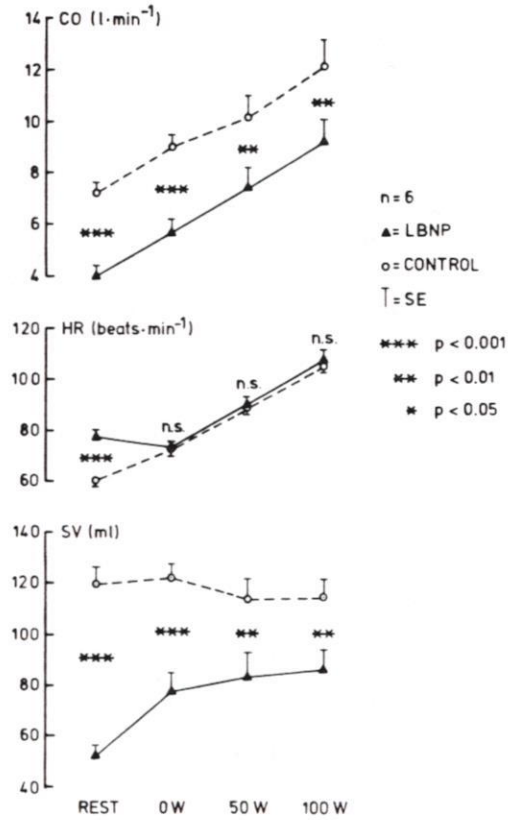


Figure 1. Cardiac output (CO), heart rate (HR) and stroke volume (SV) values at rest and during exercise in the control condition and during LBNP at -50 Torr.

Resting values for $\dot{V}_I$ and $P_{0.1}$ were unaffected by exposure to LBNP. Time courses for $\dot{V}_I$ at the transition from rest to exercise at 100 W were similar with and without LBNP (Fig. 2). At the 0 and 100 W workloads the steady-state values for both $\dot{V}_I$ and $P_{0.1}$ were significantly higher in the control condition than during LBNP ($\Delta\dot{V}_I$=3.3 and 4.9 l min^{-1} at the two workloads, respectively).

Discussion

Mode of cardiac adaptation to exercise. - The differences in SV and HR responses at the onset

the aged to vasoconstrict the skin and to override the heat induced vasodilation may be an indication of decreased sensitivity of the baroreceptors as compared to young men.

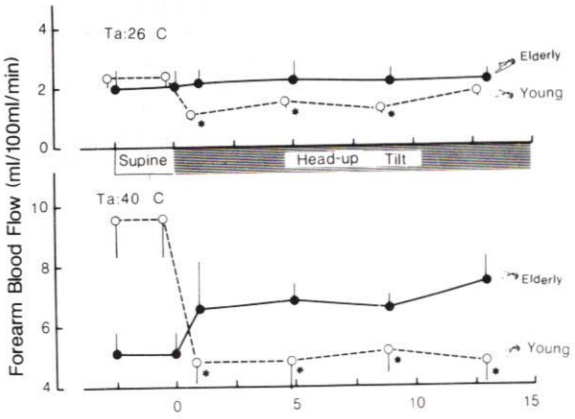


Fig. 1. Responses of forearm blood flow (FBF) to head-up tilt (70^{0}) and acute heat exposure in young and old men. Solid circle with bars, means±SE for the elderly; open circles with bars, means±SE for the young. *P<0.05 comparing vs supine value.

The average TPR in supine position became significantly lower (P<0.05) in both groups in the hot environment. At 26^{0}C, head-up tilt caused no significant changes in TPR in either age group. At the hot environment TPR tended toward decrease during tilt in the elderly, but did not change in the young.

The reduced FBF and no change in CO and TPR during tilt suggest vasoconstriction of the periphery and increased blood flow to the visceral and other vital organs. Although postural changes in the aged at 40^{0}C were accompanied by a slight decrease in TPR and vasodilation, MAP and CO were maintained and all subjects managed the orthostatic maneuvers without syncope. Thus, the maintenance of venous return in the elderly may be achieved by an attenuated increase in FBF during heat exposure (2.6 folds of the level at thermoneutrality as compared to 4.4 folds in the young), on the contrary, in the young, it may be achieved by the vasoconstriction in the visceral organs.

There were no age dependent changes of $\bar{T}$-sk during the tilt test under either environmental condition. The average Tes during the period of supine position at 26^{0}C was not significantly different in either group, being 36.60 ± 0.08^{0}C and 36.96 ± 0.04^{0}C, in the old and young groups, respectively. The Tes began to increase immediately after head-up tilting with a faster rate at the beginning, reaching a plateau level after the 10th min of the head-up tilt. The rate of the increase was higher in the young, consequently their Tes became higher, though not significantly, than that of the elderly at the termination of the test, being 36.68 ± 0.09 and 36.77 ± 0.05^{0}C in the elderly and young, respectively. At 40^{0}C the average Tes was significantly higher (P<0.05) in the elderly. The head-up tilt increased Tes of both age groups (P<0.05) with a faster rate at the beginning and kept increasing until the end of the experiment.

Since Tes accurately reflects blood temperature in man (3), the immediate rise in Tes upon tilting reflects a decrease in blood flow to periphery; a redistribution of blood flow upon tilting. It has been reported that vasoconstriction in the intestinal and renal flow during heating (2). If the sympathetic nerve activity is not appropriately working in the old, heating or orthostatism would induce an inadequate constriction in the splanchnic blood flow, resulting in a different blood distribution as we observed in the present experiment.

In conclusion, unacclimatized, healthy young and old men can manage orthostatic maneuvers with minimum incidences of heat syncope. Orthostatic tolerance in thermoneutrality and during acute heat exposure was not significantly influenced by age. However, the compensatory mechanisms of the cardiovascular system to maintain or regulate blood pressure and cardiac output differed between young and old men. The peripheral vascular responses to postural change was qualitatively and quantitatively different in both age groups. The quantitative differences such as greater rise in HR, gradual increase in TPR and the return of MAP to supine values were necessary to offset the additional stress of heat and thus maintain adequate blood flow to vital organs. The present experiment suggests that aging may result in sluggish or inadequate sympathetic nervous reflex. However, the elderly individual seems to develop a circulatory adaptation either peripherally and/or centrally to overcome the loss of this autonomic nervous control and thus tolerate orthostatism in heat. We may estimate an altered sympathetic nerve activity in the old by measuring the redistribution response of blood flow by heat exposure or passive tilting.

References

1. Collins, ;K. J., C. Dore, A. N. Exton-Smith, R. H. Fox, U. C. MacDonald, and P. M. Woodward. Accidental hypothermia and impaired temperature homeostasis in the elderly. Br. J. Med. J. 1:353-356,1977.
2. Rowell, L. B. Human cardiovascular adjustments to exercise and thermal stress. Physiol. Rev. 54:75-159,1974.
3. Shiraki, K., N. Konda and S. Sagawa. Esophageal and tympanic temperature responses to core blood temperature changes during hyperthermia. J. Appl. Physiol. 61: 98-102,1986.

The research work was supported by funds from the University of Occupational and Environmental Health and in part by NIH grant #IR15AG06074-01.

CARDIOVASCULAR RESPONSES OF AGED MEN TO ORTHOSTATISM DURING HEAT EXPOSURE

K. Shiraki, S. Sagawa, M. K. Yousef, N.Konda and K. Miki

Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; Desert Biology Research Center University of Nevada, Las vegas, Las Vegas, NV 89154

The effect of age on cardiovascular responses to passive tilting was investigated using six old (61-73 yr) and ten young (21-39 yr) men. Experiments were carried out at 26°C and after acute exposure to 40°C. Continuous measurements of esophageal and skin temperatures, and heart rate were made. Blood pressure, forearm blood flow, and cardiac output were measured at 4-5 min intervals. Measurements were made in supine position and after 70 degree head-up tilt for 15 min. Cardioacceleration during the tilt test was greater in the young than the old. Old men did not show significant decrease in FBF during tilting, suggesting a possible defect in the sympathetic nervous reflex. However, other circulatory adaptations seems to overcome this deficiency, resulting in orthostatic tolerance similar to that of the young. During head-up tilt at 26 and 40°C, Tes in the old responded differently, which may suggest an alteration of blood flow distribution, presumably due to diminished blood flow to the periphery.

One of the important manifestations of dysfunction in the autonomic nervous system is orthostatic hypotension, a function of baroreceptor activity, which seems to decrease in many elderly people (1). The objectives of our proposed study are to examine: a) the age-related differences in orthostatic tolerance in combination with heat stress, and b) to provide useful signs to predict impairment of the orthostatic tolerance.

METHOD

Six male old subjects, age ranged from 61 to 73 yr and 10 young men ranging from 21 to 39 yr volunteered for the experiment. Each subject was dressed in cotton shorts in the climatic chamber of which temperature (Ta) was kept constant at 26°C. Each subject was harnessed with skin thermocouples, esophageal probes, ECG electrodes, tape-on twin mylar electrodes for measuring cardiac output, a mercury-in-Silastic Whitney strain gausge, and blood pressure cuff. After keeping a sitting position on a comfortable wide-meshed chair for 60 min (equilibrium period), the subject moved and lay on a tilt table. During the first 15 min on the tilt table when the subject lay supine, blood pressure, heart rate (HR), cardiac output (CO) and forearm blood flow (FBF) were measured every 5 min. The skin (Tsk) and esophageal (Tes) temperatures were monitored continuously throughout the experimental period. The tilt table was raised to 70 degree within 3 s and maintained at the position for 15 min (head-up tilt). During the period of head-up tilt, starting at the first min, BP, HR, FBF, and CO were measured every 4 min. On completion of the tilt test at 26°C the subject again sat on the chair and Ta of the chamber was raised to 40°C. The subject remained seated for 105 min at 40°C (heat exposure period), then lay on the tilt table, and the same tilt procedure and measurements were carried out.

RESULTS AND DISCUSSION

In this study none of the subjects showed any signs or symptoms of syncope.

The average HR during supine position at thermoneutrality (Ta = 26°C) was about the same in both age groups, and it increased 1 min after the head-up tilt and remained a higher level until the termination of the tilt test. However, a significant increase in heart rate in the orthostatic position was observed only in the young. Heat exposure significantly increased ($P<0.05$) HR in both groups. The head-up tilt increased HR promptly and it remained significantly higher ($P<0.05$) until the termination of the tilt test. However, the magnitude of HR response was higher in the young, though not significant.

The average mean arterial pressure (MAP) of the elderly at 26 and 40°C was significantly higher ($P<0.05$) than the young. Heat exposure significantly decreased MAP of both age groups ($P<0.05$) at supine period. No tilt-related changes in MAP were observed in both age groups. At 26°C, systolic pressure significantly decreased during head-up tilt in the young group. However, the old group did not show significant decline in systolic pressure at both Ta.

Acute heat exposure slightly increased CO of both age groups, but the orthostatic position at 26 and 40°C had no significant effect on CO of either age group.

At thermoneutrality, FBF during the supine position was almost identical in both groups (Fig. 1). Although this value decreased significantly ($P<0.05$) during the head-up tilt in the young, no changes were observed in the elderly. At 40°C, the head-up tilt significantly decreased FBF in the young. On the other hand, the elderly showed, although not significant, an increase in FBF. The vasodilation response of the elderly at 40°C was significantly lower than that of the young group and FBF did not change in response to postural change from supine to upright. As skin blood flow is known to be under baroreceptor influence, the inability of

In Figure 2, the average values of water intake given in all subjects are shown in the two tiltings. Water intake was about 14 % lower in HDT than in HUT. The average values of HR, VO2, $\bar{T}sk$, and Team given at just before drinking water during exercise in all subjects were not so different between HDT and HUT, although the MAP at the time was significantly higher in HDT than in HUT. In Figure 3, the average values of

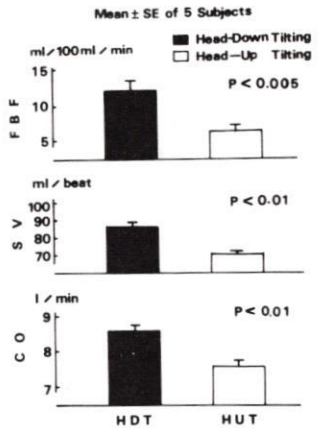


Fig. 3, Average values of cardiac output (CO), stroke volume (SV), and Fore-arm blood flow (FBF) at just before drinking water during exercise in five subjects.

CO, SV, and FBF given at just before drinking during exercise were significantly higher in HDT than in HUT. Figure 4 shows

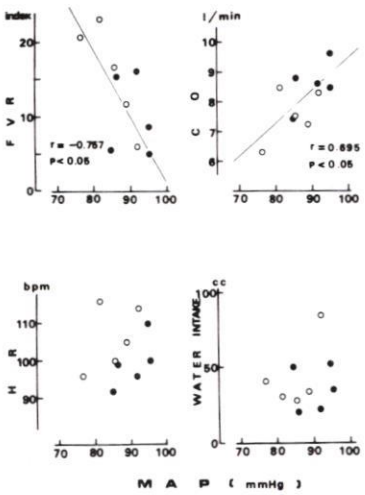


Fig. 4, Relationships between mean arterial pressure (MAP) and heart rate (HR), water intake, fore-arm volume resistance(FVR),and cardiac output (CO) given at just before drinking water during exercise in all subjects.

the relationships between MAP and HR, FVR, CO, water intake, which were presented at just before drinking water during exercise in all subjects. MAP was significantly correlated to FVR and CO, but not to HR and water intake. Figure 5 shows the relationships between SV and MAP, arteriovenous oxgen difference (a-v)O2 diff., FBF, and water intake, which were presented at just before drinking water during exercise in all subjects. SV was significantly correlated to (a-v) O2 diff., FBF, and water intake, but not to MAP. The relationships show that water intake correlated to SV, FBF, and (a-v)O2 diff. Also, water intake was significantly related to Team ($p<0.1$). Therefore, the presented results suggest that water intake increased is due to the increase in central blood volume and also to the elevated temperature in regulation center in the brain.

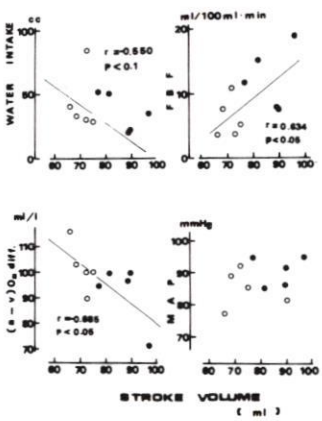


Fig. 5, Relationships between stroke volume (SV) and mean arterial pressure (MAP), arteriovenous oxygen difference (a-v O2 diff.), fore-arm blood flow (FBF), and water intake given at just before drinking water in all subjects.

Discussion

In HDT, the increased MAP suggests the increase in brain blood flow, and the slight correlation between water intake and Team which could estimate the mean body temperature means that the increase in brain blood flow may make the hypotharamus become warmer. However, although MAP at just before drinking water was significantly higher in HDT than in HUT, Team was almost the same as each other in the two tiltings. The fact suggests a weaker factor on the decrease in water intake in HUT. In fact, water intake did not correlate to MAP. On the other hand, CO, SV, and FBF at just before drinking water were significantly higher in HDT than in HUT. Also, water intake was correlated to SV given at just before drinking water as well as to (a-v) O2 diff. and fore-arm blood flow, respectively. Further, HR at just before drinking water was in average about 10 % lower in HDT than in HUT in spite of non-significance. At least, these facts indicate the increase in venous return and thus in the central blood volume in HDT. Therefore, the increased central blood volume brings fulling heart and then extending the part of receptors of water intake in the heart. As a result of this, water intake should be lowered by inhibiting the activity of the receptors in HDT.

In conclusion, during a mild dynamic exercise, 10 degree HDT should make water intake decrease, because the increase in the central blood volume with distributing a higher blood flow to the upper body probably inhibits the activity of receptors of water intake shifted on the heart.

References

1. Blomqvist, C.G., et al., Cardiovascular Responses to Head-Down Tilt in Young and Middle-Aged Men., Suppl. to the Physiologist 26, 6:81-82 1983
2. Borredon, P., et al., Arterial Pressure, Fluid Energy, Posture and +Gz Accelerations., Suppl. to the Physiologist 27, 6:44-45, 1984
3. Hargens, A. R., et al., Fluid Shifts in Vascular and Extravascular Compartments of Human ....., Suppl. to the Physiologist 25,6:63-64, 1982

10° HEAD-DOWN AND -UP TILTING ON THE WATER INTAKE AND CARDIOVASCULAR RESPONSES DURING MILD EXERCISE IN WOMAN

Kikuko YOKOZAWA[+], Shigeyo TORIKOSHI[+], Miyako INAZAWA[+], Katsuko ITOH[++], Yasuko FUKASE[+++], Junko NAGANO[+], Yoji SUZUKI[++++]

+Lab. of Human Physiol., Tokyo Woman's Christian Univ., Suginami-ku, Tokyo, Japan 105, ++ Tsurumi Univ., +++Rikkyo St. Marguerite Woman's College, ++++Lab. Health Administration, Faculty of Medicine, Univ. of Tokyo, 3-7-1, Hongo, Bunkyo-ku, Tokyo, Japan 113

To investigate the relationship between water intake and cardiovascular responses during mild pedalling in tilting positions, 5 female students have performed a 300 kpm/min exercise for 60 min period in 10 degree head-up (HUT) and head-down tilting (HDT). Through the experiments, VO2, HR, arterial blood pressure, cardiac output(CO), fore-arm blood flow (FBF), mean skin temperature($\bar{T}$sk) and external audiomutus temperature(Team) were measured. Water intake at 50 min of exercise was 14 % lower in HDT than in HUT. A mean arterial blood pressure(MAP), CO, stroke volume (SV), and FBF given at just before drinking water were significantly lower in HDT, although VO2, HR, $\bar{T}$sk, and Team at that time were not different between HDT and HUT. Water intake was significantly correlated to the values of SV, arterio-venous oxygen different, and FBF, but not to the MAP. The presented results suggest that the increase in central blood volume inhibits water intake during mild exercise in HDT.

A hypothesis in this study is that when a mild dynamic exercise is performed for a prolonged period in the two tilting positions of head-up and head-down, water intake during exercise should be decreased by the increase in central blood volume in the head-down tilting, because the increase inhibits the activity of receptors of water intake in the heart. Also, the isotonicity in the brain blood should be kept due to the blood flow increased by the head-down tilting.

On the other hand, a possibility is that if the increase in a warmer blood flow in the brain stimulates the body temperature center due to the head-down tilting , the center should function to increase water intake because of keeping internal body temperature.

In this study, the relationships between water intake and cardiovascular responses and body temperatures have been investigated during mild pedalling in head-down and head-up positions.

Subjects and Methods

Five female students participated as the subjects in the study. Their average body weight was 51.6 kg, and the average body 158.2 cm, which were almost the same as the Japanese same age (20 yrs) woman's levels. Their average VO2 max was 42.16 ml/kg/min, and also was included in Japanese standard values of young woman. Before the experiment, the subjects were imformed the purpose and details of the study.

In Figure 1, protocol of experiment was illustrated. That is, after 15 min rest, a 300 kpm/min load exercise was performed for 60 minutes in 10 degree head-down tilting (HDT) or head-up tilting (HUT). Water with about 7.5 C was at will intaken at 50 min. during exercise. The water volume drunk was determined as water intake in each subject. Through all experiments, oxygen uptake(VO2), heart rate (HR), arterial blood pressure, cardiac output (CO), fore-arm blood flow (FBF), mean skin temperature($\bar{T}$sk), and external audiomutus temperature(Team) were measured at each testing point shown in Fig.1. VO2 was determined by a metabolic analysing system which was constracted with a mass-spectrometer, gas flow-meter, and computer. HR was counted on the record of EKG by a computer system. The blood pressure was measured by means of auscultation method in the right upper arm. CO was measured by acetylen gas rebreathing method, which was analysed by a mass spectrometer. FBF was measured in the left fore-arm by means of Whitny's mercury enclosed rubber straingauge plethysmography. $\bar{T}$sk and Team were meausred by a thermister system.

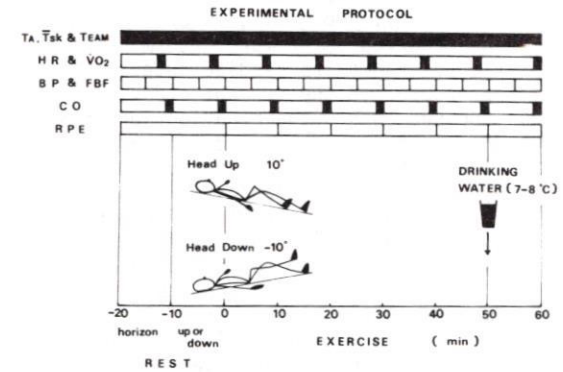


Fig. 1, Protocol and Time Table in Experiment

Results

Comparing time courses of measurements between HDT and HUT, VO2 during exercise was presented almost the same as each other in the two tiltings, although HR was lower, and mean arterial pressure (MAP), FBF and CO were higher levels in HDT. $\bar{T}$sk and Team changed during exercise were not so different between HDT and HUT.

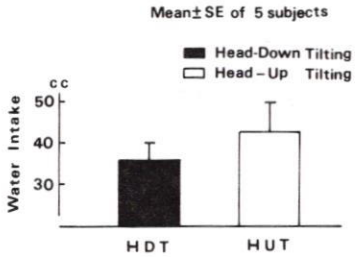


Fig.2. Water intake during exercise in HDT and HUT

position. After TGLVP, the head-up values for TPR were on the average 31% higher than the corresponding values after placebo. Therefore, head-up tilt did not appreciably affect the response of TPR to TGLVP and the increases in TPR after the drug and the tilt were essentially additive. Head-up values for MAP were on the average 7 mm Hg higher with the drug.

In the post-tilt period, TRP remained significantly higher after TGLVP than in the placebo experiments, an indication of the prolonged action of the drug, which was also apparent in the post-tilt levels of MAP and HR.

Discussion

The nature and dynamics of postural changes in the circulation have been aptly reviewed by Gauer and Thron 1965 (5). Among circulatory variables that can be regarded as primary determinants of orthostatic tolerance are cardiac output and mean arterial pressure. In the present study, our interest was focused on how the behaviour of these variables was modified by TGLVP during a standardized 70° head-up tilt test lasting for 20 min.

During head-up tilt, mean arterial pressure at heart level tended to remain higher in the drug than in the placebo experiments, with a significantly higher mean value after 8 and 16 min. This pressor effect of vasopressin and its analogs is well documented in the literature (1,2). The finding that cardiac output showed a more marked decrease in the drug than in the placebo experiments with the difference being significant after 16 min, was entirely due to a greater curtailment of stroke volume, since heart rate rose to almost identical levels in the placebo and drug experiments.

The question arises as to the mechanism underlying the exaggerated curtailment of stroke volume in the drug than in the placebo experiments, the difference being significant after 8, 12 and 16 min of head-up tilt. Three primary possibilities may be considered. First, the drug may have impaired stroke volume because of exaggerated infracardiac pooling in the head-up position, with associated impairment of cardiac filling. There is, however, no experimental evidence that vasopressin or its analogs may dilate capacitance vessels; on the contrary, many investigations have shown either a fleeting or even a sustained venoconstrictive effect of vasopressins in several mammalian species including man, as reviewed by Nakano (1). Second, the drug induced an increase in left ventricular afterload in terms of resistance against left ventricular ejection. However, there is little reason to believe that such a moderate increase in left ventricular afterload could be the cause of the greater curtailment of stroke volume in drug experiments in the head-up position (cf. ref. 6,7). Third, the exaggerated fall in stroke volume might have been due to a negative inotropic effect secondary to coronary vasoconstriction, a well-known effect of vasopressin and its analogs (1).

Whatever the cause of the reductions in stroke volume and cardiac output, these effects were, in our healthy individuals, provoked only in the head-up position. Even though TGLVP caused exaggerated increases in total peripheral resistance and mean arterial pressure, the deleterious effects on the stroke volume and cardiac ouput are very likely to be disadvantageous with regard to orthostatic tolerance.

References

1. Nakano J. Cardiovascular responses to neurohypophysial hormones. Handbook of Physiology. Section 7, Endocrinology, Vol. 4, Part 1. Bethesda: Am. Physiol. Soc., 395-442, 1974.
2. Simpson, H.C.R., J.E. Zubillaga, J.G. Collier, E.D. Bennett, V.T.Y. Ang, N. Mehta and J.S. Jenkins. Haemodynamic effects of vasopressin in man are related to posture. Clinical Science. 70: 177-184, 1986.
3. Forsling, M.L., A.A. Leedy, M. Miller. R. Davies and B. Donovan. Conversion of triglycylvasopressin to lysine-vasopressin in man. J. Endor. 85: 237-244, 1980.
4. Cort, J.H., I Albrecht, J. Novakova, J.L. Mulder and K. Jost. Regional and systemic haemodynamic effects of some vasopressins: structural features of the hormone which prolong activity. Europ. J. Clin. Invest. 5:165-175, 1975.
5. Gauer, O.H. and H.L. Thron. Postural changes in the circulation. Handbook of Physiology. Section 2, Circulation, Vol. 3. Washington D.C. 2409-2439, 1965.
6. Ross, J. Jr. and B.E. Sobel. Regulation of cardiac contraction. Annual Review of Physiology. 34:71-72, 1972.
7. Guyton, A.C. Heart Muscle; The Heart as a Pump. Textbook of Medical Physiology, Chap. 13. W.B. Saunders Co. 158-159, 1981.

CARDIOVASCULAR EFFECTS OF HEAD-UP TILT AS AFFECTED BY A VASOPRESSIN ANALOGUE

Roman Baer, Ola Eiken and Ulf Balldin

Department of Aerospace Medicine
Karolinska Institutet
Stockholm, Sweden

Introduction

Vasopressin is a smooth muscle constrictor with preferential action on peripheral resistance vessels, thereby increasing total peripheral resistance and systemic arterial pressure (1,2). This effect is thought to be mainly responsible for the improvement in orthostatic tolerance in patients with neuropathic orthostatic hypotension.

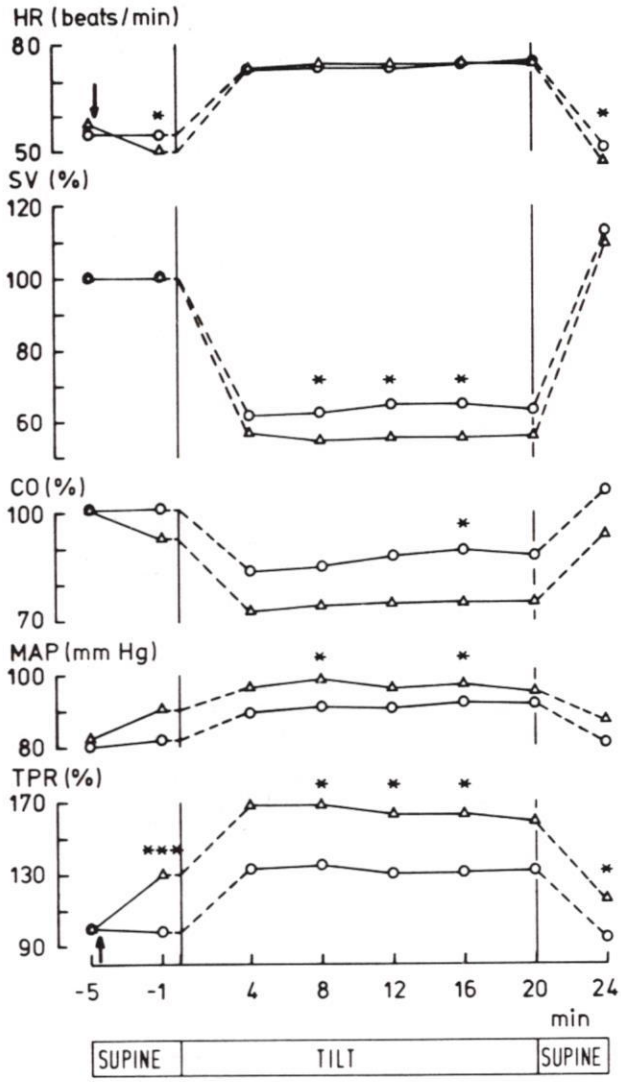
The present study is concerned with certain cardiovascular effects of a synthetic analog to vasopressin, tri-glycyl-lysine-vasopressin (TGLVP) which after conversion to LVP, exerts powerful constriction of resistance vessels (3,4). Preliminary trials in supine human subjects showed that an intravenous dose of 10 µg (50 mIE)/kg body weight induced a clearcut increase in mean arterial pressure. However, there seems to be no information on the effects of TGLVP during orthostatic stress. Important determinants of cardiovascular tolerance to orthostasis are total peripheral resistance to blood flow and cardiac output (5). Accordingly, the present study was carried out to investigate the effects of TGLVP on the tolerance to orthostasis in healthy subjects and especially how this drug affects responses of cardiac output and total peripheral resistance to this condition.

Methods

8 healthy male volunteers were exposed to 20 min of 70° head-up tilt. Mean (range) age, height and weight were 30 (22-46) years, 179 (173-186) cm and 74 (61-103) kg, respectively.

Systolic and diastolic pressures were measured by an automatic blood pressure recorder. Mean arterial pressure (MAP) was derived by adding one third of the pulse pressure to the diastolic pressure. Heart rate (HR) was recorded by a linear cardiotachometer; stroke volume (SV) by impedance cardiography.

Experimental protocol. On two different days and at the same time of the day, by single blind administration and in randomized order, the subjects received either 10 µg (50 mIE)/kg body weight of TGLVP or a corresponding volume of 0.9% saline i.v. Baseline recordings of HR, MAP and SV were obtained after 15 min supine rest on the tilt-table. This was immediately followed by i.v. injection of placebo or TGLVP. 4 min after injection, supine pre-tilt values were recorded, and the subject was subsequently placed in a 70° head-up position for 20 min or until symptoms of impending syncope occurred. Post-tilt values were obtained as averages of 2 and 6 min post-tilt recordings.



The means of cardiovascular responses, supine and during 20 min of 70° head-up tilt, to tri-glycyl-lysine-vasopressin (Δ) and placebo (o); n=8. Time for i.v. administration indicated by arrow. *=p< 0.05 ***=p<0.001.

Results

In the supine position, TGLVP caused a pre-tilt drop in HR by 8 beats/min ($p<0.001$). SV remained essentially unchanged, resulting in a slight and statistically non-significant reduction in CO. There was a 29% ($p<0.001$) rise in total peripheral resistance (TPR; estimated as MAP/CO) resulting in an 8 mm Hg increase in MAP ($p<0.01$).

During head-up tilt, TGLVP caused an exaggerated curtailment of SV as compared to placebo, the difference becoming significant after 8 min of tilt (9%; $p<0.05$). Head-up values for HR were identical after TGLVP and placebo. TGLVP caused an exaggerated fall in CO throughout the tilt period, the difference being most pronounced after 16 min (15%; $p<0.05$).

After placebo, values for TPR were on the average 32% higher in the head-up than in the supine

MSA burst rate was low when the ABP oscillation had low amplitude and low frequency at supine position, but became elevated when the ABP oscillation had high amplitude and high frequency.

As the tilting angle became large, the MSA increased in its burst rate as well as the burst amplitude. In a subject shown in Fig.3, the burst rate (BR) at horizontal level was 22 (bursts/min), and the heart rate (HR) was 52 (beats/min). When the bed was tilted up to 40°, BR increased to 52, and HR to 60. At the upright position, BR increased to 68, and HR to 82.

The BR and HR were thus quantitatively analyzed at each tilting angle. They were plotted on a graph taking the sine function of tilting angle as the abscissa and BR and HR as the ordinate (Fig. 4). In this subject, a significant positive linear correlation was found between the sine of tilting angle and BR ($Y=16.3+47.5 \sin X$, $r=0.988$, $p<0.005$), and also between the sine of tilting angle and HR ($Y=73.4+23.2\sin X$, $r=0.946$, $p<0.005$).

In the same way, the average MSA burst rates in 21 subjects were plotted on Fig. 5, showing a significant positive linear correlation between the sine function of tilting angle and the burst rate ($Y=16.2+33.9\sin X$, $r=0.716$, $p<0.005$).

DISCUSSION

The evidence that positional change from supine to upright activates the muscle sympathetic nerve was initially proved microneurographically by Burke et al.[3] in 1977. However, since their method was volitional standing-up, the MSA change due to exercise should be also contaminated. The exercise-induced reinforcement of MSA was reported by Mark et al.[4] and by us[5]. To eliminate the exercise effects on MSA, a passive and static head-up tilting was employed in our study.

The gravity that works on our body can be divided into two component, the body axis component of gravity which pull our body toward the foot direction and the force to push the bed. The body axis component of gravity can be expressed as $g \cdot \sin\theta$, where θ means the slope angle of the tilting bed (Fig. 6).

In the present study, a linear function was proved between the sine of tilting angle and the MSA burst rate during passive and static head-up tilting. This means that the MSA is activated proportionally to the increase in the body axis component of gravity.

Mechanism of the MSA enhancement in standing was discussed by Burke et al.[3]. They described that the low pressure system might be activated to enhance the MSA. The MSA was proved to respond clearly to the ABP fluctuation during head-up tilting. This may indicate that the MSA is enhanced not only by the low pressure system but also by the high pressure system. Bâth et al.[6] proved that the carotid sinus baroreceptor was particularly sensitive to phasic changes in carotid sinus pressure to modify MSA. Since the ABP showed more remarked fluctuation at larger tilting angle, the MSA might be more enhanced in this condition by phasic change in the carotid sinus pressure.

The passive and static head-up tilting up to upright position causes the venous pooling at the lower body, resulting the decrease of venous return, and this lowers the cardiac output and arterial blood pressure. This mechanism should influence the low and high pressure systems at the same time, activating the baroreflex. The generalized sympathetic nervous system activation may be induced by the baroreflex activation during head-up tilting. The enhanced MSA may contribute to the peripheral vasoconstriction which elevates the systemic blood pressure and to the maintenance of the constant cerebral blood flow.

CONCLUSION

Muscle sympathetic nerve activity in humans is enhanced by head-up tilting in linear correlation with the body axis component of gravity. This mechanism might be important for homeostatic control of blood pressure against gravity.

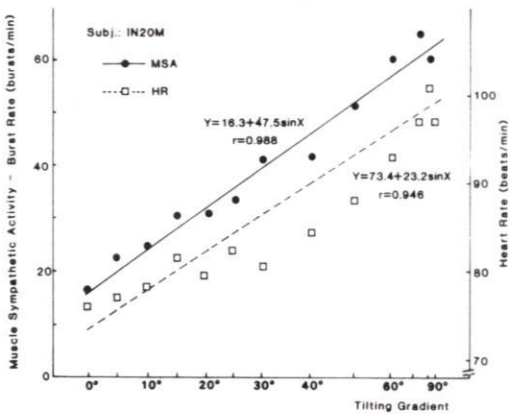


Fig. 4: Correlation between the sine function of tilting angle and the MSA burst rate and the heart rate in a subject.

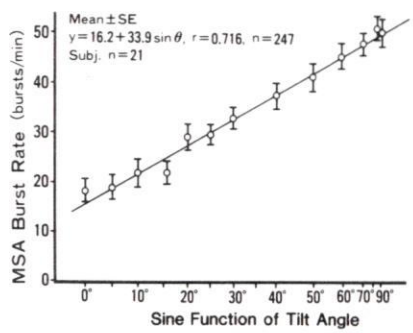


Fig. 5: Correlation between the sine of tilting angle and the MSA burst rate in 21 subjects, expressed in the mean ± S.E.

REFERENCES

1) Hagbarth K-E, Vallbo ÅB: Pulse and respiratory grouping of sympathetic impulses in human muscle nerves. Acta Physiol Scand 74: 96-108, 1968.
2) Wallin BG: Intraneural recording and autonomic function in man. In Bannister R Sir ed Autonomic Failure, A textbook of clinical disorders of the autonomic nervous system, pp36-51, 1983, Oxford Univ Press, Oxford.
3) Burke D, Sundlöf G, Wallin BG: Postural effects on muscle nerve sympathetic activity in man. J Physiol 272: 399-414, 1977.
4) Mark AL, Victor RG, Nerhed C, Wallin BG: Microneurographic studies of the mechanisms of sympathetic nerve responses to static exercise in humans. Cir Res 57: 461-469, 1985.
5) Saito M, Mano T, Abe H, Iwase S: Responses in muscle sympathetic nerve activity to sustained hand-grip of different tensions in humans. Eur J Appl Physiol 55: 493-498, 1986.
6) Bâth E, Lindblad L-E, Wallin BG: Effects of dynamic and static neck suction on muscle nerve sympathetic activity, heart rate, and blood pressure in man. J Physiol 311: 551-564, 1981.

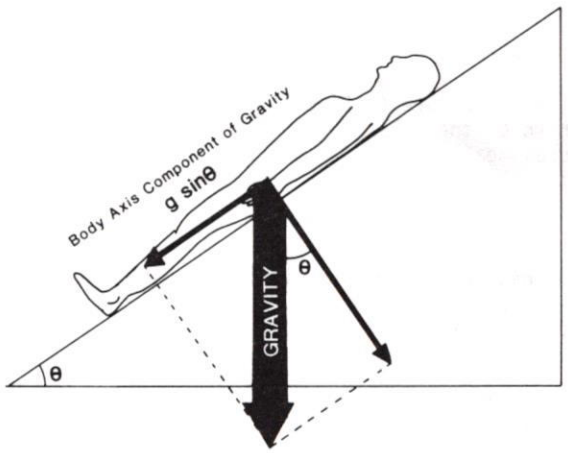


Fig. 6: A man on a tilting bed. Sine function of the tilting angle indicates the body axis component of gravity.

EFFECTS OF GRADED HEAD-UP TILTING ON MUSCLE SYMPATHETIC ACTIVITIES IN MAN.

SATOSHI IWASE, TADAAKI MANO, and MITSURU SAITO

The Research Institute of Environmental Medicine,
Nagoya University, Nagoya 464, Japan.

Discharge responses of sympathetic nerve fibers innervating the skeletal muscle in human subjects to graded head-up tiltings, in every 5° to 10° from 0° (supine position) to 90° (upright position) were analyzed microneurographically using a tungsten microelectrode inserted percutaneously and unanesthetically into the tibial nerve at the popliteal fossa. Subjects were 21 normal male and female volunteers aged 19-61 with prior informed consents. Muscle sympathetic nerve activity (MSA), recorded as pulse synchronous burst activity increased its numbers of bursts per minute, expressed as burst rate, when tilting angle became large. In a subject, whose arterial blood pressure (ABP) was measured by catheterization method, MSA responded reciprocally to fluctuations of ABP wave, being enhanced when ABP decreased and becoming silent when ABP increased. A significant positive linear correlation was established between the sine of the tilting angle (the body axis component of gravity) and the MSA burst rate. It is concluded that the changes of MSA burst with head-up tilting may be related to the homeostatic mechanism against the gravity for the maintenance of systemic blood pressure.

INTRODUCTION

When we change our body position from supine to upright, gravity of the earth causes several kinds of body fluid shift, which results transient postural hypotension. To compensate this, sympathetic nervous system is activated to stabilize the arterial blood pressure to maintain the cerebral blood flow constant. Until recently, the activity of sympathetic nervous system in humans could be evaluated only through the function of effector organs, e.g. heart rate, blood pressure. However, advances in medical electronics have made it possible to record the activity of the sympathetic nervous system directly, although limited to muscle and skin, by using a tungsten microelectrode. This method, called microneurography, to observe the sympathetic vasoconstrictor nerve activity directly, was initiated by Hagbarth et al.[1] in 1968, and became to be utilized in various kinds of fields.

In the present study, we observed the postganglionic fiber activity of sympathetic nerves innervating the human skeletal muscle, which is called muscle sympathetic activity (MSA), to analyze how this vasoconstrictor nerve activity contribute to the human blood pressure maintenance during orthostasis.

SUBJECTS AND METHODS

Subjects were 21 male and female volunteers aged from 19 to 61. They were laid on a tilting bed, possessing the rotation axis at the equilibrium point of the body. A tungsten microelectrode, with a tip diameter of 1 μm, a shaft diameter of 100 μm, and impedance of 3-5 MΩ was inserted percutaneously without anesthesia, into the tibial nerve at the popliteal fossa. The heartbeat synchronous multifiber burst activities in the postganglionic efferent fiber of the muscle sympathetic nerve (MSA) were recorded by a high impedance preamplifier, and observed by a cathode ray oscilloscope. The identification of the MSA was referred to the criteria described by Wallin[2]. The electrocardiogram (ECG) by bipolar chest leads, and respiration curve by an impedance method were recorded simultaneously. The arterial blood pressure (ABP) was measured by auscultation method, using an autosphygmomanometer. In one

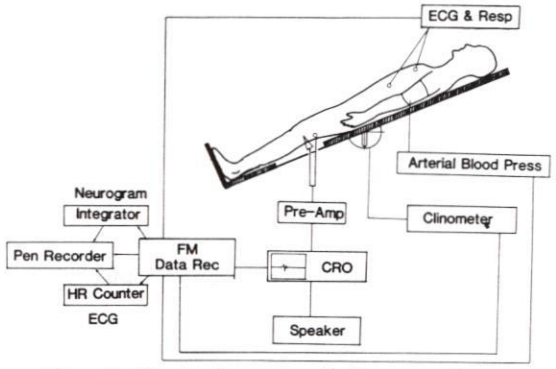


Fig. 1: Block diagram of the experiment.

subject, ABP was measured by catheterization method continuously at the brachial artery. All data were stored in a multichannel FM magnetic tape recorder, and analyzed by off-line processing (Fig. 1).

After recording the data at 0°, which signified the horizontal level, the bed was tilted in 5°interval up to 30°, and in 10° interval to 90°, which was the upright position. At each tilted state, the MSA was recorded at least for 5 min after remaining for 1 min, waiting to reach the steady state. An L-shaped board was attached to the lower end of the bed to assist the sole. The bed was tilted manually with an angular velocity of 14°/min.

The change of MSA was analyzed quantitatively as "burst rate", which means the number of burst discharges per minute, having the unit of bursts/min. It was counted from the full-wave rectified and integrated MSA trace on a pen-recorder.

RESULTS

The MSA bursts were discharged reciprocally to the ABP changes. It was discharged when the ABP fell, while became silent when the ABP rose (Fig. 2). The

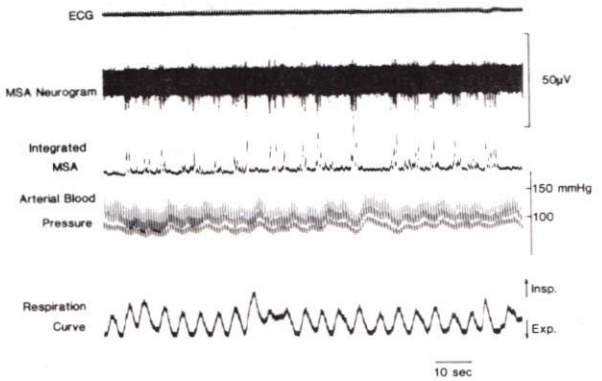


Fig. 2: Spontaneous muscle sympathetic nerve activity at the tilting angle of 60°.

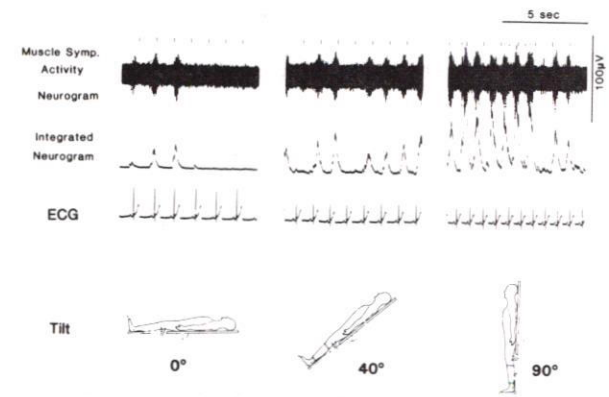


Fig. 3: Changes of MSA and ECG at the tilting angle of 0°, 40°, and 90°. MSA was enhanced in its burst rate as well as the burst amplitude. From upper to bottom, traces are neurogram of MSA, full-wave rectified and integrated neurogram, ECG, and body positions.

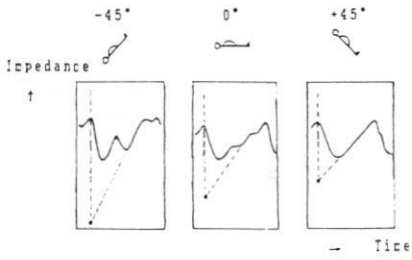


Fig.4 Impedance pulmonary pulse.

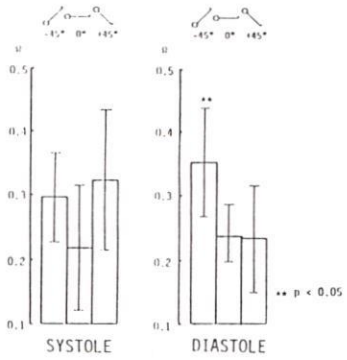


Fig.5 Postural change of early diastolic peak of impedance pulmonary pulse.

The Z_0 value in the right upper lung field changed from subject to subject. We studied changes associated with postural changes using that at 0° as control. As shown in Figure 6, the results disclosed that the changes at +45° were greater than those at -45° with a 10 % fluctuation on the average. Similar changes were also demonstrates in blood volume measured using Tc-99m-RBC. In the lungs, the volume declined more at +45° than -45°. (Fig.7). Both tidal volume and minute ventilatory volume remained constant with no impact from postural changes, but blood gas significantly declined at -45°.

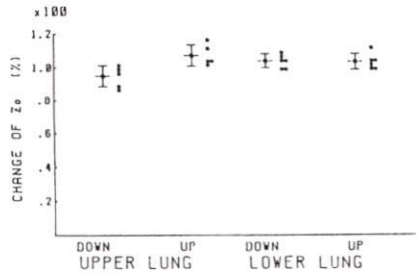


Fig.6 Postural change of Z in lung field.

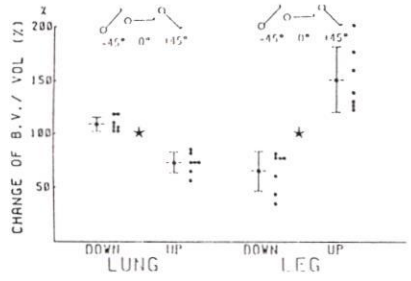


Fig.7 Postural change of blood volume in lung.

Discussion

To date much study has been conducted concerning changes in the pulmonary and circulatory functions associated with postural changes, including the sitting position, supine position and lateral decubitus. Such studies are carried out in relation to a therapeutic rationale or with an eye to improving the accuracy of examination. By contrast, the clinical usefulness of information derived from a study conducted in the head down position is ill-documented. Though it is reported that dyspnea is improved in -16° position (2), the findings mostly deal with physiological changes.

In the current study we tried a postural change of -45° in order to elucidate what changes would result from contrary positions of -45° and +45°, when 0 is used as control. It was initially though that since -45° is an unnatural posture, there would be striking changes in measurements. However, BP, HR and CO as well as pulmonary blood volume changed greater at +45° than -45°. On the other hand, there occurs a significant decline in blood gas, and this implies that some unknown changes have occurred in the pulmonary-circulatory system. Elevation of the diastolic peak in the impedance pulmonary pulses is also observed, and further study is needed before we understand what the change means, though in the case of the limbs, venous filling and backward filling are known to be accountable for it. Appearance of these after dialysis could be linked to the state of pulmonary congestion. In order words, the degree of change in early diastolic filling due to a postural change could serve as an index of pulmonary congestion. In the current study we used -45° and +45° for postural change, and we are now studying to see if adequate information could be obtained by studying the changes at -20°, or so, instead.

References

1. Ohsumi H, Okumura F, Ninomiya I : Differences in arterial blood pressure control during postural changes in man in consciousness and under general anesthesia. Nihon Seiri Shi, 1985;47: 237-242.
2. Dean E : Effect of body position on pulmonary function. Physical therapy, 1985;65:613-618.
3. Demedts M, Clarysse I, Verhamme M, Marcq M and DeRoo M : Regional gas distribution and single-breath washout curves in head-down position. J. Appl. Physiol. Respirat. Environ. Exercise Phsiol. 1983;54:361-365

THE EFFECT OF BODY POSITION ON VENTILATION AND PERFUTION IN THE LUNG

E.MORIYA[1], K.KAWAKAMI[1], M.SUDOH[2], S.IKAWA[2]

[1]Department of Radiology, [2] Space Medicine Laboratory, The JIKEI University School of Medicine, Tokyo 105 JAPAN.

The effect of body position on respiratoly systems discussed for the following positions : Supine, Head up 45° (+45°) and Head down 45° (-45°). Distribution of $\dot{V}$, $\dot{Q}$, $\dot{V}/\dot{Q}$ was measured by radionuclide method. Cardiac output, pulmonary pulses and base transthoracic impedance were by electrical impedance plethysmography. Change of blood volume in the lung was measured using Tc-99m-RBC. Blood pressure, ventilatory volume and blood gas were also measured. Cardiac output and blood pressure were significantly decreased in +45° . Early diastolic peak in the impedance pulmonary pulse was increased in -45° . Change of base impedance was greater in +45°, than in -45°, corresponding with the changes of blood volume. This result suggested that $\dot{V}/\dot{Q}$ mismatch is increased in -45°.

While the physiological changes of pulmonary and circulatory functions associated with postural changes are well-documented, such changes in the head down position are not as well documented.(1),(2),(3)

We studied pulmonary and circulatory functions in the supine position (0°), head up 45 degree position (+45°) and in the head down 45 degree position (-45°) using electrical impedance plethysmography and Radionuclide methods.

Method and subjects

Six healthy men (aged 25-45 years) were used in the study. Pulmonary pulses,base transthoracic impedance (Z_0) and cardiac output were measured by means of electrical impedance plethysmography, and total peripheral resistance was calculated from cardiac output and blood pressure. In addition, changes in pulmonary blood volume were also measured using Tc-99m-RBC. Furthermore, we studied minute ventilatory volume and blood gas. The postural changes were performed in the order of 0°, +45°, 0°, and -45°. When ten minutes had passed in each position, measurements were made of each studies, which took about 5 minutes. (Fig.1)

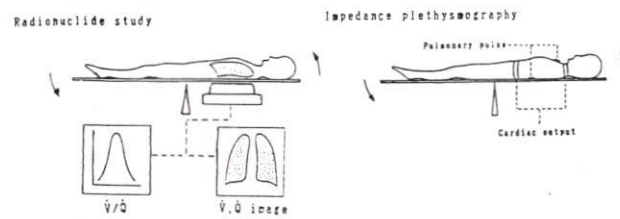


Fig.1 Radionuclide study and Impedance plethysmography.

Results

Figure 2 shows changes in blood pressure (BP) and heart rate (HR). While blood pressure rose in the +45° position, HR showed no significant difference except for a slight increase. Stroke volume (SV) and cardiac output (CO) tended to decline in the order of -45°, 0°, and +45°, and the decline was significant at +45° . As a result, total peripheral resistance (TPR) remained high at +45° .(Fig.3)

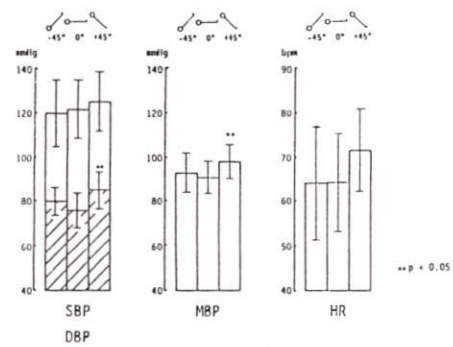


Fig.2 Postural change of blood pressure and heart rate.

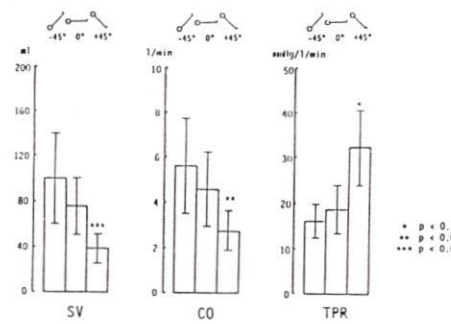


Fig.3 Postural change of stroke volume and cardiac output.

As shown in Figure 4, the early diastolic peak appearing in the impedance pulmonary pulse at 0° rose at -45° . The early diastolic peak, which was extrapolated to the pulmonary impedance pulse at shown in Fig.5, was significantly elevated at -45°.

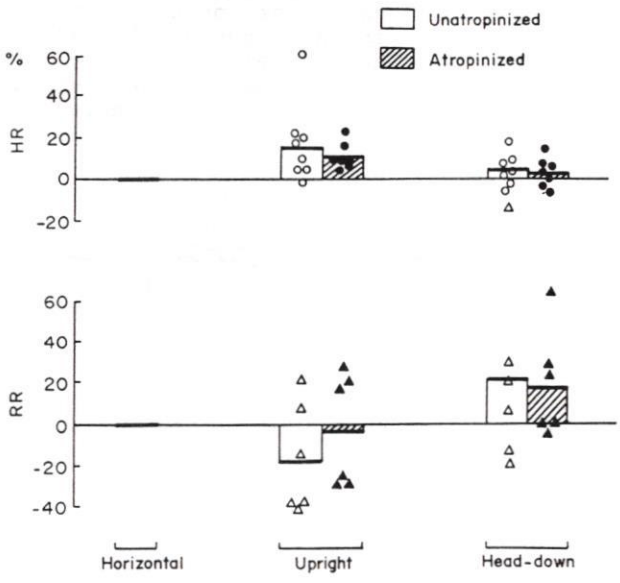


Fig. 2. Effect of atropine on the percent changes of heart rate(HR) and respiratory rate(RR) in the upright and head-down tilt.

In upright tilt, venous Pco_2 was increased ($p < 0.05$), but arterial Po_2 and venous Po_2 ($p < 0.01$) were decreased. Hct was increased in both upright ($p < 0.01$) and head-down tilts. The increased Hct by tilting is suggestive of extravascular fluid sifts(7). The findings of blood Pco_2, Po_2 and Hct were not interferred by the atropine.

On the basis of these findings we conclude that the administration of atropine is somewhat effective on improving the cardiovascular tolerance to postural changes. Thus, atropine attenuates the severe diminution of the blood flow to the head during orthostasis, and also reduces the changes of HR and RR in both orthostasis and anti-orthostasis.

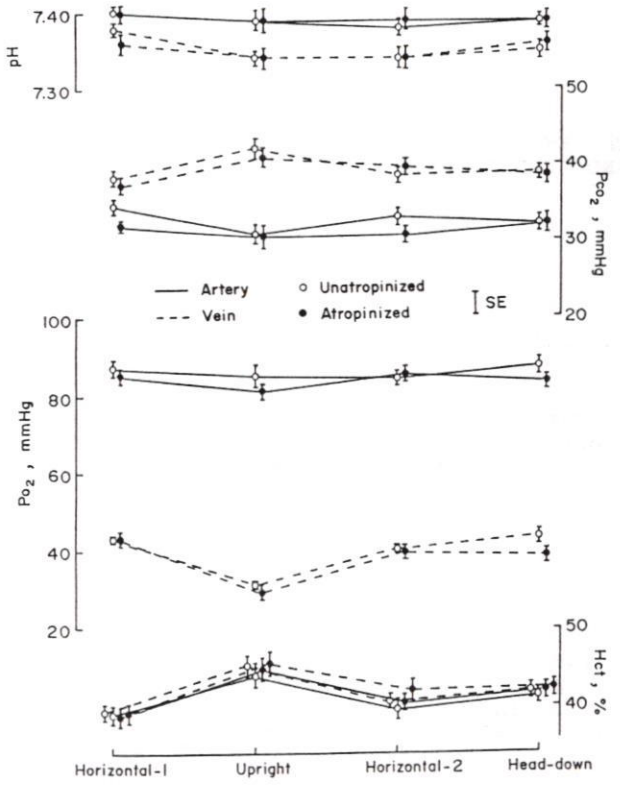


Fig. 3. Changes of the pH, Pco_2, Po_2 and Hct of the arterial and venous blood during the postural changes in dogs, and the effect of the atropine.

REFERENCES

1. Busija, D.W. and D.D. Heistad: Atropine does not attenuate cerebral vasodilation during hypercapnia. Am. J. Physiol., 242:H683, 1982.

2. Chand, N. and A. Dallaire: The effect of atropine on acetylcholine-induced depressor responses in adult domestic fowl. Arch. Int. Pharmacodyn., 241:45, 1979.

3. Chae, E.U. and S.Y. Jun: Cardiorespiratory responses to orthostasis and the effect of atropine. Preprints of the Annual Scientific Meeting, Aerospace Medical Association Washington, D.C. 1979, p.91-92.

4. Chae, E.U. and S.H. Bae: Effects of postural changes on minute ventilation, functional residual capacity and pulmonary N_2 clearance. Physiologist,22(No.6) Suppl.:33-34, 1979.

5. Conrad, K.A.: Effects of atropine on diastolic time. Circulation, 63:371, 1981.

6. Gaskell,P.: The effect of intra-arterial atropine infusions on the blood flow through the human hand and forearm. J. Physiol., 131:639, 1956.

7. Hargens, A.R., B.J. Turker and C.M. Tipton: Fluid shifts in vascular and extravascular components of humans during and after simulated weightlessness. Physiologist,25(Suppl.):63, 1982.

8. Kawamura, Y., J.S. Meyer, H. Hiromoto, M. Aayagi, Y. Tagashira and E. Ott: Neurogenic control of cerebral blood flow in the baboon. Effects of the cholinergic inhibitory agent, atropine, on cerebral autoregulation and vasomotor reactivity to changes in $Paco_2$. J. Neurosurg., 43:676, 1975.

9. Liu, C.T., R.A., Huggins and H.E. Hoff: Circulatory and respiratory responses to postural changes in the vagotomized dog. Aerospace Med., 41:654, 1970.

10. Mauskopf, J.M., S.D. Gray and E.M. Renkin: Transient and persistent components of sympathetic cholinergic vasodilation. Am. J. Physiol., 216:92, 1969.

11. Rengo, F., L. De Caprio, L. Sacca, B. Trimarco, G. Perez, M. Chiariello and M. Condorelli: Studies on the nature of the vasodilator fibers running in the lumbar sympathetic chain of the dog. Pharmacology, 13:539, 1975.

12. Roizen, M.F., A.R. Forbes, R.D. Miller, C.R. Lake and D.R. Stanski: Similarity between effects of pancuronium and atropine on plasma norepinephrine levels in man. J. Pharmacol. Exp. Ther., 211:419, 1979.

13. Scremin, A.M.F., O.U. Scremin and T. Brechner: Survival under hypoxia. Age dependence and effect of cholinergic drugs. Stroke, 11:548, 1980.

14. Viveros, O.H., D.G. Garlick and E.M. Renkin: Sympathetic beta-adrenergic vasodilation in skeletal muscle of the dog. Am. J. Physiol., 215:1218, 1968.

15. Weissler, A.M., J.H. Leonard and J.V. Warren: Effects of posture and atropine on the cardiac output. J. Clin. Invest., 36:1656, 1957.

CHANGES OF ARTERIAL AND VENOUS BLOOD FLOW DURING ORTHOSTASIS AND THE EFFECT OF ATROPINE

W.K. Park and E.U. Chae

Department of Physiology
Keimyung University School of Medicine
Taegu 630, Korea

ABSTRACT

This study was attempted to clarify the effect of atropine on the tolerance of the cardiovascular system to the upright and head-down tilt, and to investigate the change of blood flow through head and lower leg with Electromagnetic flowmeter in both tilts before and after atropine state. Fourteen anesthetized dogs(10-14kg) were tilted from supine to +77° upright and then to -90° head-down position, and the same course was taken 20 minutes after intravenous administration of 0.5mg atropine. In upright tilt, the blood flow both on the artery and vein through head and lower leg were decreased. And the atropine attenuated the decrement of the blood flow on the carotid artery, but not on the vessels of the lower leg. In upright tilt, arterial Po_2 was slightly decreased, but venous Po_2 was markedly($p < 0.01$) decreased and venous Pco_2 was increased($p < 0.05$). Hct was increased in both tilts($p < 0.01$). The findings of blood Po_2, Pco_2 and Hct were not interferred by the atropine. In conclusion, the atropine attenuates the severe diminution of the blood flow to the head during orthostasis.

INTRODUCTION

The passive tilt has been performed to study the orthostasis on the cardiovascular system(9). The orthostasis due to upright tilt was demonstrated as follows; the venous return, cardiac output and systemic arterial blood pressure were decreased, whereas there was concomitant increase of heart rate, through the negative feedback mediated by such as the baroreceptor.

Previous investigators have suggested that the tolerance to the orthostasis could be increased by blocking the cholinergic fiber with atropine which prevented vasodilation and bradycardia through the vasovagal reflex during the orthostasis(1-3,5,6,8, 10-15). However, this hypothesis has not been clearly understood.

This study was attempted to clarify the effect of atropine on the tolerance of the cardiovascular system to the upright and head-down tilt, and to investigate the change of the blood flow through head and lower leg with Electromagnetic flowmeter in both tilts before and after atropine state.

METHODS

Fourteen anesthetized dogs of 10-14kg were examined by tilting from supine position to +77° upright position(orthostasis), and then to -90° head-down position(antiorthostasis) for 10 minutes on each test. And the same course was taken 20 minutes after intravenous administration of 0.5mg atropine.

The measurements were made of the blood flow (ml/min.) on the carotid artery, external jugular vein, femoral artery and femoral vein. At the same time pH, Pco_2, Po_2 and hematocrit(Hct) of the arterial and venous blood, and heart rate(HR) and respiratory rate(RR) were measured. The measurements obtained from upright and head-down tilt were compared with those from supine position.

RESULTS AND DISCUSSION

In upright tilt, the blood flow both on the artery and the vein through head and lower leg were decreased, however the decrement of blood flow through the head was greater than the lower leg. And the atropine attenuated the decrement of the blood flow on the carotid artery, but not on the vessels of the lower leg.

HR was moderately increased in upright tilt, but slightly in head-down tilt. The percent change of HR after the atropine administration was smaller than that before the atropine state in both upright and head-down tilts. Before the atropine state, RR was decreased in upright tilt, whereas increased in head-down tilt(4). However after the atropine state, the percent change of RR was smaller than that of before the atropine state in both upright and head-down tilts.

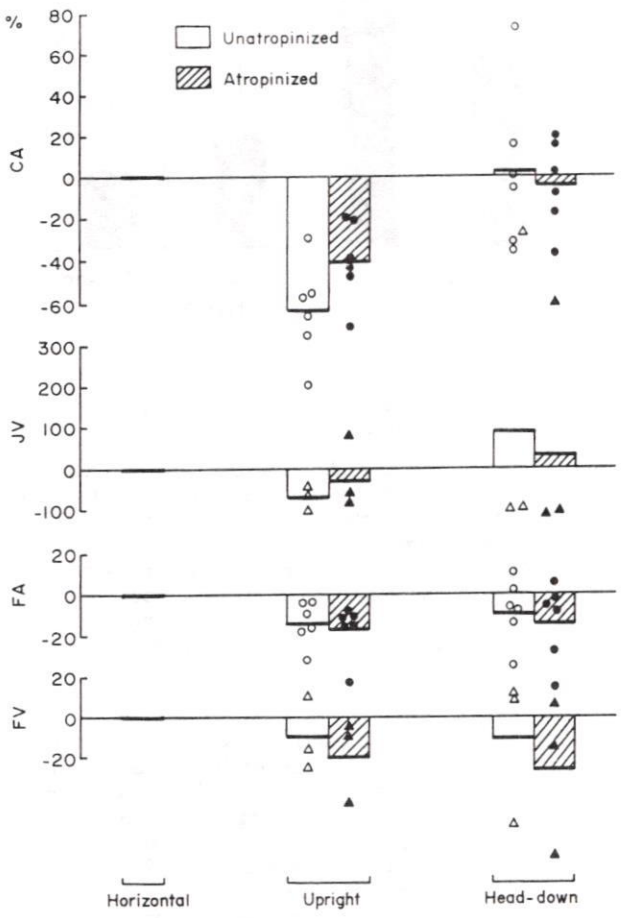


Fig. 1. Effect of atropine on the percent changes of blood flow in carotid artery(CA), external jugular vein(JV), femoral artery(FA), and femoral vein(FV) through the head and lower leg of dogs in the upright and head-down tilt. The each bar represents the mean value.

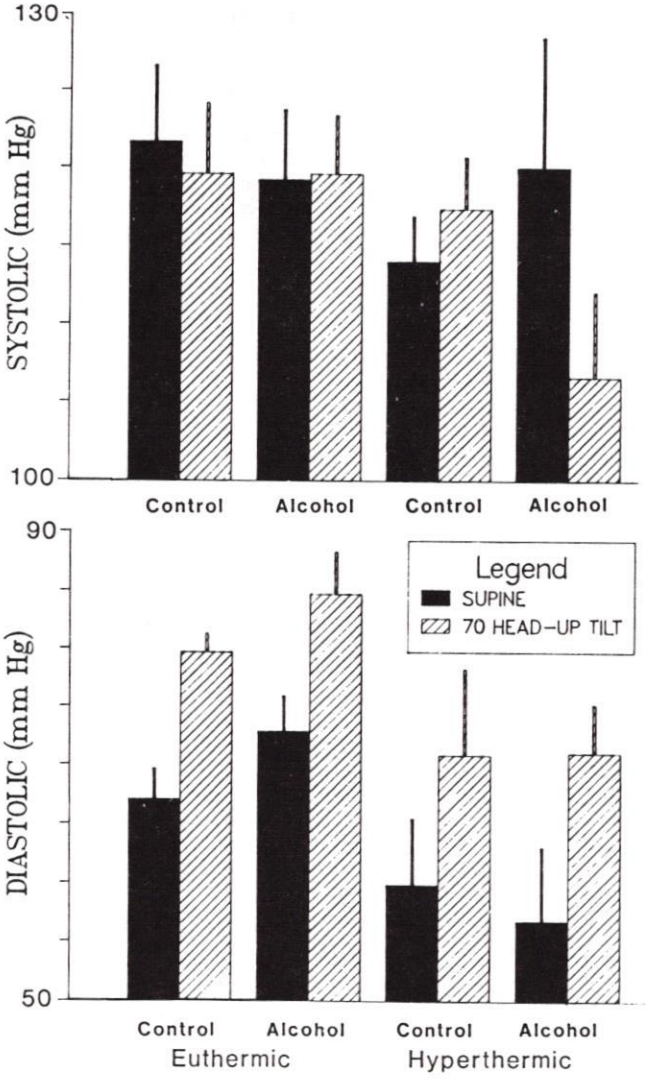


Figure 1: Systolic and diastolic blood pressures

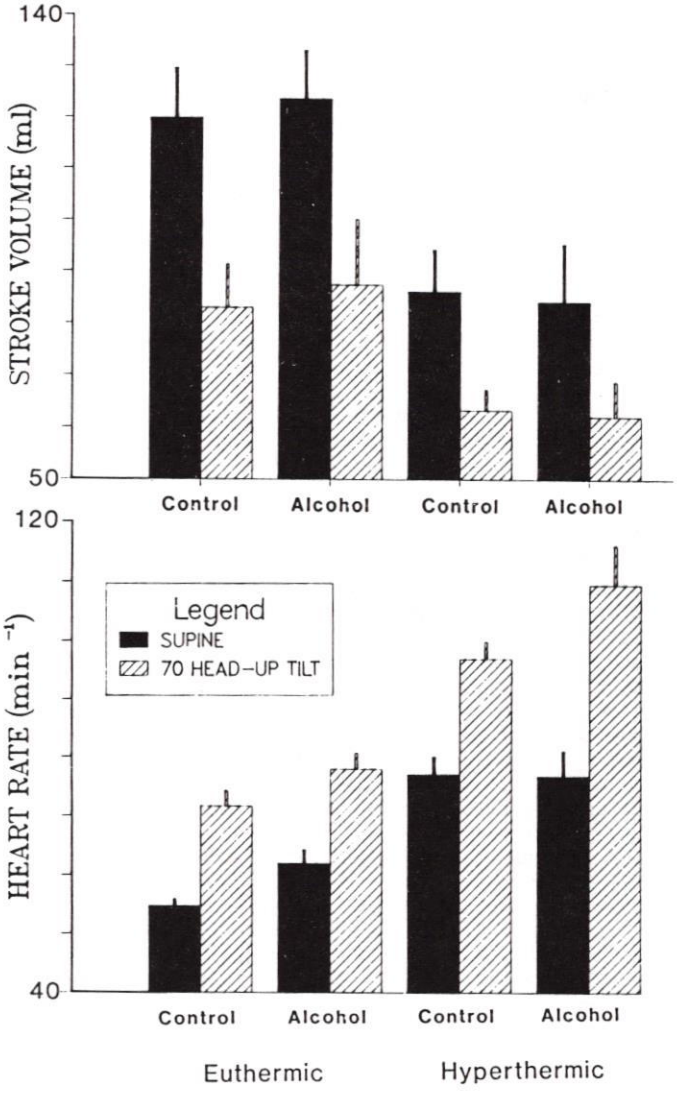


Figure 2: Stroke volume and heart rate

Assuming the upright posture elevated the heart rate ($p<0.005$) in all conditions. Increased core temperature further elevated heart rate ($p<0.001$) when compared to the euthermic conditions. Although alcohol appears to enhance heart rate in the supine and upright positions under conditions of euthermia and hyperthermia (Fig.2), the differences observed were not significant.

DISCUSSION

It has been well established that elevations in skin and core temperature either as a result of exercise (Bjurstedt et al., 1983) or hot air exposure will induce syncope during a head-up tilt (Lind et al., 1968) and will reduce the $+G_z$ tolerance (Allan and Crossley, 1972). The reduction in orthostatic tolerance during elevated body temperature has been demonstrated by Johnson et al. (1973) to result from the inability of the baroreflex mechanism to supercede the heat induced vasodilation.

The present study demonstrates that alcohol acts synergistically with elevated body temperature increasing peripheral perfusion by decreasing peripheral resistance, as indicated by the reduction in mean arterial blood pressure with a concomitant rise in heart rate.

ACKNOWLEDGEMENTS

This work was supported by the Simon Fraser University Steel Fund.

REFERENCES

Allan, J.R. and R.J. Crossley. J.Appl Physiol 33:418-420, 1972.

Arborelius, M., U.I. Balldin, B.Lilja and C.E.G. Lundgren. Aerosp Med 43:592-598. 1972.

Bjurstedt H., G. Rosenhamer, U. Balldin and V. Katkov, Acta Physiol Scand 119:25-31, 1983.

Gauer, O.H. and H.L. Thron. The Handbook of Physiology. Circulation, Sect.2, vol.III, pp.2409-2439, Am Physiol Soc, Washington, D.C.

Johnson, J.M., M. Niederberger, L.B. Rowell, M.M. Eisman and G.L. Brengelmann, J. Appl Physiol 35:798-803, 1973.

Lind, A.R., C.S. Leithead and G.W. McNicol, J. Appl.Physiol 25:268-276, 1968.

CARDIOVASCULAR RESPONSES DURING 70° HEAD-UP TILT: THE EFFECT OF ELEVATED BODY TEMPERATURE AND HIGH ALCOHOL BLOOD LEVELS

I.B. Mekjavic, C.A. Gaul, M.D. White and K.D. Mittleman

School of Kinesiology
Simon Fraser University, Burnaby
British Columbia, Canada V5A 1S6

INTRODUCTION

During immersion in thermoneutral water, the hydrostatic pressure of the water on the lower extremities causes a shift in blood volume to the intrathoracic region, thus enhancing venous return (Arborelius et al., 1972, Gauer and Thron, 1965). A rapid emergence from the water will instantaneously remove the hydrostatic force exerted by the water, resulting in pooling of the blood in the lower extremities and an inadequate cardiac filling, as a consequence of the gravitational force. The ensuing drop in mean arterial blood pressure is normally compensated by the baroreceptor reflex, which enhances heart rate and total peripheral resistance.

Immersion in water above neutral temperature will cause dilatation of peripheral blood vessels, however the pressure of the surrounding water helps to artificially maintain venous return and cardiac filling. Emergence from a hot bath will give rise to more severe reductions in blood pressure, due to the reduced overall resistance offered by the peripheral blood vessels. The action of a vasodilatatory agent, such as alcohol, may thus pose a further strain on the cardiovascular system.

The purpose of the present study was therefore to investigate the cardiovascular changes resulting from a head-up tilt, analogous to emergence from an aqueous environment, at elevated body temperature in combination with elevated levels of blood alcohol.

METHODS

Six young healthy male subjects participated in the experimental trials. All experiments were conducted at the same time of day at weekly intervals, with the order of trials randomized for each subject.

Each subject participated in a total of four trials in which their blood alcohol and thermal status was varied. In the control condition, subjects ingested a total of 7.5 ml of orange juice per kg. of body mass. In trials where the blood alcohol level was elevated subjects ingested 2.5 ml. of a 40% alcohol in 1:2 solution with orange juice. Thus the fluid intake for the two conditions was similar. Both the control and alcohol conditions were conducted with the subjects either euthermic or hyperthermic.

To elevate the core temperature, subjects were immersed in a 40°C bath. They remained immersed in the bath for a maximum of 60 minutes, though immersions were terminated upon rectal temperature reaching 38.5°C. Subjects were requested to ingest the fluid within the initial 15 minutes of immersion. Upon completion of the immersion, subjects were placed on a tilt table in the supine position, and following five minutes in this position, were tilted to a 70° head-up tilt. In the euthermic conditions, subjects rested in the laboratory and were requested to ingest the fluid in 15 minutes. They were placed on the tilt table once 60 minutes had elapsed from the onset of the fluid ingestion.

During the experimental procedures, skin temperature was measured with thermistors placed at five sites: arm, chest, thigh, calf and abdomen. Rectal temperature was monitored with a thermistor inserted 15 cm. All temperature measurements were sampled with an HP3497A Data Acquisition System (Hewlett Packard) controlled by an HP85 minicomputer (Hewlett Packard).

During the postural change from supine to 70% head-up tilt, continuous electrocardiographic tracings were obtained on an HP7404A Oscillographic Recorder (Hewlett Packard). Systolic and diastolic pressures were recorded with a sphygmomanometer at the mid-point of each five minute period in the supine and upright position. Stroke volume was measured non-invasively with an impedance plethysmograph (Bomed Manufacturing Ltd.) Blood samples were also drawn and analysed for blood alcohol content.

RESULTS

In the euthermic state, rectal temperature (mean±s.e.) was 36.78±0.1 and 36.42±0.2 for the control and alcohol conditions respectively. In the hyperthermic conditions, rectal temperature was elevated to 38.28+0.09 and 37.98±0.19, for the control and alcohol conditions, respectively. In contrast to the rectal temperature, there was no significant difference in the levels of unweighted mean skin temperature between the four experimental trials: euth./control = 29.7±0.3; euth./alcohol = 30.4±0.2; hyper./control = 30.7±1.0; hyper./alcohol = 32.1±0.1. The average blood alcohol levels were slightly higher for the euthermic condition (0.099±0.014 gms.%) in comparison to the hyperthermic condition (0.078±0.01 gms.%).

As observed from Fig.1. systolic blood pressure was maintained between 108.5±6.1 mmHg (supine in the hyperthermic/alcohol condition) and 121.2±5.7 mmHg (upright in the euthermic/control condition). There was no significant difference in the observed systolic blood pressures for the experimental conditions. In contrast, head-up tilt induced a significant ($p<0.005$) increase in diastolic pressure in conditions when subjects were euthermic, whereas the changes observed in the control and alcohol conditions at elevated core temperatures were not significant. The effect of alcohol was enhanced at elevated core temperature to cause a significant difference between the euthermic/alcohol and hyperthermic/alcohol trials for both the supine ($p<0.001$) and upright ($p<0.005$) postures.

With the exception of the hyperthermic/alcohol condition, head-up tilt induced a significant ($p<0.005$) reduction in stroke volume, as indicated in Fig.2. The effect of alcohol was not evident in both the euthermic and hyperthermic conditions, however, increased core temperature instigated a significant reduction in stroke volume in the supine position from 123.5±9.5 ml. in the euthermic condition to 78.5±11.5 ml. in the hyperthermic condition.

In summary, the Cosmos-1667 experiments have demonstrated that a 7-day space flight is sufficient in terms of time for a number of structural, metabolic and functional changes to emerge in microgravity due to the underloading of certain physiological systems. Most changes that develop in the course of adaptation to microgravity increase with flight time while some variations originate at an initial stage of adaptation to microgravity and remain unchanged (i.e. do not increase or decrease) during long-duration flights. The characteristic feature of the initial stage of adaptation to microgravity is the absence of significant changes in blood biochemistries in the presence of structural and metabolic shifts in organs and tissues. This gives evidence that the mechanisms that maintain stable homeostasis at the organism level remain operational.

References

1. Kondratyev Yu.I., Ilyushko N.A., Besedina E.G. In: The Effect of Space Flight Dynamic Factors on the Animal Body. Moscow, Nauka, pp.21-24.

2. Ilyina-Kakueva E.I. In: XIX Intercosmos Meet. Space Biol.Med.Habana, Cuba, 5-12, April 1986. Abstr. Habana, 1986, p.28.

3. Morey-Holton E.R., Arnaud S.B. The Physiologist, 1985, v.28, No.6, Suppl., pp.9-12.

4. Kvetnansky R., Torda T., Blazicek P. et al. In: Space Biol.Aerospace Med.Abstr. VIII Natl.Conf. Kaluga, 25-27 June 1986. Moscow, Nauka, 1986, pp.275-276.

5. Popova I.A., Afonin B.V., Zagorskaya E.A. et al. In: XIX Intercosmos Meet. Space Biol.Med. Habana, Cuba, 5-12 April, 1986, p.53.

6. Durnova G.N., Vorotnikova E.V. Ibid., p.21.

7. Durnova G.N., Kaplansky A.S., Glagoleva E.V. Arch.Anatomy, Histology and Embryology, 1983, v.85, No.7, pp.67-72.

8. Lesnyak A.T., Bozhikov N.V., Rykova M.P. et al. In: XIX Intercosmos Meet. Space Biol.Med. Habana, Cuba, 5-12 April 1986. Abstr. Habana, 1986, p.39.

9. Smirnov K.V., Medkova I.L., Ruvinova L.G. et al. Ibid., p.59.

10. Serova L.V., Tikhonova G.P., Denisova L.A. et al. Ibid., p.57.

responsible for bone homeostasis modify their function in such a way as to make bone structure adequate to the diminished loads. It implies that bone changes (which are pathological in terms of ground-based requirements) actually constitute a normal physiological response to the absence of gravity.

Morphological examinations of the neuroendocrine systems related to the regulation of water exchange and vascular tone (the hypothalamic-pituitary neurosecretory system, HPNS, and adrenal medulla) were suggestive of an enhanced excretion of ADH-vasopressin in the HPNS (E.I.Alekseev). This enhancement of the activity of HPNS neurons formed a response to the return to Earth gravity and provided water retention and vascular tone increase postflight.

The morphological investigation of adrenal medulla which was the first of this kind showed that the gravitational stress which the animals experienced after touchdown stimulated epinephrine and norepinephrine release from adrenal cells (N.G.Prodan) and that the greater excretion of catecholamines was expressed in higher concentrations of epinephrine and norepinephrine in blood. However, the lack of changes in the content of catecholamines and in the activity of enzymes involved in their synthesis in adrenals as well as an increase in the amount of ß-receptors in the cardiac muscle and spleen led to the conclusion that the function of rat adrenal medulla was not stimulated during flight (4).

The emergence of an acute gravitational stress after flight was accompanied with a higher concentration of corticosterone and a lower concentration of thyroxine in blood (5). Additional data concerning the pattern and level of the stress-reaction were derived from the study of the lymphoid organs (6). The data analysis made it possible to assess the severity of the gravitational stress and to discriminate changes that originated inflight from all changes detected in lymphoid organs. The flight-induced changes included a decrease (by 18%) in the thymus weight which was produced by the stressogenic effect of the launch and microgravity per se. (The decline in the thymus weight of the rats sacrificed 4-8 hours after flight cannot be attributed to the gravitational stress: it was previously demonstrated that a decrease in the thymus weight in response to an acute stress-reaction can be distinguished only 10 hours after the onset of a stressogenic effect (7)). Manifestations of an acute gravitational stress (degradation of thymus lymphocytes, neutrophil infiltration of the spleen) were less pronounced than after earlier flights of 18-20 days in duration. In regards to the lymphoid tissue it is important to note that the flight rats also displayed a decline of the proliferative activity of T-lymphocytes (which may be one of the causes responsible for a decrease in the weight of lymphoid organs during prolonged flights), a tendency towards an increase in the number of T-lymphocytes in bone marrow, and a fall of the cytotoxic activity of T-lymphocytes - normal killers in the spleen and bone marrow (8).

In addition to the above changes, the hemopoietic organs also showed inhibition of erythropoiesis although the flight time was relatively short. The inhibitory effect was indicated by a statistically significant decrease in the content of erythroid elements in bone marrow (N.A.Chel'naya) and absence of erythropoietic foci in the spleen (G.N. Durnova, E.V.Vorotnikova). Erythropoiesis inhibition was paralleled by a lower concentration of reticulocytes in peripheral blood.

The emergence of an acute stress-reaction after flight determined many metabolic changes in blood and other tissues. For instance, accelerated mobilization of glucose that led to hyperglycemia provided energy needed for adaptation processes whereas increased creatinine concentration in blood pointed to muscle protein degradation although no direct signs of enhanced proteolysis were found in the muscle tissue (5). Measurement of the rate of lipid peroxidation and formation of its products as well as antioxidative protection factors in blood, muscles, liver and heart did not reveal an increase in the lipid peroxidation products in blood or heart and did indicate it in liver and muscles (N.V.Delenyan, A.A.Markin).

Analysis of fluid-electrolyte balance and renal function permitted the conclusion that after flight the electrolyte composition of blood remained essentially unchanged, except for phosphatemia. The kidneys showed a larger weight, a lower content of potassium, sodium and magnesium, and an unchanged concentration of calcium (Y.V.Natochin, L.A.Denisova). The decrease in the water content was found in muscles and heart.

Study of a wide range of digestive enzymes (hydrolases, carbohydrases, proteases, lipases) in the stomach, intestine, salivary and pancreatic glands led to the conclusion that variations in the functional state of the digestive system after the 7-day flight were similar in sign to those observed after longer-term flights but were of much smaller magnitude (9).

Investigation of the reproductive function of the male rats after flight which included a cytological examination of the testes, sexual behavior, mating with intact females and evaluation of the development and viability of their progeny did not show any significant differences in the experimental and control animals with respect to any of the above parameters (10).

STUDY OF THE INITIAL PERIOD OF ADAPTATION TO MICROGRAVITY IN THE RAT EXPERIMENT ONBOARD COSMOS-1667

O.G. Gazenko, E.A. Ilyin, E.A. Savina, L.V. Serova, A.S. Kaplansky, I.A. Popova, V.S. Oganov, K.V. Smirnov, I.V. Konstantinova

Institute of Biomedical Problems, Moscow, USSR

The primary goal of the rat experiment onboard Cosmos-1667 was to investigate structural and metabolic changes that develop in animal organs and tissues at the initial period of adaptation to microgravity.

The study was carried out on 28 male rats of the Wistar SPF strain weighing 330-350 g. Of these 7 rats were kept for 7 days in the Bios-vivarium cage (with the volume 20 l) onboard Cosmos-1667, 7 rats were used in the ground-based control study that was performed in the biosatellite mockup and simulated all physiologically important space flight factors, except for microgravity, and 14 rats were used as controls of the flight and synchronous experiments. During the study all the animals were given a paste-like diet (1) in the amount 55 g per animal per day and water ad libitum. The experimental and control rats were decapitated by means of a guillotine 4 to 8 hours after the studies were completed.

Post-mortem examinations showed that after the 7-day flight there were no macroscopically visible changes in the viscera or the CNS. There were no significant changes in the weight of the body, heart, liver, testes, adrenals, m.quadriceps femoris, m.extensor digitorum longus and m.triceps brachii. However, the weight of the soleus, gastrocnemius, plantaris, brachialis and biceps brachii muscles as well as that of the thymus and spleen decreased significantly, while the kidney weight increased.

It was found that the 7-day exposure to microgravity was sufficiently long to produce distinct structural, metabolic and functional changes in the musculoskeletal system. During the early period of adaptation to microgravity atrophic changes developed in different muscles, particularly in m.soleus. This was first of all true of myofibers characterized by a high level of oxidative metabolism (2). However, parameters of energy metabolism remained essentially unchanged (S.M.Ivanova, O.I.Labetskaya) although all muscles taken under study showed glycogen accumulation and increased activity of phosphorylases A and B while m.quadriceps femoris displayed a lower activity of creatine kinase (L.M.Kurkina, T.E. Drozdova). The structural and metabolic changes were accompanied by variations in contractile properties of these muscles: decrease of the contraction force was seen in m.soleus and delay of the contraction development in most of the muscles examined (S.A.Skuratova, L.M. Murashko).

Histomorphometric examinations of rat bones revealed distinct manifestations of structural changes that suggested the development of osteoporosis (G.N.Durnova, Z.F.Sakharova, E.I.Ilyina-Kakueva), Among the bones examined histologically (tibial and iliac bones, lumbar vertebrae) the greatest changes were detected in the spongy matter of proximal metaphyses of the tibia and the smallest changes in the spongiosa of the iliac bones. Osteoporosis developed due to the inhibition of de novo bone formation which was suggested by the reduction of the number and activity of osteoblasts. The question whether osteoporosis in microgravity is also associated with enhanced bone resorption still remains open because the larger number and higher activity of osteoclasts were recorded only in the spongiosa of tibial metaphyses but not in the spongy matter of lumbar vertebrae or iliac bones. The increase in the osteoclast number and activity in tibial metaphyses well correlated with biochemical data which indicated a higher activity of acid phosphatase in proximal metaphyses of the tibia and forearm bones as well as with a higher activity of the parathyroid glands. Measurement of bone mechanical properties (A.V.Bakulin, V.E. Novikov) demonstrated that postflight there was a decline in maximum relative deformation and an increase in modulus of elasticity which suggested indirectly a potential decline of bone strength. Structural and metabolic changes that occur in bones during orbital flight are associated with the lack of static and a drastic decrease of dynamic loads upon the musculo-skeletal apparatus. These changes are primary (3) and elicit structural and functional variations in the neuroendocrine systems involved in the regulation of bone growth and mineral metabolism. Morphological investigations of the adenohypophysis (E.I.Alekseev), Phyroid and parathyroid glands (G.I. Plakhuta-Plakutina) give evidence that at an early stage of adaptation to microgravity there were changes indicative of inhibition of somatotrophes (growth hormone producers) and thyroid C-cells (calcitonin producers). Simultaneously, the function of parathyroid glands increased as demonstrated by a larger size of nuclei of parathyroid cells, a higher number of oxyphilous cells and mitoses. Both trends facilitated disorders in bone remodelling and development of osteoporosis. Thus, in microgravity the systems

write the following relation,

$$m(a,b,f;t)=\rho\, T(a,b,f;t), \qquad (6)$$

where $m(a,b,f;t)$ is the body mass of animal at age t and ρ the lumped density of cells. By combining Eqn. (6) with Eqn. (1), G_{max} can now be expressed as a function of totaling five parameters including age t.

In Fig. 2, Eqn. (6) was fit to data of body mass of Japanese male for the year of 1980 published by Japanese Ministry of Health and Welfare. Triangle marks represent average body mass at each ages and the line the theoretical curve computed by Eqn. (6). The parameters estimated by the Marquardt least squares method (4) were as follows; a, 2.9; b, 0.62 (1/years); f, 0.048; and ρ, 10.1(kg/one normalized unit number of cells).

Though our model is still simple, Eqn. (6) could simulate an outline of age dependence of body mass, thereby providing the age of maximal body mass.

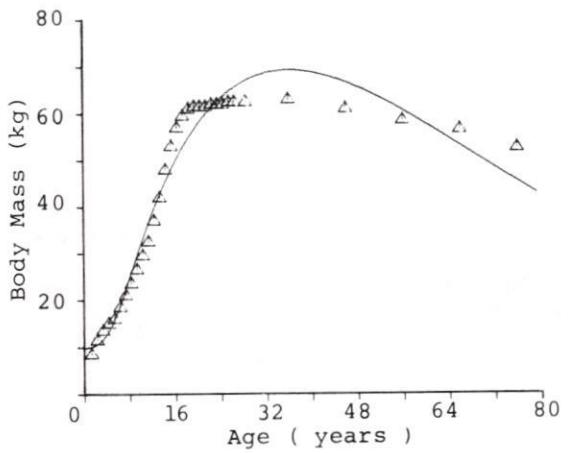


Figure 2. Simulation of body mass of Japanese male by Eqn. (6).

Parameter dependence of G_{max}

On the basis of our non steady state 2-compartmental model, we have successfully simulated human life table data (5) and noticed that the values for parameters a and b decreased while that for parameter f increased during the period from 1895 through 1980 in Japan. These changes in parameters have resulted in slight increases in body mass and remarkable increase in life span of Japanese people.

In this context, we studied the dependence of G_{max} on these parameters. In Fig. 3, G_{max} is illustrated as a function of parameter f, the other parameters being kept constant. In this figure, the longitudinal axis is scaled by the terrestrial gravity. The value of G_{max} goes up almost linearly with a gradient 7.2 when the value of f is increased.

In Fig. 4, G_{max} is plotted as a function of a and b. It is clearly shown here that G_{max} is not greatly sensitive to varying values of a, although it is slightly changing with varying b. Such characteristics of G_{max} has resulted in a plane something like a parabola. Thus G_{max} may take a minimal value with varying value of b as far as the value of a remains unchanged. Because the parameter b roughly relates to the living standard, we may point to the fact that the value of b for the present human being must be very close to an optimum as evidenced by the prolonged life expectancy in advanced countries.

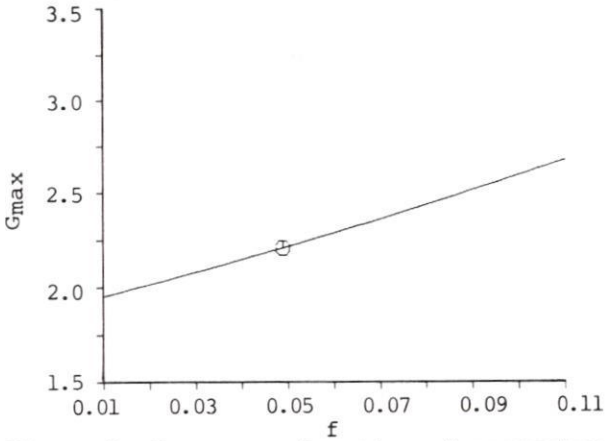


Figure 3. G_{max} as a function of parameter f. Value of G_{max} for Japanese male for the year of 1980 is indicated by an open circle.

Looking at the trends of change in the gravitational tolerance with varying values of the three parameters, it may be concluded that G_{max} for human must have remained almost unchanged in the past hundred years and will remain without any large change in the near future as well.

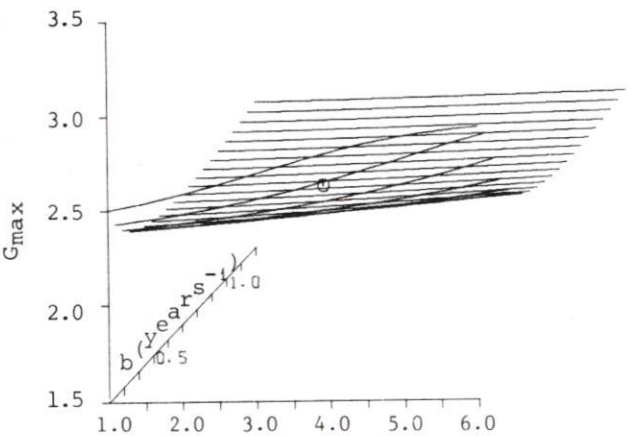


Figure 4. G_{max} as a function of growth saturation constant a and living rate b.

References

1. Economos, A.C.:The largest land mammal. J. Theor. Biol. **89**: 211-215, 1981
2. Fukuda, N. and Yago, N. :Population Dynamics of Mitochondria I. A model for the role of ACTH in the degradation of adrenocortical mitochondria. ibid. **46**: 21-30, 1974.
3. Fukuda, N. amd Yago, N. :Population dynamics of mitochondria II. Turnover and ageing of rat liver mitochondria. ibid. **58**: 131-142, 1976.
4. Marquardt, D.M.J. :An algorithm for least squares estimation of nonlinear parameters. SIAM J. Appl. Math.,11:431-441, 1963.
5. Yago, N., Tatsunami, S. and Fukuda, N.: Estimation of life table parameters for aging model of cell dynamics. Biomedical Gerontology 7: 107-108, 1983.

A UNIQUE RELATIONSHIP BETWEEN ECONOMOS' THEORY ON THE LARGEST LAND MAMMAL AND OUR DYNAMIC THEORY OF GROWTH, MATURATION AND AGEING

Shinobu Tatsunami, Nagasumi Yago and Nobuo Fukuda*

Radioisotope Research Institute, St.Marianna University School of Medicine
Kawasaki, Japan 213
and
*Division of Clinical Research, National Institute of Radiological Sciences
Chiba, Japan 260

Abstract

A power law of the effect of gravity on land mammals has been presented by A.C.Economos (J. Theor. Biol., 89, 211-215, 1981) using only one single variable, i.e. the body mass m of adult animals. He has thus clearly demonstrated the relationship between gravitational tolerance G_{max} and body mass, and estimated the most probable body weight of the largest land mammal as about 20,000 kg.

By incorporating into Economos' law our theoretical equation for body mass which was derived on the basis of modern molecular biology, we have found through computer simulation that human gravitational tolerance seems to have remained almost unchanged in the past and also may not largely change in the near future for the relative insensitiveness of G_{max} to the parametric changes in our theoretical equation.

Introduction

Economos' law of gravitational tolerance for an adult land mammal that has a body mass of m is expressed as follows;

$$G_{max} = 4m^{-0.14} \qquad (1)$$

On the other hand, we have been elaborating our own dynamic theory of growth, maturation and ageing (2,3). As one of the results of our theory, we have derived an equation for body mass using such parameters as growth saturation constant a, living rate b, cell loss constant f and lumped cell density ρ. By combining our equation with Eqn. (1), we have studied in the present paper the dependence of gravitational tolerance on those parameters.

Dynamic Theory of Ageing

Framework of our theory is illustrated in Fig.1. Here, an animal is expressed as an ensemble of two non-steady state 2-compartmental systems.

We assume the presence of only two kinds of cell populations in animals, one is proliferative cell population and the other non-proliferative, functional one. These cell populations will be referred to later as compartments. In Fig. 1, N(t) and M(t) represent normalized number of cells in each compartments, respectively.

Some of the proliferative cells are transformed into non-proliferative, functional cells under the influence of a specific protein termed differentiation factor which is supplied through the activity of a specific gene.

As illustrated, state of this particular gene is distributed between two states; one is repressed and the other induced. As far as it stays in the induced state, this particular gene remains active in synthesizing the differentiation factor. These states are assumed to be brought about either by association or dissociation of a repressor molecule.

Parameter V_1 represents rate of dissociation of the repressor molecule from that gene and vice versa parameter V_2 rate of association to the gene.

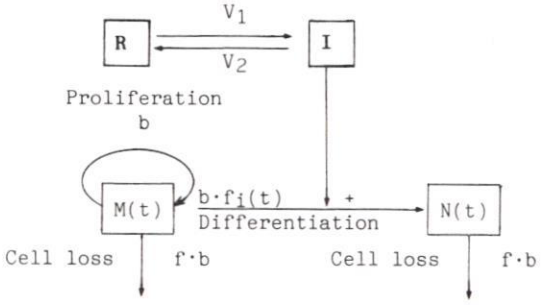


Fig. 1. Non steady state 2-compartmental systems of growth, maturation and ageing.

Most fundamental assumption lies in that the equilibrium of the two states is not steady but changes with time so that fraction of induced state $f_i(t)$ is given by the following equation;

$$f_i(t) = \frac{1}{1 + e^{a-bt}}, \quad a=\ln(V_2/V_1), \qquad (2)$$

where a is a constant that determines the initial value of $f_i(t)$, hence growth saturation constant.

Other assumptions are; 1) both rates of proliferation b and cell loss factor f are constant, and 2) rate of differentiation that depends on $f_i(t)$ can be expressed as $b \cdot f_i(t)$.

Based on these assumptions, N(t) and M(t) are described by the following differential equations,

$$\frac{dM(t)}{dt} = bM(t) - b \cdot f_i(t) M(t) - f \cdot bM(t), \qquad (3)$$

$$\frac{dN(t)}{dt} = b \cdot f_i(t) M(t) - f \cdot bN(t) . \qquad (4)$$

By integrating Eqns.3 and 4, an equation for total number of cells T(t), is obtained as follows,

$$T(t) = N(t) + M(t)$$

$$= \{1 + \ln\left(\frac{e^a + e^{bt}}{e^a + 1}\right)\} e^{-fbt} \qquad (5)$$

Simulation of body mass

Because body mass of any animal should be proportional to T(t), we may

When we added another magnet to increase the field area, DTR were 98.2 ± 3.1 % for 0.4 KG, 101.0 ± 3.4 % for 0.8 KG 100.2 ± 5.1 % for 1.2 KG.

There was no difference in the descending time ratio between the case without the magnetic field and the case with it. Even if we used the additional magnet, we still did not observe any difference in the discending time ratio.

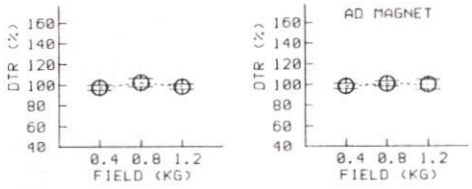


Fig. 3. DTR in various magnetic fields; the right panel for additional magnetic field.

Fig. 4 shows the ascending time ratio ATR in the various magnetic fields. ATR were 114.2 ± 12.0 % for 0.4 KG, 104.4 ± 40 .1 % for 0.8 KG and 86.3 ± 17.2 % for 1.2 KG.

When we added another magnet to increase the field area, ATR were 108.1 ± 7.2 % for 0.4 KG, 97.4 ± 8.2 % for 0.8 KG, and 99.1 ± 24.1 % for 1.2 KG.

From the results we found that there was no difference in the ascending time ratio between the case without the magnetic field and the case with it. Even when we used the additional magnet, we still did not observe any difference in the ascending time ratio.

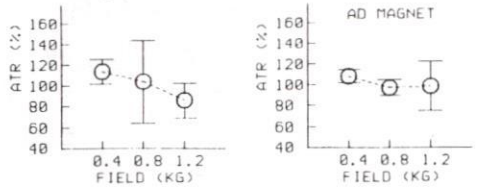


Fig. 4. ATR in various magnetic fields; the right panel for additional magnetic field.

Fig. 5 represents the oxygen saturation decrease ratio OSDR in the various magnetic fields. The OSDR were 95.3 ± 9.7 % for 0.4 KG, 91.2 ± 16.3 % for 0.8 KG and 78.4 ± 11.7 for 1.2 KG.

When we added another magnet to increase the field area, the OSDR were 96.4 ± 16.6 % for 0.4 KG, 86.3 ± 11.9 % for 0.8 KG and 76.2 ± 8.8 for 1.2 KG.

From the results we found that there was significant difference in the oxygen saturation decrease ratio between the case without the magnetic field and the case with the field of 1.2 KG.

When we added another magnet, we found that significant difference existed in the oxygen saturation decrease ratio between the case without the magnetic field and the case with the field 0.8 and 1.2 KG.

Discussion

From the results reported we consider the cause of results described above. All particles such as oxygen, hemoglobin and so on may go down with respect to the gravitation (From M.Okazaki, N.Maeda and T.Shiga: Drift of an erythrocyte flow line due to the magnetic field, Experimentia 42 842-843,1986). When the magnet is energized, the magnet may attract both deoxyhemoglobin and oxygen upward against the gravitation in this experiment.

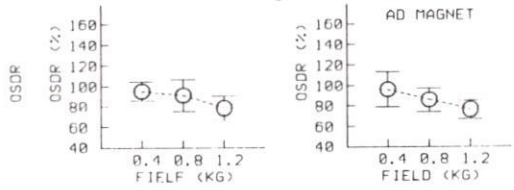


Fig. 5. OSDR in various magnetic fields; the right panel for additional magnetic field.

This suggests that the magnet has the greater intensity of the field with the wider field field area, the greater volume of deoxyhemoglobin may be made in the lung. By this mechanism the magnetic field may stimulate the respiratory function of the gas exchange in the lung. Consequently, the decrease in oxygen saturation curve is thought to be reduced owing to breath holding in the magnetic field as compared with the control data. In this meaning the mechanism would not be activated under the condition of the weightless state.

MAGNETIC EFFECT ON CARDIOPULMONARY FUNCTION IN MAN

Osamu Okai

Department of Clinical Physiology
Kyorin University School of Health Sciences
Miyashita 476, Hachioji, Tokyo 192

In the experiment we used a magnet and added another magnet to increase the field. Ten subjects, placed between the poles of the magnet, were requested to maintain voluntary apnea for a period of 30 seconds by breath holding. Oxygen saturation curve was measured from each subject and analyzed. The result was as follows: 1) There was no difference in both descending and ascending time when the magnetic field was applied. Even when we added another magnet, still no difference was observed due to the applied magnetic field. 2) There was significant difference in a decrease in oxygen saturation curve when the magnetic field of 1.2 KG was applied. When we added another magnet we also found significant difference due to the applied field of 0.8 or 1.2 KG. These results are attributable in some part to the fact that the magnet attracts the oxygen and deoxyhemoglobin whereas it does not do oxyhemoglobin which gravitates downward.

There are many studies on biomagnetism and magnetobiology but relatively few reports exists on a magnetic effect on the cardiopulmonary function. Here, we investigated the effect of the magnetic field mainly on the pulmonal function.

Method

A subject was placed between poles of the magnet whose maximum field intensities on the surface were 0.4, 0.8 and 1.2 KG. In the first experiment we used the magnet No (1), and added anather magnet No (2) to increase the field area, as shown in Fig. 1.

The physiological data from a subject was illustrated in Fig. 2. In the order from top to bottom typical recordings of electrocardiogram ECG, pulse wave PW, respiratory wave RW and oxygen saturation curve OSC were depicted. ECG was measured by the conventional ECG lead II, pulse wave measured with a plethysmograph attached to the left fore-finger tip, respiratory wave measured with a thermister attached to the nose, and oxygen saturation curve measured with an ear oxymeter attached to the left auricle.

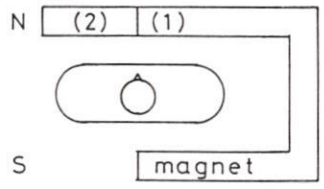


Fig. 1. Schematic representation of experimental system; an oval shows a subject, and rectangules (1) and (2) are bar magnets.

We instructed a subject to maintain voluntary apnea for a period of 30 seconds by breath holding. For the mean time ECG made no change, the amplitude of the pulse wave was reduced and the respiratory wave did no appear. The oxygen saturation curve went down to the minimum point of the oxygen saturation, and, thereafter, restored to the normal level of oxygen saturation.

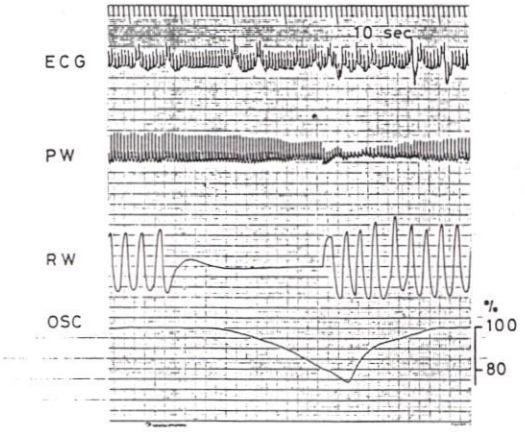


Fig. 2. Typical recordings of ECG, PW, RW and OSC.

Here we defined the time for the descending part of the oxygen saturation curve as descending time. We call the the descending time A for the control and a for the magnetic field. Then we calculated a descending time ratio by the equation DTR = a/A. Likewise we defined the time for the ascending part of the oxygen saturation curve as ascending time. So we call the ascending time B for the control and b for the magnetic field. Then we calculated an ascending time ratio by the equation ATR = b/B. Furthermore, we defined the maximum decrease in the oxygen saturation curve as oxygen saturation decrease. So we call the oxygen saturation C for the control and c for the magnetic field. Then we calculated the oxygen saturation decrease ratio by the equation OSDR = c/C.

Results

Fig. 3 shows descending time ratio DTR in the various magnetic fields. DTR were 98.1 ± 3.0 % for 0.4 KG, 104.3 ± 4.3 for 0.8 KG and 99.0 ± 3.2 % for 1.2 KG.

b) **Early changes in cardiac performance**
From the two fast channels ECG and ICG we measured of time intervals, like i.e. the left ventricular ejection time (LVET). Reproducibility of the signals allowed to make interpretations from the area under the ICG-curve during LVET.
For each astronaut, histographic distribution patterns (Fig. 2) were always made from data collected at the same time of day. For all four astronauts they show that the values were increased on mission day 1 (M1). In one astronaut, values below control were observed on mission day 3 (M3). Post-flight, elevated values were observed in two astronauts. Normalization could not be observed before the seventh post-flight day.

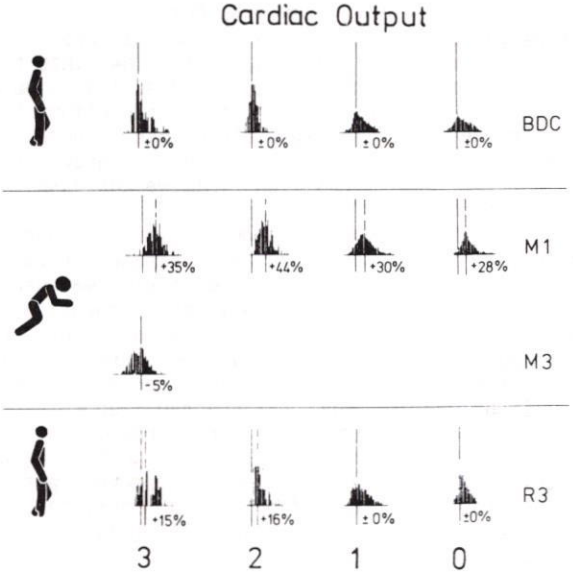


Fig. 2: Cardiac output calculated as the product of heart rate and the area under the ICG-curve during LVET. Figures refer to astronauts.

A venous occlusion manoeuvre was performed in-flight and on ground in a supine position as a dynamic test to estimate heart function. Application of the data within a ventricular function curve showed no significant performance change of the heart. This is in contrast to our findings in HDT [1] when we observed a reduction in ventricular performance.

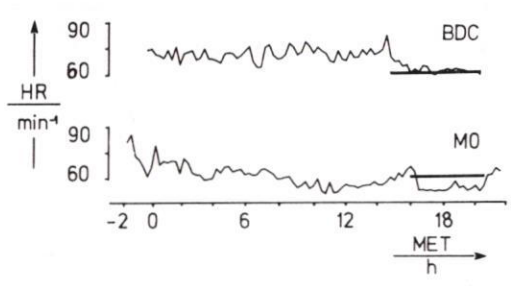


Fig. 3: Heart Rate: 24 h records from one astronaut during Baseline Data Collection (BDC) and Mission Day 0/1 (M0).

c) **Changes in cardiac autonomic control**
From our head down tilt studies [4] we deduced that a heart rate reduction might be possible within the first few days of spaceflight. This can be shown very clearly for this astronaut (Fig. 3). Right from the start, heart rate decreases. The bars at the 60 b/min level represent the sleep period. During sleep, heart rate is considerably lower inflight (M0) than preflight (BDC).
The resting heart rate of this astronaut lies below his usual pre-flight values. This suggests that an active process e.g. enhanced parasympathetic activity is responsible for the low heart rate. To corroborate this hypothesis, a breathing protocol was performed, demanding rhythmic breathing. The objective was to record the so-called respiratory sinus arrhythmia (RSA) in order to quantify parasympathetic outflow [3]. Figure 4 shows the variability of RR-interval expressed as percent of mean RR-interval. Usually, variations are about 20 %. In weightlessness, these values are considerably higher. This has to be interpreted as an increase in parasympathetic activity.

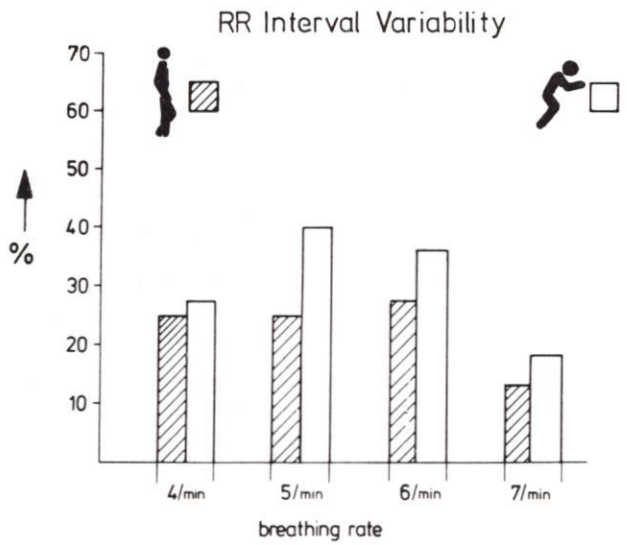


Fig. 4: Variability of RR-interval expressed as % of mean RR-interval for four different respiratory rates. Data from one astronaut.

References:

[1] Beck, L. and Baisch, F., Physiologist 27 (Suppl.) : 57-58, 1984
[2] Brown, B.H., Barber, D.C., and Seagar, A.D. Clin. Phys. Physiol. Meas. 6:109-121, 1985
[3] Eckoldt, K., Pfeifer, B., and Schubert, E. in: Central Interaction Between Respiratory and Cardiovascular Control Systems Ed.: H.P. Koepchen, S.M. Hilton, A. Trzebski Springer Verlag Berlin, Heidelberg, New York 1980, p. 216-223
[4] Samel, A. and Baisch, F., J. Aut. Nervous System, Suppl.: 205-207, 1986
[5] Tedner, B., Dissertation, Karolinska Institutet, Stockholm 1985

BODY IMPEDANCE MEASUREMENT DURING SPACELAB MISSION D1

F. Baisch, L. Beck

DFVLR
Institute for Aerospace Medicine
Cologne, FRG

Quantification of body fluid redistribution and loss during space flight and observation of the effects on the heart were the aims of this experiment. The impedance of two body segments (Z-torso and Z-body) to a 100 kHz 1mA constant current, the first derivative of the torso segment and the ECG were recorded with a 24-hs personal recorder. Data were obtained from two astronauts during launch and reentry and inflight from another two. The recumbent period prior to launch is decisive for fluid redistribution in the compartments covered by this method. The amount of fluid shifted is comparable to that produced by daily positional changes. A fluid loss of about 2.5l can be infered through the values of Z-body and anthropometric factors. Cardiac output, as assessed by dZ/dt, was increased -more than 30% of control- even on the 2nd inflight day; on the 4th day its values were however lower than pre-flight. It was not possible to demonstrate deconditioning effects on the heart of the payload specialists during this multidisciplinary Spacelab Mission. Heart rate and its variability strongly suggest increased cardiac parasympathetic activity.

The scientific questions tackled by the D1 experiment are

a) Time course of fluid shift and fluid loss
b) Early changes in cardiac performance during u-g
c) Changes in cardiac autonomic control

Basically, the equipment included an impedance module and a 24h personal recorder. Two astronauts wore this equipment during launch, another two astronauts carried out inflight measurements. The impedance electronic was designed in the Institute of Biomedical Technique in Stuttgart. An alternating constant current of 100 kHz and 1 mA was led through the body. The impedance time course of the body segments shoulder to waist (Z-torso) and shoulder to knee (Z-body), the first derivative of the torso segment (ICG) and the ECG were recorded. Correlations with the specific conductance of different biological tissues have shown that the 100 kHz impedance technique could cover a body shell of about 1.5 to 2.5 cm depth [2]. For the calculation of fluid loss and fluid shift, a resistivity of 60-90 Ohm x cm was assumed.

a) **Time course of fluid shift and fluid loss**
During Baseline Data Collection the following 24h time course was be observed: in the morning, the impedance values have a peak; during the day a decrease with oscillations takes place. Reason for the decrease is food intake. Position changes and movement artefacts cause the oscillations. An impedance decrease measured in a given body segment correlates with an increased amount of fluid, provided comparable postures are kept. During the night, impedance increases again. This can be interpreted as a fluid loss, since the content of the bladder can not be registered by this method [5].This time course is observed in both, the Z-body and Z-torso curves. Variations range within +/- 5% of the respective absolute impedance values (Z-thorax ≈ 31 Ohm, Z-body ≈ 55 Ohm).
Before launch, i.e. when the astronauts are in a supine position with legs up, fluid flow into the thorax segment could be observed during a very short time. In this position, counterreactions start already, which initiate fluid loss. There was no event in the records that could be interpreted as marking the transition into weightlessness, when entering earth orbit.
Both observed segments showed similar courses after the initial changes: an increase of impedance values reflecting that body fluid was drawn from both, the body and the torso segment. Body impedance values remained increased. For one astronaut, Z-torso impedance values normalized in the course of the mission. In the recovery phase, pre-flight values were not reached before seven days. According to the body shell model, the inflight fluid shift in the thorax segment can be described as a fluid loss. In the recovery phase, this effect is intensified for a short period; normalization takes about seven days (Fig. 1, top panel).
The summary of calculated fluid loss data shows the following course (Fig. 1). Signs of fluid loss can already be observed during the prelaunch position on the launching pad. For one astronaut, the fluid loss was over after a few hours, for the others it took two days. Adaptation to weightlessness takes lesser time than readaptation to the 1-g environment.

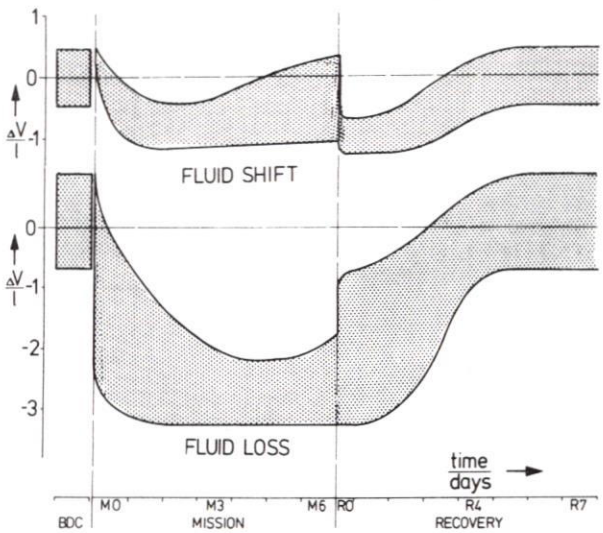


Fig. 1: Schematic representation of fluid shift (top panel) and fluid loss (bottom panel) on the basis of impedance data of four astronauts.

desorganisation may be, in part, attributable to abnormal bone formation. Osteoid seam surfaces were reduced at the endosteal and trabecular levels and the thickness was decreased in the endosteum. In the Spacelab-3 flight, tibial osteoblasts were studied (5). There was no change in cytoplasmic activity between flight and non flight rats but the cytoplasmic area of flight osteoblasts tended to be reduced. This would result in less collagen secretion. It is not known in our study whether the mineralization rate occured normally: tetracycline labeling was not realized because of other experiments concerning hydromineral metabolism (tetracyclines are known to modify some ionic metabolisms). Previous works indicated that the bone matrix at the arrest line periosteal region was abnormal and hypomineralized (14). The Cosmos 1667 flight would indicated that bone formation defect (osteoid apposition plus mineralization) did extend in trabecular area and endosteal surface of the tibial metaphysis.

The osteoclastic population, determined with a specific histoenzymologic method (10) was unaffected by this 7-day space flight. This result is comparable with that of 5-day Cosmos 1514 (8) (in tibia) and 22-day Cosmos 1129 (15). There is no large change in weight-bearing bone resorption in rats, contrary to bone formation.

A decrease in trabecular bone mass in the distal femoral metaphysis occured in previous Cosmos (16 - 2). The calcium, collagen hydroxyproline and inorganic phosphorus content analysis in rats flown aboard Spacelab-3 indicate an alteration in the quality of the femur. During the Cosmos 1667 flight, there is evidence of trabecular bone volume maintaining in the area located under muscular insertions in the proximal femur metaphysis. TURNER et al. (17) demonstrated that the effects of space flight (Cosmos 936), sciatic nerve section and pelvic suspension produced a characteristic pattern of inhibition of bone formation which was site specific within the tibia (space flight produced maximum inhibition of bone apposition at the anterior base and the least inhibition at the medial edge). All these results supported the hypothesis that the preservation of muscular tractory can have a protective effect on the skeleton.

In the non-weight-bearing bones (thoracic and lumbar vertebrae), bone mass and bone resorption parameters were found unchanged. In the Spacelab-3 flight, the bone weight and osteocalcin were decreased in lumbar vertebra (7). Osteoid parameters were not measurable in our study, but Spacelab-3 results would indicate a decrease in bone formation within 7 days of weightlessness exposure. However, we must be careful before comparing these two sudies: Spacelab-3 rats were younger (66 days old) than Cosmos 1667 rats; bone and serum osteocalcin values are known to be age dependent in rat (18). After the Cosmos 1129 flight, FRANCE et al. (19) provided informations suggesting an incomplete osteoid mineralization in vertebrae and KAZARIAN (4) reported that immediately after the flight there was a 20 - 25 % decline in the ability of thoracic and lumbar vertebrae to resist axial loading to failure. As such, this Cosmos 1667 flight appeared to be too short to induce bone mass parameters decrease in vertebral bodies. In the Cosmos 1514 flight, an increase of the osteoclast number was observed (8). Consequently the effects of space flight on the skeleton appeared to be different in young male and young pregnant rats.

In conclusion, significant changes in bone appear within 7 days of space flight and data from other Cosmos series suggest that the bone changes are not transient. This study confirms that non-weight-bearing bones are not as much at risk as the elements of the weight-bearing bones. Furthermore, marked differences observed between areas with and without muscular insertions, emphasize the most important role of mechanical factors in bone mass preservation.

REFERENCES

1 - SPENGLER D.M. et al., Proceed. Soc. Experim. Biol. and Med. , 174, 224-228, 1983.

2 - WRONSKI T.J. et al., The Physiologist , 23: Suppl., S 79-S 82, 1980

3 - SIMMONS D.J. et al., Am. J. Physiol. , 244, R 319-R 325, 1983.

4 - KAZARIAN L.E., Advances in Physiological Sciences, Gravitational Physiology edited by J. HIDEG and O. GAZENKO: New York: Pergamon, 19, 129 - 138, 198[illegible].

5 - DOTY S.B.: The Physiologist . 28, 6, S 225 - S 226, 1985.

6 - RUSSELL J.E., SIMMONS D.J.: The Physiologist , 28, 6, S 235 - S 236, 1985.

7 - PATTERSON-BUCKENDAHL P.E. et al., The Physiologist , 28, 6, S 227 - S 228, 1985.

8 - VICO L. et al., J. Physiol. (Paris), 1986 (in press).

9 - CHAPPARD D. et al., J. Histotechnol. , (in press), 1986.

10 - CHAPPARD D. et al., Bas. Applied Histochem. , 27, 75-85, 1983.

11 - KIMMEL D.B., JEE W.S.S.: Calcif. Tissue Int. , 32: 112-113, 1980.

12 - GLOBUS R.K. et al., Endocrinol. , 114, 6, 2264 - 2270, 1984.

13 - WOLFF J.: Das Gesetz de Transformation der Knochen. Berlin: Hirschold, 1892.

14 - TURNER R.T. et al., Proceed. Soc. Exp. Biol. Med. , 180, 544 - 549, 1985.

15 - JEE W.S.S. et al., Am. J. Physiol. , 244, R 310 - R 314, 1983.

16 - YAGODOVSKI V.S. et al., Aviat. Space Environ. Med. , 47, 734 - 738, 1976. 17 - TURNER R.T. et al., The Physiologist , 28, 6, S 67 - S 68, 1985.

18 - PATTERSON-ALLEN P.E. et al., Anal. Biochem. , 120, 1 - 7, 1982.

19 - FRANCE E.P. et al., The Physiologist , 25, 6, S 147 - S 148, 1982.

	PRIMARY SPONGIOSA		SECONDARY SPONGIOSA	
	Flight	Control	Flight	Control
Trabecular Bone Volume	16 ± 3.4 ****	37.5 ± 2.6	8.7 ± 4.3 ***	17 ± 4.4
Mean Trabecular Plate Thickness	24.2 ± 2.6 ***	32.5 ± 4.4	30.5 ± 5.8 *	38.3 ± 5.4
Mean Trabecular Plate Density	6.6 ± 0.9 ***	11.6 ± 1.3	2.7 ± 1 **	4.5 ± 1.2
Mean Trabecular Plate Separation	130 ± 24 ***	54.1 ± 6.1	374 ± 143 *	203 ± 86
Number of Osteoclasts per mm² of Trabecular Bone			151.7 ± 51	159.5 ± 42
Active Resorption Surfaces			3.9 ± 1.4	5.9 ± 1.9
Osteoid Surfaces			0.85 ± 0.3 **	1.9 ± 0.9
Mean Thickness of Osteoid Seams				

Osteoid Surfaces		
	58.7 ± 10.4 ****	83 ± 5.4
Mean Thickness of Osteoid Seams	6 ± 0.6 **	7.2 ± 0.8
	Flight	Control
	ENDOSTE	

**** Significantly different at p < 0.001
*** Significantly different at p < 0.01
** Significantly different at p < 0.02
* Significantly different at p < 0.05

TABLE 1 : TIBIAL HISTOMORPHOMETRIC PARAMETERS (mean +- SD) IN FLIGHT (n = 7) AND IN CONTROL (n = 7) ANIMALS.

	FLIGHT	CONTROL
Trabecular Bone Volume	24.7 ± 7.5	30.7 ± 10.2
Mean Trabecular Plate Thickness	77 ± 12	82.8 ± 12.2
Mean Trabecular Plate Density	3.1 ± 0.7	3.6 ± 1.1
Mean Trabecular Plate Separation	253 ± 83	216 ± 113

TABLE 2 : FEMORAL BONE MASS PARAMETERS (mean +- SD) IN FLIGHT (n = 7) AND IN CONTROL (n = 7) ANIMALS.

	THORACIC VERTEBRA		LUMBAR VERTEBRA	
	Flight	Control	Flight	Control
Trabecular Bone Volume	29.6 ± 4.4	29.7 ± 6.7	27 ± 4.8	24.6 ± 4.5
Mean Trabecular Plate Thickness	48.8 ± 5.2	55.2 ± 3.4	41.8 ± 4.7	57.5 ± 5.8
Mean Trabecular Plate Density	6.2 ± 1.5	5.4 ± 1.5	6.5 ± 1.3	4.3 ± 0.8
Mean Trabecular Plate Separation	121 ± 37	142 ± 59	117 ± 28	180 ± 38
Number of Osteoclasts per mm² of Trabecular Bone	60.2 ± 24.2	67.6 ± 11.2	67.6 ± 18.4	81.77 ± 19
Active Resorption Surfaces	3 ± 1.4	3.2 ± 0.5	2.68 ± 0.7	4 ± 1

TABLE 3 : VERTEBRAL PARAMETERS (mean +- SD) IN FLIGHT (n = 7) AND IN CONTROL (n = 7) ANIMALS.

EFFECTS OF 7-DAY SPACE FLIGHT ON WEIGHT-BEARING AND NON-WEIGHT-BEARING BONES IN RATS (COSMOS 1667)

L. VICO., D. CHAPPARD, A.V. BAKULIN, V.E. NOVIKOV, C. ALEXANDRE.

LBTO – GIP Exercice - Université de Médecine - 42023 Saint-Etienne - Cedex - France.

Previous 3-week COSMOS spaceflights indicated a significant reduction of bone mass in weight- and non-weight-bearing bones probably due to a decrease in bone formation activity. On COSMOS 1667, 7 flight and 7 control male rats were studied by bone histomorphometric methods. 1) Weight-bearing bones : in proximal tibial metaphysis, the trabecular bone volume was markedly declined in flight animals. Trabeculae were decreased in number and thickness; this probably leads to an alteration of bone mechanical properties. Formation activity (reflected by osteoid seam thickness and osteoid surface measurements) was decreased at the trabecular and endosteal levels. Resorption activity (osteoclast number and active resorption surfaces measured by a histoenzymologic method) remained unchanged. The imbalance that appeared to occur between these cellular activities may be responsible for the loss of trabecular bone mass. In proximal femoral metaphysis, trabecular bone volume was measured in area located under muscular insertions. Deleterious effects of weightlessness were not observed. Therefore, muscular tractory may have a protective effect on weight-bearing bones. 2) Non-weight-bearing bones : in thoracic and lumbar vertebrae, no change was found neither in bone mass nor in bone cellular parameters. This short flight appeared to confirm that non-weight-bearing bones are not as much at risk as weight-bearing bones during spaceflight. Furthermore, marked differences observed between areas with and without muscular insertions, emphasize the most important role of mechanical factors in trabecular bone mass preservation.

INTRODUCTION

Available data were provided in growing male rats which have been orbited on board of the soviet Biocosmos space flights (ranging from 18.5 to 22 days): the mechanical properties were found to be altered (1) on long bones, the periosteal bone formation in the tibial and humeral diaphysis was found to be inhibited (2), a decreased trabecular bone volume and an increased fat content of the bone marrow were reported (2) in the proximal tibial metaphysis. In mandibles, a delay in maturation of the collagen and mineral fractions was observed (3) and the vertebral crush strength was found to be declined (4).

In rats flown in the NASA Spacelab-3 mission of 7 days duration, alteration of the femur and humerus qualities and decrease in osteoblast function were shown (5 - 6 - 7). In the Biocosmos 1514 flight (5 days duration), pregnant rats were orbited: no change occured in weight-bearing bones and an increase of the osteoclast number was found in vertebrae (8).

We report in this study the histomorphometric bone changes induced by a 7 day space flight (Biocosmos 1667).

MATERIALS AND METHODS

Male Wistar rats (105 days old) weighting 333.14 +- 12.3 g, were randomized into 7 ground-based controls and 7 flight animals placed in orbit in individual cylindrical cages for a period of 7 days (10-07-85 to 17-07-85).

Histomorphometric study was done on proximal metaphysis of tibia and femur and on thoracic and lumbar vertebral bodies. Specimens were embedded in methacrylates as previously described (8). Heigth sections were stained according to a modified Goldner's trichrome (9) for bone mass and osteoid parameters, six others were stained for Osteoclastic Tartrate Resistant Acid Phosphatase (OTRAP) by a histoenzymologic method (10) and were used for the determination of the osteoclast number.

In tibial metaphysis, measurements were done in the primary spongiosa located under the growth plate-metaphyseal junction and in the secondary spongiosa located under the primary spongiosa (11). In femur metaphysis, measurements were done in a area located under the femoral neck (collum femoris) and vicinal to the trochanter major, in regard to muscular insertions. In vertebrae, measurements were done in the mid-part of the bodies.

The fractional area of mineralized tissue or Trabecular Bone Volume was determined. The Mean Trabecular Plate Thickness, Density and Separation (MTPT, MTPD, MTPS) reflected the spatial arrangement of trabecular bone structure. The number of osteoclasts per mm^3 of trabecular bone and the Active Resorption Surfaces expressed as the percentage of total trabecular surfaces covered with tartrate resistant acid phosphatase positive, reflected the osteoclastic activity. The Mean Thickness of Osteoid Seams in µm and the Osteoid Surfaces expressed in mm^2/mm^2 of trabecular surfaces represented osteoblastic activity parameters. All data are given as the mean +- SD and the Mann and Whitney non parametric test was used to compare flight and control animals.

RESULTS

In tibia (table 1), the flight rats exhibited a significant decreased of trabecular bone volume. It was reduced by 55 % in the primary spongiosa and by 47 % in the secondary spongiosa. MTPT was significantly less in the flight group by 24 % for the primary spongiosa and by 20 % for the secondary spongiosa. MTPD was also significantly less than that of the controls: 43 % for the primary spongiosa and 40 % for the secondary spongiosa. As a consequence, MTPS was significantly higher in flight rats: 140 % for the primary spongiosa and 84 % for the secondary spongiosa. At the contrary, in the proximal femur metaphysis where there was contiguous muscle, no difference was observed between the two groups in all these parameters (table 2).

Parameters reflecting the resorption activity were measured in the secondary spongiosa of the tibial metaphysis: no difference neither in osteoclast number nor in active resorption surfaces was seen. Osteoid surfaces in the secondary spongiosa were significantly decreased (56 %) in flight animals. Mean thickness of osteoid seams were too thin to be measurable. At the tibial endosteal level, osteoid surfaces and mean thickness of osteoid seams were significantly less in flight animals by 27 % and 15 %, respectively.

No change was observed neither in thoracic nor in lumbar vertebrae (table 3). As far as the osteoblastic activity is concerned, the mean thickness of osteoid seams and the osteoid surfaces were not measurable because of their minute amount. The resorption activity was not modified by 7 days of weightlessness exposure in both vertebrae.

DISCUSSION

The current study would demonstrated that trabecular bone mass of growing male rats was rapidly and importantly reduced in the proximal tibial metaphysis as early as the 7th day of weightlessness exposure. A trend of decreasing bone mass and mineral content in tibiae of suspended rats (model that unweights only the hindlimbs) was established within 5 days (12). In as short a period as one week, the bone loss appeared to be more important in microgravity that in unweight conditions in growing male rats. However, in the 5-day Cosmos 1514 flight (8), the tibia metaphysis of pregnant rats did not exhibited any modification compared to controls. It could be advocated that the bone loss become visible between the 5th and the 7th day of weightlessness exposure, however nothing is known about effects of hormonal changes of pregnancy during space flight: comparison remains very risky. In this study, the bone loss was found to be associated with a decrease in trabecular density and thickness. The bone trabeculae are known to dispose themselves in such a way as to provide mechanical support (13). Our findings are consonnant with results of strength testing in the Spacelab-3 (7) that indicate an increase fragility of humeri. The trabecular bone loss accompagnied by architectural

If it is assumed that the SAS does vary in weightlessness being an adaptive reaction, then inhibition of its receptor component develops slowly and persists for a longer time in the postflight period while changes in the secretory ability of the SAS varies rapidly depending on the readaptation characteristics.

The decline of tissue reactivity to catecholamines is also suggested by inadequate reactions of the hypothalamic-pituitary and renin-angiotensin systems of regularon in response to a significant stimulation of the SAS hormonal component after prolonged space flights: lack of changes in the concentration of pituitary tropic hormones as compared to the preflight level and decrease of plasma renin activity. Since the stimulation of renin secretion in man is primarily determined by sympathoadrenal mechanisms with direct involvement of adrenergic receptors, then the decline of their functional activity may be the factor that leads to the reduction of plasma renin activity. This, in turn, causes a low concentration of aldosterone in blood (Fig. 4). After long-term flights the renal excretion of aldosterone was significantly higher than after short-term flights (Fig. 4).

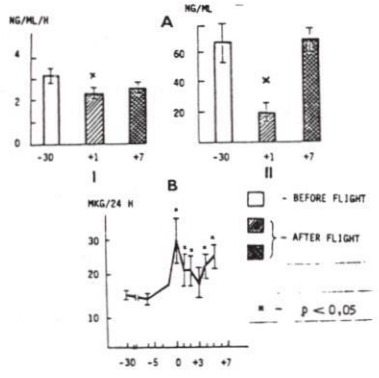


Fig. 4 Renin activity (I) and aldosterone concentration (II) in blood (A) and renal excretion of aldosterone (B) after long-term flights.

Thus, functional rearrangement of the systems of hormonal regulation develops in a different manner, depending on the flight duration. Short-term flights of up to 14 days induce a moderate stress of the sympatho-adrenal system with an adequate effect of catecholamines at the tissue level. Unlike this, long-term flights lead to changes that suggest a reduction of the functional activity of receptors in response to space flight effects.

Similar changes were detected in prolonged bed rest studies where cell sensitivity to hormones may vary in the fashion observed in weightlessness. It is very likely that this factor accounts for the decrease in the cortisol concentration and the increase in the ACTH concentration as well as for the reduction of water permeability of the nephron distal compartment and the high ADH content of blood observed at certain bed rest periods. The hormonal activity of blood per se does not determine the level of the organ response because the hormonal effects can be modulated. It is clear that these problems form an important area of research in space medicine and need further study.

References

1. Davydova N.A., Tigranyan R.A. The sympatho-adrenal system of cosmonauts after 7-day flights. Kosm.Biol. Aviakosm.Med., 1982, 16, 2, 88-91.

2. Kalita N.F., Tigranyan R.A. The endocrine state of cosmonauts after prolonged space flights. Kosm.Biol.Aviakosm.Med., 1986, 20, 4, 84-86.

3. Popova I.A., Noskov V.B., Smirnova T.A. et al. Preliminary results of metabolic investigations in a prolonged space flight. Proceed. XVIII Intercosmos Conf. on Space Biol.Med.Moscow, 1985, 75.

4. Tigranyan R.A., Voronin L.I., Kalita N.F. The biochemical status of adreno-cortical disfunction after space flights. Kosm.Biol.Aviakosm.Med., 1984, 18, 6, 18-22.

5. Davydova N.A., Tigranyan R.A., Kvetniansky P., Macho L. The reaction of the sympatho-adrenal system of cosmonauts after space flights of varying duration. In: Stress. The Role of Catecholamines and Other Neurotransmitters. Gordon and Breach Sci.Publ., 1983, 2, 977-989.

6. Grigoriev A.I., Ion regulatory function of the human kidney in prolonged space flights. Acta astronautica, 1981, 8, 9-10, 987-993.

at R+1 and R+7 (Fig. 3). This increase in cortisol was not associated with considerable changes in the blood content of ACTH. This could be ascribed to a lowered sensitivity of the efferent organ (adrenals) to the hormonal effects. The renal excretion of 17-hydroxycorticosteroids remained essentially unchanged. This gives evidence that the moderate stress occurring immediately after flights of no more than 14 days in duration does not trigger strong adaptive mechanisms that function at the level of hypothalamic-pituitary regulation. It is very likely that this reaction is limited to the SAS stimulation and subsequent reaction of the systems responsible for catecholamine effects at the tissue level.

In view of this it was important to detect postflight changes in the activity of the renin-angiotensin-aldosterone system and the system(s) responsible for homeostasis regulation at the tissue level. At R+1 the PG A+E concentration decreased significantly which can be regarded as a response of the vascular tone regulation to an enhanced pressor effect mediated via adrenergic stimulation. It cannot however be ruled out that the decrease of the prostaglandin concentration in blood is determined by changes not only in vascular tone regulation but also in other metabolic patterns, for instance fluid-electrolyte metabolism.

On the first postflight day most cosmonauts showed decreases of diuresis and sodium, potassium and osmotically active substances in urine. Irrespective of the flight time essentially every crewmember exhibited a mismatch between urine osmolarity and diuresis level. Immediately postflight when the level of diuresis decreased, the osmotic concentration did not grow (as it occurs in the normal physiological conditions) but diminished. The ADH concentration in blood was higher than preflight which pointed to an inadequate reaction of renal cells to the hormone.

The stimulation of the antidiuretic system on the first day after short-term flights was accompanied by a significant increase in plasma renin activity and aldosterone concentration in blood and urine. Obviously, this increase of the aldosterone concentration in blood is produced by a higher plasma renin activity via angiotensin.

By contrast, on the first day after long-term flights the SAS was noticeably stimulated but the blood concentrations of ACTH, STH, TTH, cortisol, cAMP and depressor prostaglandins as well as the renal excretion of 17-hydroxycorticosteroids and 17-ketosteroids did not differ from the preflight level. It looked as if the long-term flights induced lesser changes than the short-term flights. But this was not consistent with physiological examinations of the crewmembers. This led us to the conclusion that long-duration flights gave rise to a qualitatively different hormonal reaction caused by prolonged exposure to weightlessness.

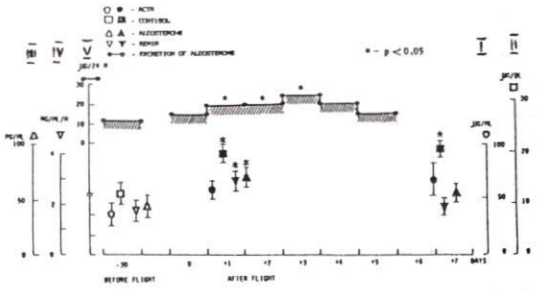


Fig.3 Blood concentration of acth(I),cortisol (II), aldosterone(III), plasma renin activity(IV) and excretion of aldosterone(V) after short-term flights.

First of all, mention should be made of a significant stimulation of the SAS hormonal component. Under normal conditions changes of this sign but of lower magnitude lead to the stimulation of adrenergic receptors accompanied by an increase in the cAMP concentration and in the cAMP/cGMP ratio which was recorded after short-term flights. Following long-duration flights the cAMP concentration remained unchanged and the cAMP/cGMP ratio declined; in other words, in spite of a high concentration of epinephrine in blood its action upon adrenergic receptors did not grow, this being suggestive of some functional blockade of adrenoreception. These data emphasize once again the necessity of investigating not only hormone concentrations in blood but also receptors of target-organs, the latter being of greater significance. The lower reactivity of adrenergic receptors is also confirmed by other data, viz. enhanced inactivation of catecholamines and simultaneous reduction of the formation of methylated products of epinephrine and norepinephrine metabolism. This indicates a change in the inactivation of the transmitters after their interaction with receptors. In addition to the above variations, it was found that prolonged space flights resulted in a greater production and enhanced metabolism of dopamine and DOPA that do not produce a distinct biological effect on the target organs but can complete with epinephrine and norepinephrine for the receptor binding sites, thus decreasing their functional activity. An alternative cause of the lower adrenoreactivity may be the total decline of the SAS activity in weightlessness. As it was demonstrated by the joint Soviet-Czechsolovakian experiment during the 237-day flight, the secretion of catecholamines was not stimulated and their metabolism was decreased in weightlessness.

HORMONAL REGULATION IN SPACE FLIGHTS OF VARYING DURATION

I.A. Popova, B.V. Afonin, N.A. Davydova, A.I. Grigoriev

Institute of Biomedical Problems, Moscow, USSR

In the course of adaptation to space flight effects and subsequent readaptation to Earth gravity regulatory systems, develop significant changes. This gives an impetus to the study of changes in hormonal regulation as a function of flight time. In this context the key problem, which is the subject of the present report, is the blood content of hormones and responses to them of target organs.

Methods

Blood biochemistries were measured twice before flight, normally at F-60 and F-30 days, and twice after flight, normally at R+1 and R+7. Urine samples were collected for 72 hours 30 and 5 days preflight, on the recovery day, and during the first 10 days postflight.

The following agents were quantitatively measured in plasma or serum: epinephrine, norepinephrine, cAMP, cGMP, pressor prostaglandins (PG F_2) and depressor prostaglandins (PG A+E), STH, TTH, ACTH, cortisol, aldosterone, plasma renin activity, insulin, triiodothyronine (T_3), thyroxine (T_4), and testosterone. The following agents were determined in urine: 17-hydroxycorticosteroids and 17-ketosteroids, aldosterone, epinephrine, norepinephrine; catecholamine precursors - dopamine and DOPA and catecholamine metabolites - metanephrine, normetanephrine, vanillyl-mandelic and homovanillic acids.

Hormonal and biologically active substances were measured by RIA, using commercial test-kits.

Results and Discussion

A detailed description of the pertinent investigations in individual flights can be found elsewhere (1-6).

It is important to note that after space flights of 4 to 14 days in duration the sympatho-adrenal system (SAS) was stimulated and the renal excretion of epinephrine, norepinephrine, precursors of their synthesis and catecholamine metabolites was increased. The coefficients epinephrine/norepinephrine, norepinephrine/dopamine and dopamine/DOPA in urine were also increased, indicating a higher rate of catecholamine synthesis and secretion. The coefficient epinephrine/norepinephrine was increased to a greater extent than the coefficient norepinephrine/dopamine which suggested a predominant stimulation of the hormonal component over the transmitter component of the SAS (Fig. 1).

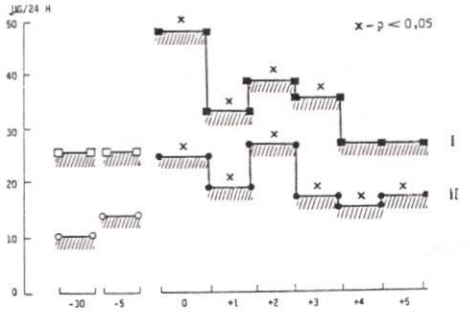


Fig.1 Renal excretion of norepinephrine (I) and epinephrine (II) after short-term flights. Abscissa: days before (-) and after (+) flight x-significant difference with the preflight data.

After long-duration (1-8 months) flights the blood concentration and renal excretion of catecholamines were higher than preflight. This increase on the 1st postflight day was related to epinephrine. The changes in the parameters characterizing catecholamine synthesis and metabolism were indicative of a stress-reaction which was more significant than after short-term flights (Fig. 2).

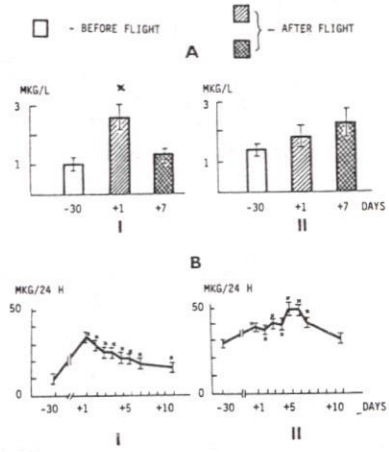


Fig.2 Blood concentration (A) and renal excretion (B) epinephrine (I) and norepinephrine (II) after long-term flights.

The hormonal reactions of the pituitary-adrenal system after short- and long-term space flights were markedly different.

Following 4-14-day flights the blood level of cortisol increased significantly

on test days 2 or 3 and the absolute values of most circulation parameters become identical by the end of exposures. The similarity in circulation responses to the two simulations allows us to assume with a high degree of probability that exposure to an actual space flight of the same duration produces identical changes in some of the circulation parameters. This assumption has been already confirmed with respect to CVP. As to other circulation parameters, their variations are to be reliably measured in real weightlessness.

To understand better the changes in circulation parameters and to develop countermeasures against them in actual space flights, it is necessary to use more informative techniques, e.g. catheterization. It is clear that such techniques can be applied only in the presence of a highly qualified specialist(s) and sophisticated equipment onboard the spacecraft.

References

1. Arborelius M., Balldin U.T., Libja B., Lundgren C.E. Hemodynamic changes in man during immersion with the head above water. Aerospace Med., 1972, 43, N 6, 592-598.

2. Bonde-Petersen F., Hinghofer-Szalkay H., Hordinsky J. Microgravity as an additional tool for research in human physiology. ESA-BP-09, January 1982, Paris.

3. Dietlein L.F., Rambaut P.C., Nicogossian A. Future thrusts in life sciences experimentation in space. Kosm.biol., 1984, 18, N 1, 8-14.

4. Gauer O. Recent advances in the physiology of whole body immersion. Acta Astronautica, 1975, 2, 31-39.

5. Grigorian R.D., Lissova O.I., Beregovsky B.A. Experimental and theoretical researches of hemodynamic during simulation of weightlessness. In: "Proceedings of VIII All-Union conference of space biology and aviaspace medicine", Kaluga 25-27, June 1986, Moscow, "Nauka", pp.46-47.

6. Katkov V.E., Chestukhin V.V. Blood pressure and oxygenation in different cardiovascular compartments of a normal man during postural exposures. Aviat.Space Environ.Med., 1980, 51, 11, 1234-1242.

7. Katkov V.E., Chestukhin V.V., Nikolayenko E.M., Rumyantsev V.V., Gvozdev S.B. Central circulation of a normal man during 7-day head-down tilt and decompression of various body parts. Aviat.Space. Environ. Med., 1983, suppl.1, 54, 524-530.

8. Khosla S.S., Dubois A.B. Osmoregulation and interstitial fluid pressure changes in humans during water immersion. J.Appl.Physiol.Respirat.Environ.Exercise Physiol., 1981, 51, 3, 686-692.

9. Krasney J.A., Pendergast D.R., Powell E., Mc Donald B.W., Plewes J.R. Regional circulatory responses to head-out water immersion in anesthetized dog. Idem., 1982, 53, 6, 1625-1633.

10. Kirsch K.A., Röcker L., Gauer O.H., Krause R., Leach C., Wicke H.J., Landry R. Venous pressure in man during weightlessness. Science, 1984, 225, July 13, 218-219.

11. Kirsch K.A., Röcker L., Krause R., Gauer O. Venous pressure in man during weightlessness results of the Spacelab-1 mission. Pflug.Archiv., 1985, suppl. to v.403, R33.

12. Löllgen H., Gebhardt U., Beier J., Hordinsky J., Borger H., Sarrasch V., Klein K.E. Central hemodynamics during zero gravity simulated by head-down bedrest. Aviat.Space.Environ.Med., 1984, 55, 10, 887-892.

13. Löllgen H., Klein K.E., Beier J., Nieding G., Hordinsky J.R., Baisch F. Comparison of simulation of weightlessness by head-down tilt (HDT) and water immersion (WI). In: "Life sciences research in space". Proceedings of the second European Symposium, Porz Wakn., Germany, 4-6 June, 1984, pp.169-174.

14. Nixon J.V., Murray G., Bryant C., Johnson R.L., Mitchell J.H., Holland O.B., Gomez-Sauchez, Vergne-Morini P., Blomquist G. Early cardiovascular adaptation to simulated zero gravity. J.Appl.Physiol.:Respirat.Environ.Exercise.Physiol., 1979, 46, 3, 541-548.

15. Norsk P., Bonde-Petersen F., Warberg J. Hemodynamics and plasma argenine vasopressin during water immersion in normal man. In: "Life sciences research in space". Proceedings of the second European symposium, Porz Wakn, Germany, 4-6 June, 1984, pp.187-190.

16. Shulzhenko E.B., Will-Wiliams I.F. Possibility of a Long-Term Water Immersion by the Method of "Dry" Plunging. Kosm.biol., 1976, 10, N 2, 82-84.

tive values of most parameters under study. For instance, the absolute value of CVP by the end of head-down tilt and immersion was 0.8±0.6 and 0.1±1.1 mm Hg, respectively, that of mean PAP was 8.8±±1.0 and 10.7±1.1 mm Hg, respectively, and that of cardiac index was 3.7±0.1 and 3.6±0.2 l/min/m^2, respectively. It should be emphasized that the absolute values of venous pressure in the intrathoracic area were significantly ($p < 0.05$) lower than those recorded at the onset.

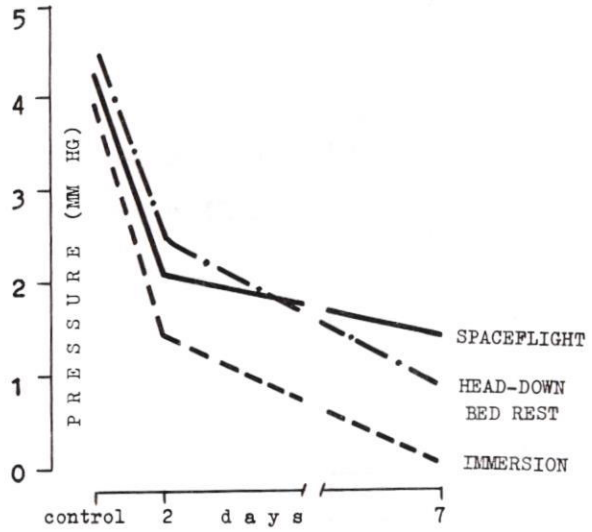


Figure 8. Changes of central venous pressure during 7-days spaceflight and simulation of weightlessness.

It should also be stressed that the sign of changes in circulation parameters after the first day of exposure to simulated weightlessness was identical to that observed during routine tilt tests (decreases of CVP, PAP, volume characteristics of the right ventricle, etc.). This proves the existence of effective compensatory mechanisms which are to generate an optimal hemodynamic situation that develops in the normal man in the upright position.

The similar circulation responses to the two simulation methods suggest with a high degree of probability that circulation responses in actual space flight are of the same character.

Comparison of the effects of 7-day space flight, head-down tilt and immersion on central venous pressure. CVP variations in microgravity attract great attention because this parameter is, first, a very accurate indicator of changes in the circulating blood volume and, second, an important factor in changes of fluid-electrolyte metabolism and renal function which may develop as a neuroreflex reaction or due to the release of atrial natriuretic peptides. This is the reason why Dietlein et al. in their publication "The main lines of biomedical investigations in U.S. space manned missions" underline that "measurement of such parameters as central venous pressure in flight should be performed in a greater number of astronauts and during a much longer period of time than it was done before".

Figure 8 illustrates CVP variations in the 7-day Spacelab-1 flights recorded according to the method of Kirsch (1985) as well as in head-down tilt and immersion tests of the same duration. For the sake of simplicity we averaged the CVP values recorded in two crewmembers before flight and on flight days 1 and 7 and presented them in mm Hg. At R + 1 this parameter decreased from 4.1 to 2.2 mm Hg and at R + 7, to 1.7 mm Hg. It can be readily seen that time-course variations of this parameter during flight were very close to those observed during exposure to the two simulations.

Table. Comparison of influence of head-down bed rest (HDBR) 15° and water immersion (WI) on some parameters of central circulation (according to the beginning of every influence).

P A R A M E T E R S	7-th hour		7-th day	
	HDBR	IM	HDBR	IM
Central venous pressure	0	0	-	-
Pulmonary artery pressure	+	-	-	-
Brachial artery pressure (mean)	+	0	0	0
Cardiac index	0	0	-	-
Stroke index	0	0	-	-
Blood volume in the right heart	0	-	-	-
End systolic volume of right ventricle	+	-	-	-
End-diastolic volume of right ventricle	+	-	-	-
Work of right ventricle	+	-	-	-
Work of left ventricle	+	0	0	-
Total pulmonary vessels resistance	+	-	-	-
Total peripheral resistence	0	0	0	+
Heart rate	0	0	0	0

+ increasing; - decreasing; 0 stable

Conclusion

Comparison of the central circulation effects of two methods, i.e. 7-day head-down tilt and "dry" water immersion, that simulate the physiological action of weightlessness gives evidence that during the first hours of exposure the effects are more distinct in immersion. This may be associated with its primary effect. The circulation parameters cease to change

blood volume in the right heart, right atrium work, total pulmonary resistance, right ventricle end-diastolic and end-systolic volumes.

As compared to head-down tilt at -15°, exposure to "dry" immersion (n=9) causes changes in central circulation (Fig. 7).

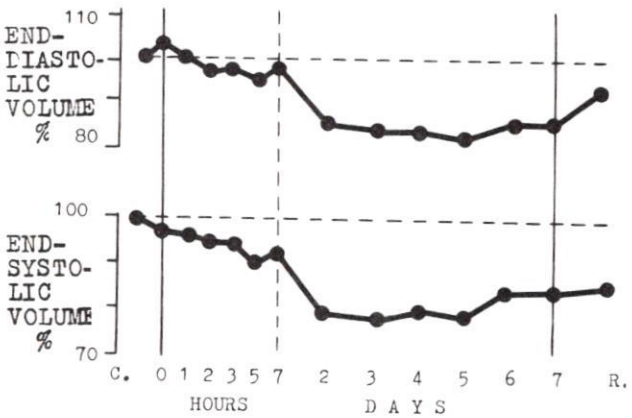


Figure 6. Changes of end-diastolic and end-systolic volume of right ventricle during 7-days water immersion. C - control; R - recovery.

Comparison of the primary effect of immersion versus head-down tilt -15° on blood circulation. Central circulation parameters exhibited noticeable changes 20 min after the onset of immersion (n=9) (Fig. 7). For instance, during immersion versus head-down tilt of the same duration there were additional, statistically significant ($p<0.01$) increases of CVP by 44%, mean pulmonary artery pressure by 39%, right ventricle work by 67%, and total pulmonary resistance by 26%. In these conditions blood volume in the right heart grew from 299±18 to 371±16 ml ($p<0.05$).

Cardiac index increased by 0.5 l/min/m^2 only at the expense of increment in stroke index (by 6 ml/m^2) since heart rate remained essentially unchanged.

In this situation the parameters of mixed venous blood oxygenation, pO_2 and HbO_2, tended to increase.

The above changes may be produced, first, by the hydrostatic effect of immersion and, second, by the concomitant factors. Simulation studies have shown that due to the hydrostatic effects in the supine position the difference in blood volumes between the vessels located above and below the axial (or great) vessels is 400 to 700 cm^3. Upon transition into orbit (and probably upon immersion into the water bath) this differential volume moves upwards in the transverse direction and propagates along the vessels in inverse proportion to their rigidity (Grigoryan et al., 1986). The concomitant factors that result in increases of the above parameters of central circulation involve positive pressure breathing (evidently, of a small value), rapid transition of interstitial fluid to the vascular bed, myorelaxation and relative hyperthermia (Khosla and Du Bouis, 1981; Krasney et al., 1982; Bonde-Petersen, 1982; Löllgen et al., 1984).

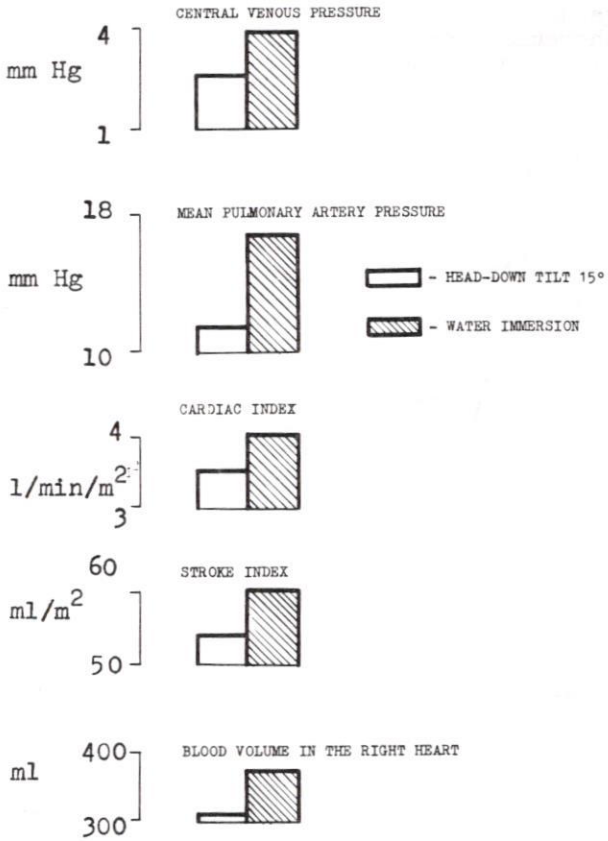


Figure 7. Comparison of influence of short-term head-down tilt 15° (20 min) and water immersion.

Comparison of the effect of 7-day head-down tilt -15° and immersion on central circulation. Comparative effects of head-down tilt and immersion (relative to the onset of each exposure) are shown in Table. It is seen that adaptation of the circulation system to the two effects has both common and different features.

During the first hours of exposure the two models different primarily in the PAP Response, total pulmonary resistance, and right ventricle work. During head-down tilt these parameters increased by the 5 - 7th hour, reaching the values recorded immediately after the onset of immersion. It appears that in the course of 7-hour head-down tilt the events develop at a slower rate than during 7-day immersion. This may be associated with its primary effect discussed above. Thereafter qualitative variations of most parameters are identical.

In addition to the similarity of the qualitative changes seen after 2 - 3 days of head-down tilt and immersion, both exposures cause identical quantita-

of the circulating blood volume as early as one day after the onset of head-down tilt. This may be one of the factors responsible for a rapid fall of CVP in our study.

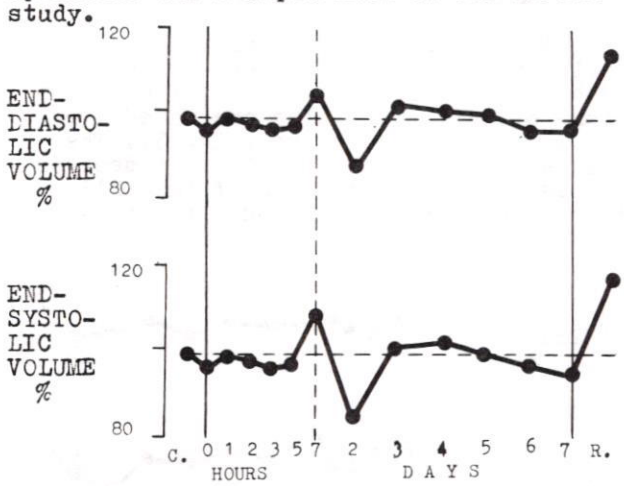


Figure 3. Changes of end-diastolic and end-systolic volume of right ventricle during 7-days head-down bed rest. C - control; R - recovery.

Immersion. Exposure to 7-day immersion caused changes in virtually every parameter of central circulation. By test day 2 there was a pronounced decrease of PAP ($p < 0.01$), by day 3 of CVP ($p < 0.05$) and by day 6-7 of systolic arterial pressure ($p < 0.05$) (Fig. 4). It can be seen that during the entire period of immersion venous pressure in the intrathoracic area was significantly lower than pretest.

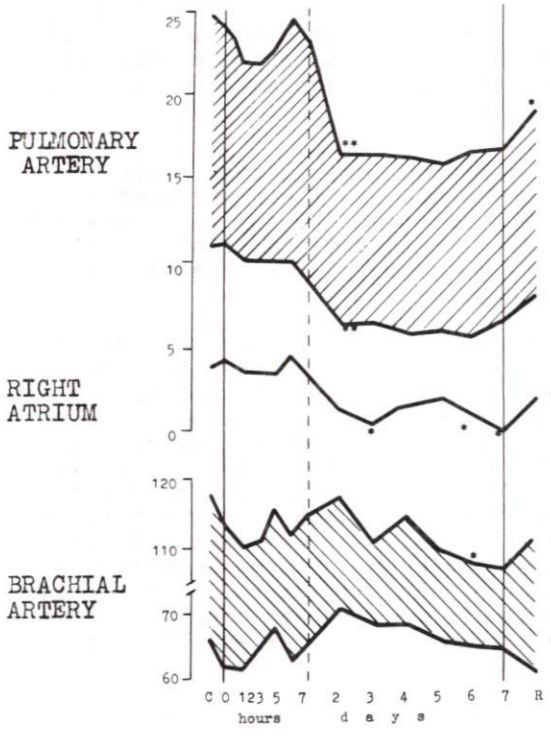


Figure 4. Changes of pressure (mm Hg) in different cardio-vascular compartments during 7-days water immersion. C -control; R - recovery.

During immersion the parameters derived from the thermodilution curve also showed marked changes (Fig. 5). By day 2 there was a significant decrease of cardiac and stroke indices which made 0.67 l/min/m^2 and 8 ml/m^2, respectively ($p < 0.05$). Blood volume of the right heart began to decline during the first hours of immersion and by day 2 decreased by 57 ml which made 15% ($p < 0.05$). This parameter remained diminished by the end of exposure. The mean transit time of the indicator increased and by immersion day 4 reached a plateau that was higher than pretest.

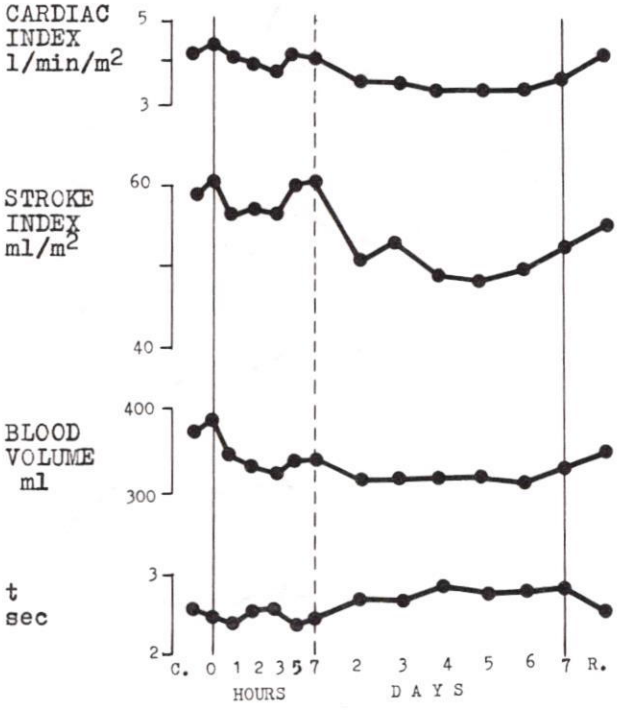


Figure 5. Cardiac index, stroke index, blood volume in right heart and indicator mean transit time (t) of this area during 7-days water immersion. C - control; R - recovery.

Time-course variations of end-diastolic and end-systolic volume of the right atrium were also very distinct (Fig. 6). Beginning with the first hours of immersion they consistently decreased, with the decrease being the greatest by immersion day 2 ($p < 0.05$). Later on these parameters did not vary significantly, remaining below the pretest level.

Throughout the immersion test acid-base equilibrium and oxygenation of mixed venous blood remained relatively constant, giving evidence that circulation changes were adequate to metabolic requirements of organs and tissues.

Our findings show that "dry" water immersion leads to changes in most parameters of central circulation which become stabilized by immersion days 2 or 3. By this time the following parameters diminish and remain lowered thereafter: CVP, PAP, cardiac index, stroke index,

in great detail (Katkov et al., 1983).

The data obtained were treated with a computer and statistical analysis was carried out using the Student's t-test.

Results and Discussion

Antiorthostatic hypokinesia. Among the parameters measured CVP and pulmonary artery pressure (PAP) showed the most pronounced responses to head-down tilt (Fig. 1). In 6 out of 8 subjects CVP remained essentially unchanged while PAP

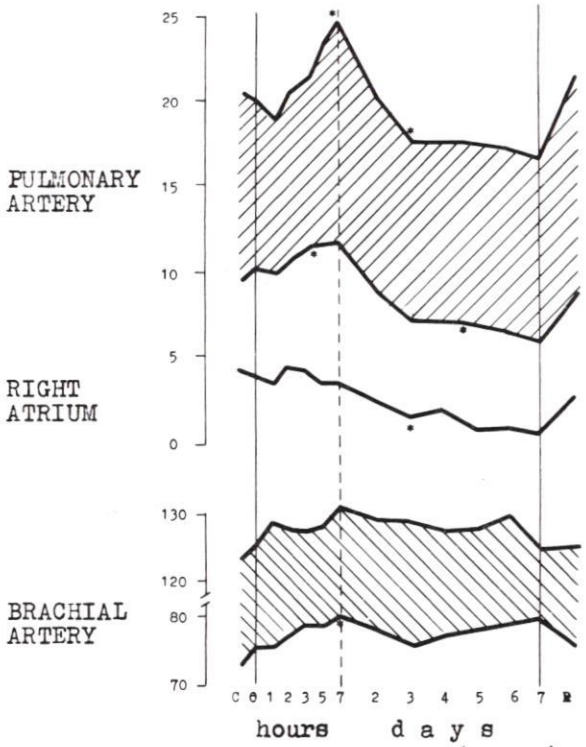


Figure 1. Changes of pressure (mm Hg) in different cardio-vascular compartments during 7-days head-down bed rest. C - control; R - recovery.

increased 2 or 3 hours after the onset of exposure. The increase, particularly of systolic pressure, reached a maximum by the 7th hour of tilt. This was combined with increases in total pulmonary resistance (by 20%) and right ventricle work.

On experimental day 2 CVP began to diminish but PAP returned to the pretest level. On experimental days 3-5 both parameters became lower than in the control and remained such till the end of the experiment. This was accompanied by a decrease in total pulmonary resistance ($p < 0.05$) while right ventricle work did not change ($p > 0.05$).

During head-down tilt most parameters derived from the thermodilution curve did not show any significant variations (Fig. 2). It can be seen that blood volume in the right heart and mean transit time of the indicator through this area remained essentially stable; by the end of the test cardiac index tended to decrease and stroke index declined significantly on experimental day 6 ($p < 0.05$) when compared to the pretest value.

The above observations include primarily end-diastolic and end-systolic volumes of the right ventricle, the variations of which were also evaluated from the thermodilution curve (Fig. 3). The only exception is their distinct decrease by test day 2. By the end of immobilization these parameters tended to decrease.

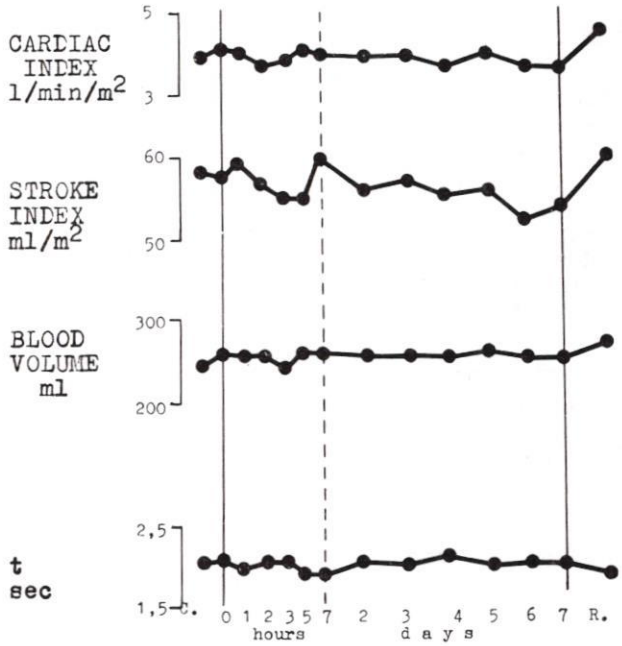


Figure 2. Cardiac index, stroke index, blood volume in right heart and indicator mean transit time (t) of this area during 7-days head-down bed rest. C - control; R - recovery.

During the immobilization period acid-base equilibrium and oxygenation of mixed venous blood did not vary considerably which indicated that blood circulation was adequate to the metabolic requirements.

Our results that point to a relative stability of CVP during the first day of exposure to head-down tilt are consistent with the data reported by other authors who also used the catheterization technique (Nixon et al., 1979; Löllgen et al., 1984). By contrast, PAP increased noticeably by the 5 - 7th hour of the tilt test. In our opinion, that was primarily induced by an increase in total pulmonary resistance of the Kitayev reflex type. This mechanism is to maintain constant pressure in pulmonary capillaries which is needed to prevent lung edema.

Alongside, increased pressure in the pulmonary artery - left atrium area may, as known, exert a tangible effect on hormonal and fluid-electrolyte metabolism (Gauer-Henry reflex). This leads to enhanced diuresis and subsequent decrease

CENTRAL CIRCULATION DURING EXPOSURE TO 7-DAY MICROGRAVITY (HEAD-DOWN TILT, IMMERSION, SPACE FLIGHT)

V.E. KATKOV[x], L.I. KAKURIN[x], V.V. CHESTUKHIN[xx], K. KIRSCH[xxx]

[x] Institute of Biomedical Problems, Moscow, [xx] Institute of Transplantology and Artificial Organs, Moscow, [xxx] Institute of Physiology, Free University, West Berlin

Transition from Earth's gravity (1 G_z) to microgravity induces changes in almost every parameter of central circulation. This so-called primary reaction has been adequately investigated in simulation studies in which man was immersed in the standing or sitting position or man was transferred from the head-up to the recumbent position (Arborelius et al., 1972; Gauer, 1975; Norsk et al., 1984; Katkov and Chestukhin, 1980; Lollgen et al., 1984). The reaction involved an increase of venous pressure in the intrathoracic area (right atrium, pulmonary artery, left atrium) that plays an important part in the regulation of fluid-electrolyte metabolism as well as an increase of cardiac output and stroke volume.

However, the exposure time in these studies was limited to minutes and occasionally to hours. This is the reason why many crucial problems still remain unresolved. These can be formulated as follows: first, what are the precise (quantitative) values of the parameters taken under study; second, what occurs with them (primarily with venous pressure in the intrathoracic area) when the exposure time increases to 7 days; third, are the circulation changes adequate to metabolic requirements.

Answers to these questions can be found in ground-based simulation studies. It is known that the most common methods simulating the physiological effects of microgravity are head-down tilt or antiorthostatic hypokinesia and immersion. A very important present-day task is to identify similarities and dissimilarities in their effects. If they are similar in qualitative and quantitative terms, then it can be claimed with a high degree of probability that weightlessness causes similar changes; if the effects differ significantly then it is necessary to look for another and better method of simulation.

Unfortunately, accurate cardiovascular studies cannot be readily performed in actual weightlessness which makes it difficult to make a comprehensive comparison of simulation and flight data. Bearing this in mind, we have decided to make use of individual but sufficiently informative circulation parameters recorded in weightlessness. In particular, we have concentrated on invasive measurements of central venous pressure (CVP) carried out during the Spacelab-1 7-day space flight according to the method of Kirsch who has kindly shared the data obtained.

In this context we have specified the following goals:

- to identify changes in blood circulation, acid-base equilibrium and oxygenation during 7-day simulated weightlessness: head-down tilt at -15° and immersion;

- to determine similarities and dissimilarities between these changes;

- to compare CVP variations occurring during 7-day space flight, head-down tilt -15° and immersion.

Methods

The basic procedure was a prolonged (up to 12 days) implantation of catheters to different compartments of the cardiovascular system of healthy men-volunteers. Every one of them gave an informed consent.

The test subjects (17 volunteers) were subdivided into two groups that well matched each other with respect to their age, weight and height. Group 1 (8 subjects with the average age 33 years, weight 77 kg and height 179 cm) took part in 7-day head-down tilt at -15° and Group 2 (9 subjects with the average age 33 years, weight 86 kg and height 179 cm) in 7-day "dry" water immersion. In the latter case the test subjects remained in recumbency in the water bath wrapped in a water-proof film (Shulzhenko, Vil-Vilyams, 1976).

Two or three days before the onset of simulation a Swan-Ganz catheter tipped with a thermistor was implanted into the pulmonary artery and a Teflon catheter, into the brachial artery. Pressure in the right atrium, pulmonary and brachial arteries was measured using highly sensitive manometers located at the right atrium level. Cardiac output was recorded by the thermodilution technique. The thermodilution curve was used to determine blood volume in the right heart and variations in the right ventricle end-diastolic and end-systolic volumes. Acid-base equilibrium and oxygenation parameters were measured by an automatic gas analyzer. Circulation parameters and blood biochemistries were determined daily and during the first day almost every hour. The methods of catheterization and registration and measurement equipment used were previously described

3. Adamovich B.A., Zlatorunsky A.A., Ilyin E.A., Noskin A.D., Serova L.V., Golov V.K., Milyavsky V.I., Ovcharov V.K., Stakhov A.A., Magedov V.S., Popov V.I., Yurov B.N., Poleshchuk V.S. 1979. Habitability, life support systems, scientific equipment and flight control. In: Biological Investigations on Biosatellites of the Cosmos Series. Moscow, Nauka, pp.18-53.

4. Ilyin E.A., Korolkov V.I., Kozlovskaya I.B., Krotov V.P., Klimovitsky V.Ya., Nazin A.N., Savina E.A. 1985. Physiological reactions of the animal body at an early period of adaptation to weightlessness. Abstr. XVIII Intercosmos Meet. on Space Biol.Med., Gagra, USSR, 27 May-1 June, pp.132-133.

5. Kozlovskaya I.B., Babaev B.M., Barmin V.A., Beloozerova I.N., Kreidich Yu.V., Sirota M.G. 1984. The effect of weightlessness on motor and vestibulomotor reactions. Proceed. Sixth Ann. Meet. IUPS Commission on Gravitational Physiology. The Physiologist, Suppl., v.27, N 6, pp.111-114.

6. Kozlovskaya I.B., Barmin V.A., Kreidich Yu.V., Repin A.A. 1985. The effects of real and simulated microgravity on vestibulo-oculomotor interaction. Proceed.Seventh Ann.Meet.IUPS Commission on Gravitational Physiology. The Physiologist, Suppl., v.28, N 6, pp.51-55.

7. Kozlovskaya I.B., Sirota M.G., Kreidich Yu.V., Babaev B.M., Beloozerova I.N. 1985. The effect of weightlessness on the gaze fixation reaction of monkeys. Abstr.XVIII Intercosmos Meet. on Space Biol.Med., Gagra, USSR, 27 May-1 June, p.136.

8. Krotov V.P., Sandler H., Badakva A.M., Heins J., Nazin A.N., Hallpryn B. 1986. Changes in blood pressure and blood flow velocity of the monkey in space flight. Abstr. VIII Natl.Conf. Space Biol.Aerospace Med., Kaluga, USSR, 25-27 June, Moscow, Nauka, pp. 281-282.

9. Shlyk G.G., Korolkov V.I., Kozlovskaya I.B., Shirvinskaya M.A., Efimova M.Ya., Poshekhonov O.F., Abramov O.N. 1986. Evaluation of adaptive capabilities of the higher nervous activity of monkeys using instrumental reflexes in the Cosmos studies. Abstr.VIII Natl. Conf.Space Biol.Aerospace Med., Kaluga, USSR, 25-27 June. Moscow, Nauka, pp.303-304.

10. Oganov V.S., Skuratova S.A., Rakhmanov A.S., Magedov V.S., Shirvinskaya M.A., Shlyk G.G. 1986. Assessment of the state of skeletal muscles of monkeys in real and simulated weightlessness. Abstr. VIII Natl.Conf. Space Biol. Aerospace Med., Kaluga, USSR, 25-27 June. Moscow, Nauka, pp.287-288.

11. Kozlovskaya I.B., Sirota M.G., Beloozerova I.N. 1985. The effect of weightlessness on the motor system of monkeys. Abstr. XVIII Intercosmos Meet. Space Biol.Med., Gagra, USSR, 27 May-1 June, p.136.

12. Dotsenko M.A., Korolkov V.I., Lobachik V.I., Zhidkov V.V., Rudneva R.I., Besedina E.G., Gordeev Yu.V., Zaitseva E.I., Truzhennikov A.N. 1985. Changes in fluid-electrolyte metabolism of the monkeys during Cosmos-1514 flight. Abstr. XVIII Intercosmos Meet. Space Biol.Med., Gagra, USSR, 27 May-1 June, pp.125-126.

light signal was used to identify and describe time-course variations of the motor function in weightlessness, which never returned to the norm by the end of flight (5,10,11).

Examination of the monkeys at the recovery site showed that all the four animals were in good condition after their 5- or 7-day flights. They were active and their reaction to the people around were adequate.

As a result of their 5-day flight the monkeys Abrek and Bion lost 7.4 and 8.6% of their body weight. This should be attributed not only to the effect of weightlessness but also to their decreased food and juice consumption: during flight Abrek consumed 2.5 times and Bion 4 times less food and juice than during the same period of time before flight. This resulted in body dehydration. Examinations carried out during the first two days postflight revealed decreases in plasma volume by 27% and extracellular and interstitial fluid by 33% (12).

After the 7-day flight the body weight of Vernyi and Gordyi remained unchanged, Blood and plasma volumes diminished insignificantly. The average food consumption of the monkeys made 55% and 90% of the amount normally consumed preflight.

Blood analysis at the recovery site showed signs of an acute stress-reaction related to deorbiting and deceleration as well as to the rendezvous with the experimenters.

Postflight the monkeys underwent detailed clinico-physiological examinations. Bion diet 69 hrs after recovery because of small intestine volvulus. At autopsy no significant signs of chronic stress, inhibition of erythropoiesis, increased destruction of red blood cells or atrophy of limb muscles were detected (2).

Thirty days after flight Vernyi and Gordyi were exposed to the synchronous control study in the biosatellite mockup, in which all physiologically important factors of space flight, except for weigh weightlessness, were simulated.

Conclusion

Physiological investigations of rhesus-monkeys flown onboard biosatellites of the Cosmos series constituted a new stage of Soviet research programs of space biology and gravitational physiology. These investigations have, first of all, demonstrated that this animal model is adequate to the goals specified with respect to their priority. Moreover, the data obtained can be extrapolated to man which is of key importance for the theory and practice of medical support of manned space missions.

Measurements performed with the use of direct methods have shown that at an early period of adaptation to weightlessness the excitation of vestibular neurons connected with semicircular canals and otoliths increases. Changes in the vestibulo-oculomotor interaction during this period of time have been identified and described quantitatively.

Measurements of blood flow velocity in the common carotid artery did not reveal any significant variations at the early period of adaptation to weightlessness. Taking into consideration this observation as well as distinct edema of the face and neck of the monkeys during 5-7 days of exposure to weightlessness, it can be postulated that the cause of unpleasant sensations reported by cosmonauts and astronauts such as heavines in and blood rush to the head is not an increased arterial flow to the upper body but some other factors or mechanisms. At present it can be suggested that in weightlessness outflow of venous blood and cerebrospinal fluid becomes somehow hampered. Another possibility cannot be excluded - changes in vascular permeability in the region of facial soft tissues that are normally characterized by a low interstitial pressure which produces edema of the face, particularly lips, and neck.

The above investigations have demonstrated that by the end of 5-7 days in weightlessness most parameters under study tend to the norm. However, during this period of time they do not return to the preflight level.

Further primate studies onboard biosatellites will help unravel the pattern of adaptation of various physiological systems to weightlessness. At the present time Soviet scientists are busy preparing various experiments on monkeys onboard the biosatellite to be launched next year. Emphasis will be placed on neurophysiological investigations of sensory systems and behavior of animals in the space flight of up to 14 days in duration. It is hoped that this increase in flight time will help examine physiological responses of the animals not only during the initial but also the intermediate period of adaptation to weightlessness.

References

1. Ilyin E.A., Gazenko O.G. 1984. Problems of gravitational physiology and their solution in Cosmos flights. Proceed.Sixth Ann.Meet. IUPS Commission on Gravitational Physiology. The Physiologist, Suppl. v.27, N 6, pp.3-6.

2. Ilyin E.A. 1981. Future investigations onboard Soviet biosatellites of the Cosmos series. Acta astronautica, v.8, N 9-10, pp.1149-1157.

For example, Abrek and Bion exhibited a distinct decrease of heart rate, which reached its peak at night and in the morning, a drop of body temperature by 0.5°C by the end of flight, as well as a change in HR and body temperature circadian variations. By contrast, Vernyi and Gordyi did not show any significant changes in HR, body temperature and its variations as compared to the preflight values (1,4).

The vestibular function and vestibulo-oculomotor interaction were examined using two provocative tests (2). The first test provided an adequate stimulation of the otolith apparatus by means of vertical displacement of the primate chair. This displacement device was activated at 8.00 a.m. daily. The chair was lifted to a height of 50 mm at a slow speed and was allowed to fall down within 1.1 sec. The test was conducted every day for 3 min during which the chair was taken up and down 12 times.

The second test was used to produce an adequate stimulation of semicircular canals and to investigate vestibulo-oculomotor interaction. Every morning after the first test was completed the pretrained monkey was presented a positive and a differentiation light signal of 0.5 sec in duration. The light signals appeared on a special panel in a random sequence either to the left or to the right from the panel center at an angle of no more than 40°. In response to the positive light signal the monkey was to turn his head towards the signal, fix his gaze at it and push the stick of the arm actograph. A correct response was rewarded with 0.3 g juice. If the monkey made an erroneous response, i.e. if he did not push the stick in response to the positive light signal or if he pushed the stick in response to the differentiation light signal, the monkey failed to receive a portion of juice and the next signal was presented with a delay. The test continued for 20-25 min daily; during this time the monkey was presented light signals up to 400 times.

Analysis of the electrical activity of neuronal populations of the median vestibular nuclei recorded inflight in response to dynamic stimulation of the vestibular apparatus revealed excitation of both the otolith organ and semicircular canals. Changes in the otolith responses developed earlier than those in the canal responses. By flight days 5-6 the neuronal responses of the vestibular nuclei to an adequate stimulation of the vestibular apparatus returned to the preflight level (4-7).

This increase in vestibular excitation was accompanied by changes in the vestibulo-oculomotor interaction. After gaze fixation at a light signal the amplitude and velocity of head movements decreased, the rate of eye nystagmic movements increased, the precision of eye fixation at the target decreased, and correction eye movements emerged. These changes in the regulation of eye and head movements diminished with flight time but did not disappear before the end of flight (4-7).

Measurements of the blood flow linear velocity in the common carotid artery of Bion and Gordyi revealed its variations of different sign: in Bion it decreased while in Gordyi it increased during the first hours of exposure to weightlessness. However, this parameter did not essentially differ from the preflight level at later hours or days of flight (8). This finding viewed in combination with the edematous changes of the face and neck suggests that the latter as well as other symptoms, e.g. the feeling of heaviness in the head or nasal congestion, which appear during the first days in orbit are produced not by a greater blood flow to the head but by something else. The first thing to be taken into consideration is impaired outflow of venous blood and cerebrospinal fluid and, in addition, increased vascular permeability, at least in the tissues with a low interstitial pressure to which the soft tissues of the face and neck belong.

Examination of EKGs of the monkeys did not demonstrate any amplitude or time variations or pathological lesions in the myocardium. According to the rheoplethysmographic data recorded during the Cosmos-1667 flight, cardiac output was at a maximum on flight day 1 and at a minimum at flight day 5. On the 1st flight day the values of stroke volume and peripheral blood flow resistance in the common carotid artery were also maximal (1,8).

Every flight day a provocative test that required stereotyped leg movements (pushing the stick of the leg actograph) in response to a light signal was carried out. As a reward or reinforcement the animals were given a small amount of juice. The monkeys Abrek and Gordyi refused to perform this test throughout the flight. Vernyi began to avoid this test on flight day 4. In view of the fact that the leg test is a more complicated motor act than the arm test it can be assumed that short term exposure to weightlessness impairs significantly the mechanisms triggering sophisticated motor acts. On the basis of manned studies in space it can also be assumed that this functions should be restored completely as soon as adaptation has developed. With respect to simpler motor acts, i.e. pushing the stick of the arm actograph in response to a light signal, no changes were seen in weightlessness. These observations give evidence that weightlessness produces no effect on mental processes such as signal perception and processing, decision taking and execution (6,9).

Analysis of electromyograms and kinematic parameters of pushing the stick of the leg actograph in response to a

Table 1. Primate studies in Cosmos flights

Parameter	Cosmos-1514		Cosmos-1667	
	Abrek	Bion	Vernyi	Gordyi
Age	3 yrs 7 mo	5 yrs	3 yrs 3 mo	3 yrs 1 mo
Weight	3500 g	4640 g	4040 g	4150 g
EEG of the cortical sensorimotor area	+		+	+
Neurogram of vestibular nuclei	+		+	+
EOG	+		+	+
Mechanogram of head movements	+		+	+
EMG of leg back muscles	+			
Total motor activity	+	+		
Deep body temperature	+	+	+	+
Skin temperature	+	+		
EKG	+	+	+	+
Rheoplethysmogram	+	+	+	+
Blood flow linear velocity		+		+
Arterial pressure		+		+

In the primate capsule the light: dark cycle was 16:8, i.e. the daytime was kept from 8.00 a.m. to midnight and the night-time from midnight to 8.00 a.m. Ambient temperature was maintained in the range 24-25°C in the head area.

Every day from 10.00 a.m. to 12.00 and from 6.00 p.m. to 8.00 p.m. the animals were given a paste-like diet that consisted of natural foodstuffs with a well balanced content of proteins, fats, carbohydrates, high-energy and trace elements. The daily diet contained 25.41 g proteins, 20.2 g fats and 111.28 g carbohydrates. The ratio of proteins, fats and carbohydrates was 1:0.8:4.3.

Water content of the daily diet was 70% and its caloric value was 700 kcal.

When performing conditioned instrumental reflexes in the morning and in the evening, the monkeys could receive through a nozzle 75 ml juice which was a mixture of wild-rose berry syrup and pomegranate juice (150 ml juice per day at the most). The following environmental parameters were maintained in the cabin: oxygen - 150-210 mm Hg; carbon dioxide - about 10 mm Hg; relative humidity 30-70%; temperature 21-25°C; barometric pressure 715-780 mm Hg; ammonia below 5.5 mg/m^3; acetone, formaldehyde, methanol, acetaldehyde, propane 1.5 mg/m^3; oxygen concentration 130-168 mg O_2/m^3.

The maintenance and handling conditions in the Cosmos study did not produce any specific adverse effects on the animals which increased the "purity" of the results obtained.

The telemetery monitoring of the health status of the monkeys during flight covered the following parameters: heart rate (HR), respiration frequency, body temperature, food and juice consumption, behavior as judged from the TV data. All physiological parameters during flight were recorded on a tape recorder.

Results

In the flight program the highest priority was given to the study of the vestibular system and its interaction with the oculomotor apparatus as well as to the investigation of fluid redistribution to the upper body. Other experiments, although they were paid much attention, were of lower priority.

It should be emphasized that the physiological responses of the rhesus-monkeys to weightlessness at an early flight period showed distinct individual variations. During the first 1 or 2 days all the animals were, as a rule, inactive and sleepy. But thereafter they returned to the normal at a different rate. For instance, behavioral responses of the monkey Abrek returned to the normal by the end of flight day 2 while those of the monkey Bion only by the end of flight day 4. The monkeys Vernyi and Gordyi did not show a noticeable inhibition of their activity during the first flight days and they did not display a high activity later on. It is important to note that during the first two days of flight the face and neck of the monkeys were edematous. The edema decreased gradually but did not disappear entirely by flight day 7. This indicated that throughout the initial period of adaptation to weightlessness the water content of the soft tissues in the upper body remained increased (1,4).

Marked individual responses of the monkeys to the effects of weightlessness were also confirmed by other findings.

PHYSIOLOGICAL INVESTIGATIONS OF PRIMATES ONBOARD BIOSATELLITES COSMOS-1514 AND COSMOS-1667

O.G. Gazenko and E.A. Ilyin

Institute of Biomedical Problems, Moscow, 123007, USSR

It is known that the early period of adaptation to weightlessness occupies the first 5 to 7 days of space flight. During this time period many physiological changes that constitute the so-called space adaptation syndrome develop. A comprehensive study of this syndrome was the primary goal of physiological investigations of four monkeys flown onboard Cosmos-1514 and Cosmos-1667 in 1983 and 1985. The flight duration was 5 and 7 days, respectively.

Methods

The investigations were carried out on rhesus-monkeys, higher nonhuman primates, that have been studied in great detail.

The mental function of rhesus-monkeys is so complex that their psycho-emotional behavior and elementary operational acts can be explored. Obviously, this is of great interest for biological assessment of space flight effects on the central nervous system and sensory (optic, vestibular and motor) organs.

Rhesus-monkeys and humans have many similar physiological characteristics, e.g., structure of the musculo-skeletal and respiration systems, blood morphological and biochemical parameters, blood serological and antigenic characteristics, duration of the menstrual cycle.

The major portion of the day the monkeys keep the vertical or semi-vertical posture. Due to this, they have well developed gravireceptors in the circulation system and the mechanism of cardiovascular regulation identical to that in man. This morpho-functional characteristics of rhesus-monkeys makes it possible to use them in studies of the effects of weightlessness and acceleration on the cardiovascular and other gravity-dependent systems. Results of these studies can with a high degree of certainty be extrapolated to man.

The description of the rhesus-monkeys used in the Cosmos studies is given in Table 1. The table also lists the physiological parameters recorded using implanted or attached electrodes.

The training period of the monkeys continued, on the average, for 1.5 yrs. This period included candidate selection on the basis of clinico-physiological parameters, monkey acclimatization with the flight capsule, development of instrumental reflexes, and surgical implantation of various electrodes.

The biosatellite carried two monkeys and other biological objects (rats, fish, amphibians, insects, plants, unicellular organisms). Each monkey was kept in a moulded chair in the bottom of which there was a hole to collect urine and feces. The monkey was rigidly fixed to the chair in the pelvic area but its torso and arms and legs remained more or less free. Before launch and reentry the animals were pulled to the back of the chair by special restraints.

The monkeys were flown in special capsules (1,2). Each capsule was equipped with an air heater, light source, paste-like diet and juice nozzles, blower, waste collector, light signal panel, and sticks of the arm and leg actographs to perform conditioned motor responses (Fig. 1). In flight the two monkeys were able to see each other.

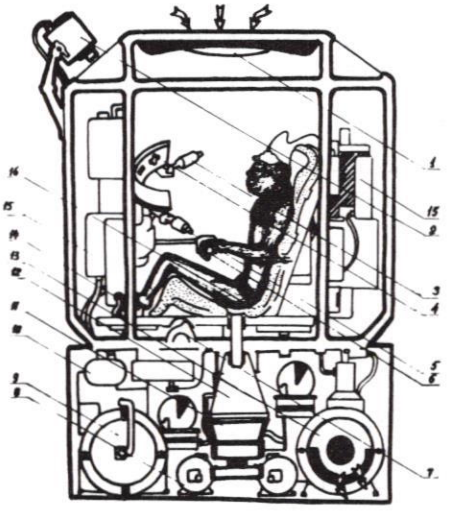


Figure 1. Primate capsule used in Cosmos biosatellites. 1 - light source; 2 - TV camera; 3 - juice nozzle; 4 - light signal panel; 5 - food nozzle; 6 - stick of the arm actograph; 7 - device for vertical displacement of the primate chair; 8 - blower; 9 - food container; 10 - juice container; 11 - air decontamination filter; 12 - waste collector; 13 - air bactericidal filter; 14 - stick of the leg actograph; 15 - scientific equipment; 16 - moulded primate chair.

They concluded that the prone position seems quite feasible in flights of at least two hours' duration with head support and proper torso bedding and that further examination of the practical aspects of prone pilot installations would appear desirable, emphasizing cockpit dimensions, hold-down gear, escape hatches, instrument placement, and visibility (mirrors, etc.) (25).

There have been many studies over the years which demonstrated that the supine position also provides a very high G tolerance. However, for both physiologic and psychological reasons, the prone position is much superior to the supine. One of the important differences is the severe dorsal-ward displacement of the heart, and the consequent severe overdistention of the ventral region of the lungs, which occurs at high G levels in the horizontal supine position. These effects are associated with a much greater danger of lung injury and larger dependent pulmonary arterial-venous shunting than in the prone position (21-23).

In any event, at this point I believe it is appropriate to repeat the statement of F-16 pilot Lt. Col. Steve Sniteman recorded in a recent CBS Evening News broadcast: "High G tolerance gives you the capability to turn and shoot somebody down. If you don't have high G tolerance, you are a grape. If my plane could pull 15 Gs and if I went into combat and was trained to do that, that is what I would want to do." This is a direct challenge to the aerospace medical research and engineering communities. The surest and safest way to meet this challenge is to design future fighter planes and train their pilots to fly these planes in the horizontal prone position.

After all, Superman flies in the prone position. We should redesign our fighter plane cockpits and train our fighter pilots to fly in the prone position so they can perform as supermen, too (2,3).

1. BURTON, R.R. AND J.E. WHINNERY. Operational G-induced loss of consciousness. Something old; something new. Aviat. Space Environ. Med. 50:812-817, 1985.
2. WOOD, E.H. Contributions of aeromedical research to flight and biomedical science. Cause and prevention of GLOC. J. Aerospace Envir. Med., 57:(10, Suppl.):A13-23, 1986.
3. WOOD, E.H. Development of anti-G suits and their limitations. Aviat. Space Environ. Med. (in press).
4. GRIFFITHS, D. Today's pilots need more than the "right stuff". Business Week, October 28, 1985; pp. 109.
5. ROPELEWSKI, R.B. New fighters' high G loads draw increased USAF focus. Aviat. Week and Space Technology, June 17, 1985; pp. 18-20.
6. CLARK, D.M. Anti-blackout suit development 1942-1946. Final Report U.S.N. Bureau of Aeronautics Contract 1946; No. Suppl. 8258.
7. WOOD, E.H. AND E.H. LAMBERT. Some factors which influence the protection afforded by pneumatic anti-G suits. J. Aviat. Med. 23: 218-228, 1952.
8. ALLEN, P. The story of Canada's unsung tactical weapon: The Frank's Flying Suit. J. Can. Aviat. Hist. Soc. 21(4):111-112, 1983.
9. WOOD, E.H., E.H. LAMBERT, E.J. BALDES, AND C.F. CODE. Effects of acceleration in relation to aviation. Fed. Proc. 3:327-344, 1946.
10. WOOD, E.H., C.F. CODE, AND E.J. BALDES. The protection afforded the human by hydrostatic as compared to pneumatic anti-G devices. Comm. on Aviat. Med., Natl. Res. Council, Office of Scientific Res. and Dev., Nov. 1943, Report No. 207.
11. WOOD, E.H., E.F. LINDBERG, C.F. CODE AND E.J. BALDES. Effect of partial immersion in water on response of healthy men to headward acceleration. J. Appl. Physiol. 18:111-117, 1963.
12. CODE, C.F., E.H. WOOD, R.E. STURM, E.H. LAMBERT, AND E.J. BALDES. The sequence of physiologic events in man during exposure to positive acceleration. Fed. Proc. 4:14, 1945.
13. WOOD, E.H., E.H. LAMBERT, C.F. CODE, AND E.J. BALDES. Factors involved in the protection afforded by pneumatic anti-blackout suits. Comm. on Aviat. Med., Natl. Res. Council, Office of Scientific Res. and Dev., Aug. 24, 1944, Report. No. 351.
14. WOOD, E.H. AND E.H. LAMBERT. The effect of anti-blackout suits in blood pressure changes produced on the human centrifuge. Fed. Proc. 5:115, 1946.
15. WOOD, E.H., E.H. LAMBERT, AND C.F. CODE. Involuntary and voluntary mechanisms for preventing cerebral ischemia due to positive (G_z) acceleration. The Physiologist 24:S33-36, 1981.
16. MASER, M. The G suit in combat. Air. Surg. Bull. 2:236-238, 1945.
17. CODE, C.F. The quantitative determination of the protection offered by anti-blackout procedures and devices. Sept. 1943, Report to Subcomm. on Accel. of the Natl. Res. Council.
18. WOOD, E.H. AND E.H. LAMBERT. Factors influencing the efficacy of anti-G equipment at present in use. Comm. on Aviat. Med., Office of Scientific Res. and Dev., Rept. No. 442, 1945.
19. LAMBERT, E.H. Comparison of the protective value of an anti-blackout suit on subjects in an airplane and on the Mayo Centrifuge. J. Aviat. Med. 21:28-37, 1950.
20. WOOD, E.H. AND G.A. HALLENBECK. Voluntary (self protective) maneuvers which can be used to increase man's tolerance to positive acceleration. Fed. Proc. 5:118, 1946.
21. WOOD, E.H., A.C. NOLAN, D.E. DONALD, AND L. CRONIN. Influence of acceleration on pulmonary physiology. Fed. Proc. 22:1024-1034, 1963.
22. WOOD, E.H., AND HOFFMAN, E.A. The lungs, "Achilles' Heel" of air breathers in changing gravitational-inertial force environments. The Physiologist 27(6):547-548, 1984.
23. WOOD, E.H., D.J. SASS, E.L. RITMAN, J.E. GREENLEAF, C.M. COULAM, A. NATHAN, AND E.C. NOLAN. Some effects of acceleration in man and chimpanzees from the use of non-human primates in space. NASA Conference Publication 005:103-164, 1965.
24. WOOD, E.H., C.F. CODE, AND E.J. BALDES. Protection against effects of acceleration afforded by assumption of the prone position. Comm. on Aviat. Med., Office of Scientific Res. and Dev., July 10, 1943; Report No. 158.
25. CLARK, W.G., J.P. HENRY, P.A. GREELY, AND D.R. DRURY. Studies on flying in the prone position. Comm. on Aviat. Med., Office of Scientific Res. and Dev., 1945, Rept. No. 466.

Addendum Reference: HARRISON, N.H. AND T.N. GIBSON. British aviation medicine during WWII. Part II: G production. Royal Air Force Inst. of Aviat. Med., I.A.M. Rept. No. 610, Oct. 1981.

Compilation of this report was supported in part by DARPA/STO Contract No. N66001-87-C-0079.

and head levels in healthy humans (Figure 9) document that the effectiveness of an anti-G suit is directly proportional to its capability of producing arterial hypertension at heart level during positive acceleration (14).

Fig. 9

During a control exposure (Figure 10, center panel) to 5 $+G_z$, blood pressure fell to zero at head level in spite of a normotensive level at the heart. Inflation of the suit at 5 G (right panel) produced a systolic hypertension at heart level of about 200 mm Hg. This was sufficient to overcome the hydrostatic gradient of nearly 125 mm Hg. between heart and head levels and, therefore, to maintain a blood pressure at head level sufficient to support cerebral and retinal blood flow throughout the exposure.

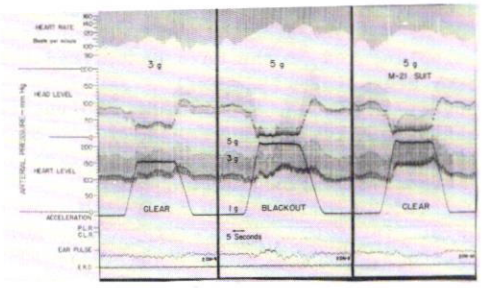


Fig. 10

The protection afforded by the M-1 maneuver is directly proportional to the degree of hypertension at heart level that the pilot can achieve during combat maneuvers (7).

Our studies during the 1940s indicated that a very well-trained man can increase his G tolerance by as much as 3 G by using this maneuver (7). However, this degree of protection would not allow a very well-trained pilot to maintain vision at levels of acceleration of more than 7-8 $+G_z$.

Fortunately, however, the protection afforded by simultaneous use of a G suit and various types of voluntary straining maneuvers are directly additive (7,18). This is the means that F-16 pilots use to prevent blackout and loss of consciousness during very high-G maneuvering of this modern fighter plane.

However, at 13.5 G, for example, which F-16 Pilot Sniteman would like to be trained to withstand (2), the blood would be as heavy as mercury so that a systolic pressure of nearly 340 mm Hg. at heart level would be required just to maintain a column of blood up to the head and a systolic pressure of at least 400 mm Hg. at the heart would be required to maintain a blood pressure at brain level sufficient to provide the minimum cerebral blood flow required to sustain vision and consciousness at this level of acceleration.

Colored motion pictures of subjects on the Mayo Human Centrifuge during such exposures document tremendous engorgement of the skin progressing downwards from ear level (20). Photoelectric recordings of ear opacity (i.e. blood content of the ear), made in 1943 during inflation of the progressive arterial occlusion suit, combined with a very vigorous M-1 maneuver, have documented that the blood content of the ear can actually be increased above the control (1 G) level throughout sustained exposures to 9 G. This has occurred to the degree that all unprotected, i.e. nonpressurized, areas of the skin below neck level were covered with petechial hemorrhages (2).

These findings indicate that the very high levels of protection required to prevent blackout and loss of consciousness at levels of acceleration of more than 7-8 G_z are potentially dangerous.

Because of the very large vertical intrathoracic pressure gradients at high levels of acceleration caused by the increased weight of pulmonary blood and tissue, and the simultaneous negligible increase in weight of the near-zero specific gravity intrapulmonary gases - the function and anatomical integrity of fragile lung parenchyma are very susceptible to changes in the gravitational-inertial force environment (20,21).

Studies in dogs and chimpanzees have demonstrated that the normal vertical gradient in pleural pressure at 1 G is magnified five-fold at 5 G so that alveolar collapse and pulmonary arterial venous shunting and edema occur in dependent regions of the lung, simultaneously with severely overdistended alveoli and zero perfusion in the most superior regions (21,23).

Thoracic roentgenograms of healthy humans, obtained just prior to and after an exposure to 6 G, illustrate that a striking reduction in lung volume and increases in density in dependent regions of the lung do occur at high levels of acceleration (21,22).

These foregoing remarks and figures indicate that normal human anatomy and cardiorespiratory physiology, particularly in the upright seated position, are poorly designed for exposure to high force environments. Furthermore, efforts to increase tolerance to positive accelerations of more than 6-9 G require combined use of a G suit and continuous, properly executed, straining maneuvers which, if relaxed for a few seconds, can lead to blackout and - with a high probability of a fatal crash - unconsciousness. Furthermore, more intensive use of these maneuvers to sustain even higher G levels carries potential danger of injuries to the lungs and the cardiovascular systems.

Studies carried out in a number of laboratories over the years indicate that these problems could be largely avoided by assumption of the prone position (2). A 1943 report (24) documented that: In the prone position humans can tolerate very high accelerations without visual symptoms, and that excessive pressure on the chin at high accelerations could probably be largely eliminated by a properly designed chin rest/or a chin cap.

Two years later in 1945, Drs. William Clark, Jim Henry, and co-workers carried out a much more complete study of the prone position in the human centrifuge in the Aeromedical Laboratories of the University of Southern California. Their prone position assembly incorporated a counter-weighted head support so that the subject could raise, lower, and turn his head during high G exposures.

None of their eight subjects experienced visual symptoms during exposures to 12 G when the head was horizontal with the trunk. However, if the head were raised 4-6 in. above the horizontal, completed blackout occurred at 10-12 G in some subjects.

PHYSIOLOGICAL RESPONSES DURING WHOLE BODY SUSPENSION OF ADULT RATS

J. M. Steffen, R. D. Fell and X. J. Musacchia

Depts. Biology, Exercise Physiology and Physiology/Biophysics, University of Louisville, Louisville, KY 40292

ABSTRACT

The objective of this study was to characterize responses of adult rats to one and two weeks of whole body suspension. Body weights and food and water intakes were initially reduced during suspension, but, while intake of food and water returned to presuspension levels, body weight remained depressed. Diuresis was evident, but only during week two. Hindlimb muscle responses were differential, with the soleus exhibiting the greatest atrophy and the EDL a relative hypertrophy. These findings suggest that adult rats respond qualitatively in a manner similar to juveniles during suspension.

INTRODUCTION

The hypokinesia (decreased muscle use) and hypodynamia (reduced mechanical loading) induced by suspension techniques have been utilized to simulate muscular (Musacchia et al., 1983) and skeletal (Doty and Morey-Holton, 1984) responses as well as cardiovascular (Musacchia and Steffen, 1984), fluid/electrolyte (Deavers et al., 1980), hematological (Dunn et al., 1985) and immunological (Rose et al., 1984) alterations associated with microgravity. A potential limitation of the current ground-based model has been a reliance on the use of immature, rapidly growing juvenile animals as experimental subjects. Although much useful data has been obtained from these studies, the results could be limited when comparisons to adult human responses are required. Whether adult subjects respond to suspension in a manner comparable to juveniles or whether adaptive responses differ between these groups has not been completely elucidated. Therefore, we have undertaken a study designed to characterize the responses of adult rats to whole body suspension.

MATERIALS AND METHODS

Adult (450g) male Sprague-Dawley rats were suspended for up to 14 days with a 25° head down tilt utilizing an adaptation of the procedure previously described for juveniles (Musacchia et al, 1980). To accomodate animals of a larger size, the perforated aluminum back braces and denim/velcro harnesses were enlarged appropriately. The following parameters were determined for three days prior to suspension and daily during suspension: body weight, food and water intakes and urine volume. A group of animals was sacrificed as time zero controls for determination of starting muscle weights (soleus, gastrocnemius, plantaris, EDL, quadriceps and tibialis anterior). Muscles were excised from experimental subjects after seven and fourteen days of suspension.

RESULTS AND DISCUSSION

A rapid reduction of food and water intake following suspension resulted in a loss of body weight (Table 1). Weight loss stabilized at approximately a 15% decrease after 4-5 days of suspension and remained at this level for the remainder of the experimental period. Food and water intakes slowly recovered to presuspension levels after 5-6 days of suspension and therefore cannot easily account for the continuing depression of body weight. Adults exhibited a slightly diminished output of urine during the first two days of suspension, but urine volume increased to levels 50-75% greater than presuspension values by the second week of suspension. The absence of an early diuretic effect in adults contrasts with previous observations in juveniles (Deavers et al, 1980) and could be related to reductions in water intake during this period.

Hindlimb muscle responses to suspension unloading were most evident in adults during the second week of suspension, in contrast to juveniles (Musacchia et al., 1983). Differential hindlimb muscle sensitivity to the atrophic effects of disuse followed the pattern observed in juveniles, with the soleus muscle most responsive (>20% weight loss) over the 14 day period. The gastrocnemius, plantaris and quadriceps atrophied to a smaller extent (<15% weight loss) than the antigravity soleus. The anterior compartment muscles (EDL and tibialis anterior) did not atrophy and exhibited a relative hypertrophy when muscle weights were normalized for body weight differences. The absolute response of muscles from suspended adults appears to be less than that observed in juveniles.

In summary, responses of adults to suspension are qualitatively similar to previous observations reported for juveniles. However, there do appear to be specific quantitative differences which may be of importance. Included among these is the apparently slowed rate of response of adult muscle to suspension unloading. (Supported by NASA grant NAG 2-386).

number of linked cells are required for initial analysis of stimulus vectors); at the first central, integrative level within a system (it is also laid out in linked domains); at central structures comparing signals coming in from the two sides (lack of strict symmetry); and at central reflex and conscious stations, where prior sensory analyses are compared for action (as between visual, kinesthetic and vestibular information, to determine the position of self in gravitational space for appropriate motor response).

How neural tissue compares information must be resolved experimentally. However, in macular sensory fields the initial process would appear to be vector addition to obtain a resultant that is transmitted by neural code to the brain. The coding is accomplished by altering existing background discharges in eighth cranial nerve neurons. Georgopoulos et al. (1986) have analyzed responses in a population of neurons in monkey motor cortex and have provided evidence for vector summation (addition) in coding of arm movement. They suggest that this process might be used in general by neuronal assemblages coding motion direction, which would include linked hair cells in bioaccelerometers. However, as suggested by Land's work and by macular morphology described briefly here and elsewhere, comparisons involving resultants could be universally utilized by neural tissue to interpret the environment and to direct motor responses.

If the premises discussed above are correct then study of the vestibular system in space and in related, ground-based research has more far-reaching consequences than any of us dreamed when we began. Physiological studies of hair cell responses and resulting nerve activity in anatomically defined sensory fields, and of end organ adaptability to new acceleratory environments are particularly required. Such integrated anatomical and physiological investigations could not only lead to new understanding of how vestibular receptors function, but also to greater knowledge of functioning of neural tissue in general.

ACKNOWLEDGEMENTS

This research was supported by NASA NAG 2-325 and NAS2-10535. I thank Kathleen Donovan, Charles Rogers, and Lynn Cutler for technical assistance.

REFERENCES

1. Ades, H.W. and H. Engström. 1965. In: A. Graybiel, ed. The role of the vestibular organs in the exploration of space. NASA, Washington, D.C. pp. 23-41.
2. Baumgarten, R.J. von, G. Baldright, G.L. Schillinger, Jr., O. Harth and R. Thuemler. 1975. Acta Astronaut. 2:49-58.
3. Brou, P., T.R. Sciascia, L. Linden and J.Y. Lettvin. 1986. Sci. Amer. 255:84-91.
4. Egorov, B.B. and G.I. Samarin. 1970. Kosm. Biol. 2:85-86.
5. Georgopoulos, A.P., A.B. Schwartz and R.E. Kettner. 1986. Science 233:1416-1419.
6. Konilova, L.N., I.Ya. Yakoleva, I.K. Tarasov, G.I. Gorgiladze. 1983. Physiologist (Suppl.) 26: S35-36.
7. Land, E.H. 1977. Sci. Amer. 245:108-128.
8. Lewis, E.R. and C.W. Li. 1975. Brain Res. 83: 35-50.
9. Lychakov, D.V. and Ye.A. Lavrova. 1985. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina (in Russian) 19:70-75.
10. Ross, M.D. 1985a. Aviat. Space Environ. Med. 56:338-343.
11. Ross, M.D. 1985b. Physiologist (Suppl.) 28: S57-58.
12. Ross, M.D., K. Donovan and O. Chee. 1985a. Physiologist (Suppl.) 28:S219-220.
13. Ross, M.D., K.M. Donovan and C. Rogers. 1985b. Bárány Soc. Proc. (In press).
14. Ross, M.D. and K.M. Donovan. 1986. Scanning Electron Microsc. (In press).
15. Ross, M.D., D. Peacor, L. Johnson and L.F. Allard. 1976. Ann. Oto. Rhino. Laryng. 85: 310-338.
16. Ross, M.D., C.M. Rogers and K.M. Donovan. 1986. Acta Otolaryngol. (Stockh.) 102:75-86.
17. Vinnikov, Ya.A., D.V. Lychakov, L.R. Pal'mbach et al., 1980. J. Evol., Biochem. Physiol. (Leningrad) 16:574-579.

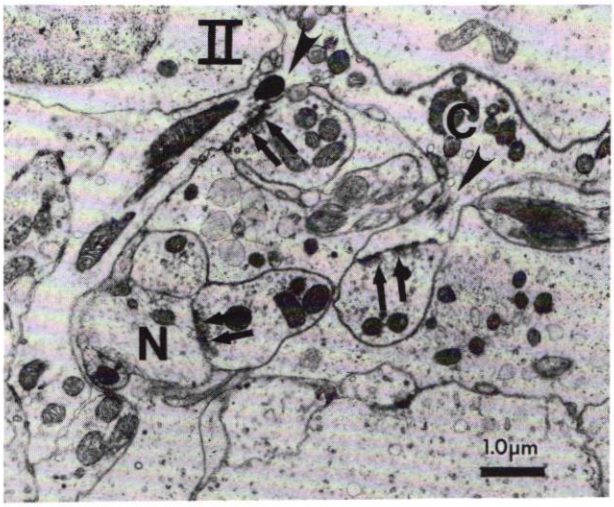


Figure 3: Two collaterals of afferent-type (arrowheads) emerge from this calyx (C). The collateral at left contacts a type II (II) hair cell. Efferent-type terminals (double arrows) synapse on the afferents and also on another nerve fiber (N) in the field (lower left). (11,000X)

metry in some portion of the macular end organs was suspected as a possible cause of space motion sickness (Space Adaptation Syndrome) by Egorov and Samarin (1970) and by von Baumgarten et al. (1975). Experimental support for this concept was obtained by Kornilova et al. (1983) through their study of Soviet cosmonauts. But a morphologic basis for such asymmetry has been difficult to demonstrate until now.

The importance of ground-based studies in the context of space research cannot be over-emphasized. We may take the example of our own work on neural innervation patterns and implications from findings on otoconia in rats that were space-flown. Previous common knowledge of macular organization was based upon study of single sections, or of a limited number of serial sections. This work strongly indicated that each type of hair cell had its own kind of connection with the brain stem: type I cells had calyces and type II cells had boutons or demicalyces. Occasionally, a type II cell was additionally innervated by a calyx or a calyceal collateral (Ades and Engström, 1965). As a result, the first place significant integration of signals from the two kinds of receptors could occur was in the central nervous system. Only when we began to assemble long series of sections, and to trace specific cells and nerve endings, did we begin to learn that type I and type II hair cells are integrated peripherally into the same neural circuitry, and that the innervation patterns are varied by location and are complex. Moreover, patches of hair cells forming individual sensory fields are linked to one another through shared type II hair cells. Within a single field, hair cell polarizations differ slightly from cell to cell so that vector addition must occur. Taken together, the findings indicate that the maculas, like the retina, have a morphology that indicates that complex processing of sensory information occurs peripherally. Additionally, macular end organs appear to be dynamic on morphological grounds, because of the presence of kinocilia having all the ultrastructural features of motile cilia (Ross et al., 1985b; Ross and Donovan, 1986). The end organ should be highly adaptable (given sufficient time) to new but not overwhelming changes in a gravitational environment. Space Adaptation Syndrome, then, may reflect peripheral as well as central adjustment to microgravity.

Short-term peripheral adaptation can be tested through physiological experiments on future space flights. Morphological correlates might be alterations in number and/or configuration of ribbon junctions, and in proportions of various kinds of vesicles at efferent-type synapses. Demonstration of such changes, should they take place, will require the most detailed kinds of reconstructions to prove their existence.

The value of reconstructions in all vestibular research in which comparisons are to be made between spaceflight and control material must be stressed. Our current, most primitive reconstructions have already revealed facts not observed through research with single sections or by study of montages of serial sections. Results of computer-assisted reconstructions demonstrate that many of the type II hair cells of the M-type sensory field have their heads (the detecting part) within the territory outlined by type I cells. This is important functionally, because type II cells routinely have shorter kinocilia and stereocilia than do type I cells and may respond after type I cells of the same sensory field are stimulated. Certain type II cells extend their heads into territory between sensory fields, however. These may serve to "talk to" adjacent fields. They would help define boundaries during low-grade stimulation but could provide for overlap in sensory fields as strength of force increases.

The findings that the two kinds of hair cells are integrated into the same neural circuitry and that maculas are organized into linked domains may prove to be the most significant findings of this ground-based research. The most exciting conceptual result is the idea that the macula, like the retina, is a microcosm of the brain. Maculas have the advantage for study in that they are more simply organized than the retina. Like the retina, however, which has rods and cones, maculas have different kinds of detecting elements. Even in maculas of vertebrates having but one basic type of hair cell, the type II variety, there is evidence of subclasses. Lewis and Li (1975) defined 6 morphologically and functionally different kinds of type II cells in frog. In rat, which has both type I and type II hair cells, 6 different kinds (type I and type II cells considered together) were distinguished on the basis of stereociliary tuft morphology (Ross et al., 1985b).

This diversity in hair cells is a starting point for discussion of comparison as the basis for information processing by maculas, and by neural tissue in general, as first proposed by Land (1977) for the visual system. Land showed that two detecting systems, which respond to different wavelengths of light, are required for color vision. He has suggested that somewhere in the visual system, in retina and/or cortex, the processed information (called "lightness") coming from the two systems is compared. Reflectance alone does not determine the color seen, but perception of one patch of color is influenced by patterns of color around it (Land, 1977; Brou et al., 1986).

It is a feature of retinal function (and of all sensory receptors) that detection of a stimulus depends upon change. Visual recognition that two objects are different requires that a boundary difference between them be distinct and also be detected. It is commonly known that even if contrast at boundaries is pronounced, images stabilized on the retina vanish (see discussion and experiments outlined in Brou et al., 1986). The importance of change in signal detection is one reason why thinking of maculas as passive detectors of gravity, a constant force, must be erroneous (Ross, 1985b).

The notion of comparisons as fundamental to retinal functioning, espoused by Land (1977), has further analogies to the maculas and to the working of nervous systems in general. Comparisons may be the basis of neural operations at all levels: at end organs (a specific

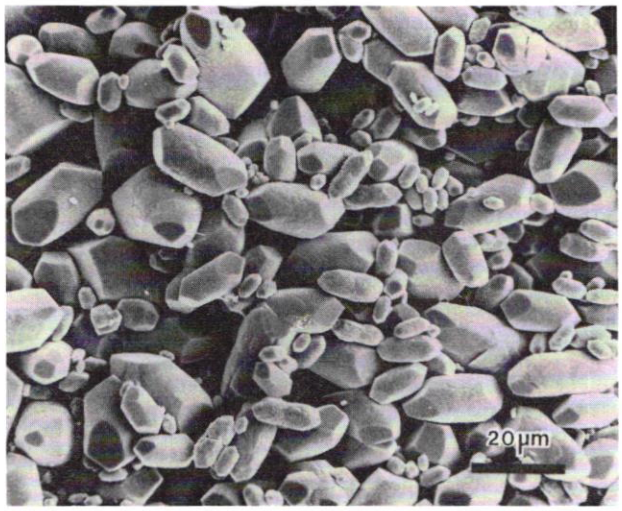


Figure 1: The lateral border of the left utricular macula of a 51-day-old rat is illustrated here. Compare otoconia with those in Figure 2. (800X)

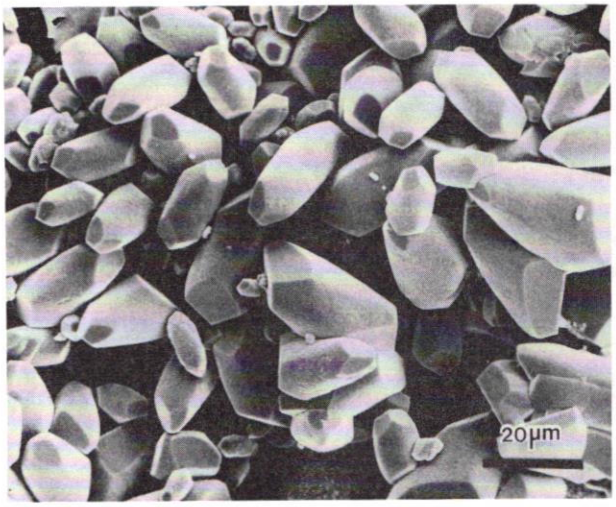


Figure 2: Otoconia at the lateral border of the right utricular macula, shown here, are larger than those of the left, shown in Figure 1. (800X).

Scanning electron microscopy: Otoconia from fixed (3 older rats) and unfixed (6 young rats) inner ears were obtained from space-flown rats and from 18 ground controls. Details are given in Ross et al., 1985a, and in Ross and Donovan, 1986.

RESULTS

Otoconia: Otoconia from both groups of space-flown rats showed no signs of demineralization. Both flight groups also showed accumulations of very small otoconia along the lateral border of the otoconial patch, but weight-matched controls did not exhibit numerous miniature otoconia. The tiny otoconia often appeared to be closely associated with body surfaces of large otoconia, as though they grew from them. Saccular otoconia showed a smoothing out of otoconial body surfaces compared to ground controls. This smoothing occurred throughout the patch and was not confined to a specific region as were the utricular differences noted.

Because we had not noticed such miniature otoconia in otoconial patches in previous work with rats of the Charles River strain, it appeared essential to study more ground controls obtained from Taconic Farms. The question of possible laterality in otoconial distribution had to be answered because few matched pairs of otoconial patches were available. This was because some flight and ground-control specimens had been turned over to examine under- as well as top-sides of the patches for possible morphological changes.

Subsequent investigation of three groups of Taconic rats, ranging between 51 and 93 days of age, showed that differences in otoconial size existed along the lateral borders of the two utricular maculas in the same animal (Figures 1 and 2). No increased proclivity for right or left side dominance in distribution of miniature otoconia could be found in the small sample studied.

Macular neuroepithelium: Ultrastructural research using serial sections has shown that type II cells are integrated into the neural circuitry supplying type I hair cells. That is, type II hair cells are in close apposition with calyces and synapse with them through ribbon junctions. Calyceal collaterals also contact type II hair cells extensively, but these can be of efferent as well as of afferent type (Figure 3). Efferent-type calyceal collaterals are often beaded and vesiculated and usually end opposite subsynaptic cisterns. The final source of afferent innervation of type II hair cells is from branches of nerves terminating otherwise as calyces.

A second kind of efferent-type nerve terminal occurs in the vestibular system. This kind is highly vesiculated and chiefly terminates on calyceal collaterals, close to their origins (Figure 3), and on neural elements in the field (Figure 3). The terminals show presynaptic densities, which serve to orient vesicles at the synapse; and a subsynaptic web is often present. The origin(s) of fibers terminating in these ways is (are) still not known with certainty. Adding to the complexity are afferent-type fibers having vesiculated terminals on type II hair cells or on other afferent- or efferent-type neural elements in the neuroepithelium.

It was also learned that there are three different kinds of nerve innervation patterns in the saccular macula: the "U" type, in which the parent nerve loses its myelin below the macular neuroepithelium; the "MU"-type, in which the nerve is myelinated to the base of the neuroepithelium but a short unmyelinated segment occurs before the calyx; and the "M"-type pattern, in which the calyx springs directly from the myelinated nerve. A recent study of a series of 415 sections showed that these same kinds of terminal patterns occur in the utricle. A single M-type terminal together with its associated hair cells was reconstructed from these sections. Its calyx, which contained five type I cells, was apposed by eight type II cells. Six of the eight type II cells had their heads within the area outlined by the type I cells. While it was not possible to demonstrate specific cell polarizations with the program used, it was apparent that many of the heads of the hair cells were oriented at angles to one another.

DISCUSSION

Results obtained from rats flown on SL-3 are indicative of the ultimate importance of the new tool, microgravity, in the study of the vestibular end organs. Space-flight experiments using rats and frogs (Vinnikov et al., 1980; Ross et al., 1985a) continue to demonstrate that macular end organs are able to cope with microgravity. Otoconia do not demineralize and disappear, at least over short-term space flight. Other findings which suggest a slight increase in otoconial mass (Lychakov and Lavrova, 1985; Ross et al., 1985a) require much additional testing. In our own case, exploration of the possibility that Taconic rats had laterality in otoconial distribution resulted in demonstration of end organ asymmetry in this strain. This finding will have to be taken into account as our space-related research continues. Asym-

IMPLICATIONS OF OTOCONIAL CHANGES IN MICROGRAVITY

Muriel D. Ross

NASA Ames Research Center
Mail Stop 239-17
Moffett Field, CA 94035

ABSTRACT

Otoconia of maculas of Sprague-Dawley rats (Taconic Farms) flown aboard Spacelab-3 showed no signs of demineralization. Other findings were accumulations of miniature otoconia at the lateral border of utricular patches and a smoothing of surfaces of saccular otoconia. These features were not observed in age- and weight-matched ground controls. Subsequent study showed otoconial asymmetry to be normal in this strain. Further research in space, taking this into account, is clearly required. Findings of ground-based studies would suggest that neural structures of maculas are adaptable to microgravity but might show changes over time. Moreover, maculas have the potential for integration of the sort ascribed to brain and retina, although on a less complex scale. They may act as comparators, and asymmetry may be an important property. Coordinated studies in space and on the ground could lead to new understanding of how maculas function and adapt to new acceleratory environments; and to insights about the functioning of neural tissue in general.

INTRODUCTION

The vestibular macular end organs are the only sensory receptors dedicated solely to the detection of gravitational and translational linear acceleratory forces. Signals generated at the periphery are integrated centrally with visual and kinesthetic inflow to keep the organism oriented properly in its normal, 1-g environment. It is self-evident that appropriate studies of vestibular maculas in the virtual absence of one of their normal stimuli, gravity, could tell us a great deal about how they function on Earth.

Recently, we were fortunate to obtain inner ears from rats flown on board Spacelab-3. Only the otoconial patches could be studied in detail because of the time interval between death and dissection of the temporal bones (see Material and Methods section, below). Results of our investigation demonstrated unequivocally that exposure to the entire spectrum of environmental conditions experienced during the flight and return on Spacelab-3 had no deleterious effect on otoconia (Ross et al., 1985a; Ross and Donovan, 1986). The conditions were lift-off acceleratory force, microgravity 7 days in duration, deceleration during landing, and 1-g for 12 hrs prior to tissue harvest. Part of the postflight time at 1-g was spent on a Lear jet flying from Edwards Airfield in California to Kennedy Space Center in Florida.

Other observations were made that are more open to question. These were that miniature otoconia were prominent on the lateral side of the utricular otoconial mass in space-flown rats but not in age- and weight-matched, ground-based controls; and that body surfaces of saccular otoconia were smoother than those of control rats (Ross et al., 1985a; Ross and Donovan, 1986). These findings are fraught with the danger of experimental error because of the necessity of removing the otoconial patches from the maculas. They must be subjected to further, rigid testing both on the ground and in space. One question, that of possible normal asymmetry in otoconial distribution, has already been answered through further ground-based studies. In comparing the lateral borders of right and left utricular maculas for the Taconic Farms rat strain, one side shows larger otoconia than the other (Ross and Donovan, 1986).

The results of SL-3 and of related, ground control experiments are reviewed here as are other findings obtained over the past few years from ultrastructural work with serial sections. The latter research is beginning to demonstrate that macular end organs are dynamic analyzers of vectors of linear acceleratory forces (Ross, 1985a, b). Such basic research in concert with well-controlled flight experiments is valuable in providing a better understanding of the functional organization of these living linear accelerometers, and of their adaptability to new acceleratory environments. Our research is also revealing similarities between the organization of the maculas and the retina and the brain. Hypothetically, the maculas, like the retina, could function on the basis of comparisons (Land, 1977). Such comparisons, made through vector addition, may be fundamental to the functioning of neural tissue wherever it occurs. Thus, space experiments on the vestibular system are possibly uniquely capable of answering basic questions of neurobiology even as they can be used to meet more practical goals of space life sciences.

MATERIAL AND METHODS

Sprague-Dawley rats were used throughout. Pathogen-free animals ~60 days old and weighing 225-275 gms obtained from Charles River generally are employed for basic ultrastructural research, including serial reconstructions. Older and younger animals, including fetal rats, have been studied, however. Space-flown animals and their controls were obtained from Taconic Farms. Within each of these groups were 6 animals ~51 days old, weighing ~200-265 gms; and 3 animals ~93 days old, weighing ~375-400 gms. Controls of the Taconic strain used for laterality studies were of 3 different ages: 3 animals were 51 days old, 200-212 gms in weight; 3 were 72 days old, 270-300 gms in weight; and 3 were 93 days old, 360-400 gms in weight.

Preparation for transmission electron microscopy: Details of tissue preparation have been presented by Ross, 1985a; and in Ross et al., 1986. The specific primary fixative used in our most recent series from a utricular macula (415 sections) was 2.5% glutaraldehyde + 0.5% paraformaldehyde + 1.0% osmium tetroxide in 0.1M phosphate buffer, pH 7.4.

A point not sufficiently emphasized previously is that both inner ears must be in fixative within 2 mins. This requirement has been determined empirically. Because no temporal bones were given to us within this time-frame, macular tissues of space-flown animals showed artifact and could not be responsibly reported upon. Only otoconia, which we have previously shown to be impervious to detectable morphological alteration if kept in situ for up to 72 hrs following death (Ross et al., 1976), could be used for study.

brain signals. In: Problems of Higher Nervous Activity and Neurophysiology. Moscow, Nauka, 1975, 43-71.

8. Ross M. Vertebrate gravity sensors as dynamic systems. The Physiologist, 1985, Suppl.28, 6.

9. Durinyan R.A. Cortical Control of Brain Nonspecific Systems. Moscow, Medizina, 1975.

10. Kozlovskaya I.B., Kreidich Y.V., Burmin V.A. et al. Effect of immersion hypokinesia on man's eye and head movements during the gaze fixation reaction. Kosm.Biol.Aviakosm.Med., 1982, 16, 5, 41-45.

11. Mano T., Nishimura T., Mitarai G. et al. Effect of partial body weightlessness on the vestibulo-ocular reflex in man. Proceed. 12th Intern.Symp.Space Techn.Science. Tokyo, 1977, 809-814.

compensatory eye conter-rotation with pauses that coincided with the intervals when the head was fixed at the shoulder. The examinations carried out on mission days 1 and 5 demonstrated that the otolith reaction of eye counter-rotation with the eyes closed did not disappear but slightly diminished. As indicated by electrooculograms, this reaction developed at a much slower rate (lack of pauses) and was accompanied by a nystagmus on day 1. With the eyes open and the gaze fixed complete destabilization was observed on mission days 1 and 5.

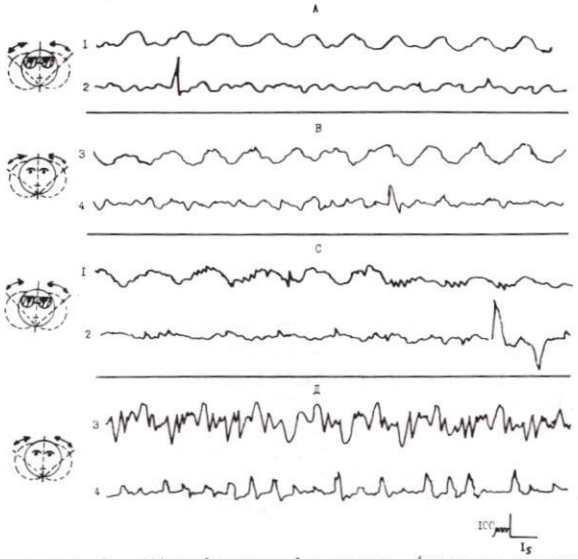


Figure 4. Electrooculograms during active head movements (in the frontal plane) before flight (A,B) and during flight (flight day 2) (C,D). 1,3 - eyes closed; 2,4 - eyes open, no gaze fixation; a - EOG horizontal lead; b - EOG vertical lead. Calibration: 100 mkV, 1 sec.

Thus, the flight study of the oculomotor function within the framework of the experiment Optokinesis was the first one in which changes in the vestibulo-oculomotor interaction were recorded objectively and quantitatively. These changes, on the one hand, indicated an increase in dynamic excitation of the optic and vestibular inputs (decrease of the thresholds of the optokinetic and the vestibular nystagmus) and, on the other, they suggested a decrease in static vestibular excitation (reduction and loss of saccades during pursuit of a moving spot with the head in a fixed position).

Similar changes were reported by Gualtierotti et al. 6 : static excitation of several vestibular receptors was decreased and dynamic excitation was markedly increased - the receptor cell that was static before flight acted as a dynamic structure during flight. The weightless state affects not only the function of receptors of the vestibular apparatus but also modifies the receipt and transmission of sensory signals at every level of the central nervous system.

In conformity with existing concepts of clinical vestibulology, saccadic changes observed in weightlessness can be attributed to the involvement of the brain stem and cerebellum, disorganization of vestibular-cerebellar interactions, and modification of pontic-vestibular-cerebellar interactions.

Floating eye movements recorded in weightlessness may reflect changes in the function of stabilizing, controlling central brain formations, i.e. midbrain reticular formation and brain cortex 7, 8,9 . Mention should also be made of the unloading of the musculoskeletal system and proprioceptive deprivation which certainly modulate the reactions under study 10,11 . It is very likely that the decrease of the proprioceptive flow modifies the function of vestibular nuclei and midbrain structures and therefore has a bearing on changes in vestibular excitation. On the other hand, in these conditions the reverse corticofugal flow may diminish and inhibitory effects of the cortex upon subcortical structures may decline (sensory gates open) which may manifest as a decrease of the thresholds of sensory reactions.

Obviously, changes in blood and CSF circulation that occur in weightlessness and modify the normal brain supply and function also play an important role in the development of sensorimotor reactions in this unusual environment.

References

1. Kozlovskaya I.B., Sirota M.G., Beloozerova I.N. Effect of weightlessness on the gaze fixation reaction in primates. XVIII Intercosmos Meeting on Space Biology and Medicine, Gagra, USSR, 1985, 137.

2. Kornilova L.N., Bodo G., Kaspransky R.R. et al. Oculomotor reactions of ocular and vestibular origin in the weightless state. XVIII Intercosmos Meeting on Space Biology and Medicine, Gagra, USSR, 1985, 55-57.

3. Kornilova L.N., Bodo G., Kaspransky R.R. et al. Oculomotor responses induced by vestibular and visual stimulation in weightlessness. Proceed.Intern. Symp.Ophthalmo-Neuro-Otology, Budapest, Hungary, 1985, 65-70.

4. Baumgarten R., Benzon A., Berthoz A. et al. Effect of rectilinear acceleration and optokinetic and caloric stimulation in space. Wash.Science, 1984, 225, 4658, 208-212.

5. Young L., Oman Ch., Watt D. et al. Spatial orientation in weightlessness and readaptation to Earth gravity. Wash.Science, 1984, 225, 4658, 205-208.

6. Gualtierotti T., Bracchi F., Rocca E. Orbiting frog otolith experiment. Milan, 1972.

7. Kratin Yu.G. Innter inhibition as a basis of biological analysis of

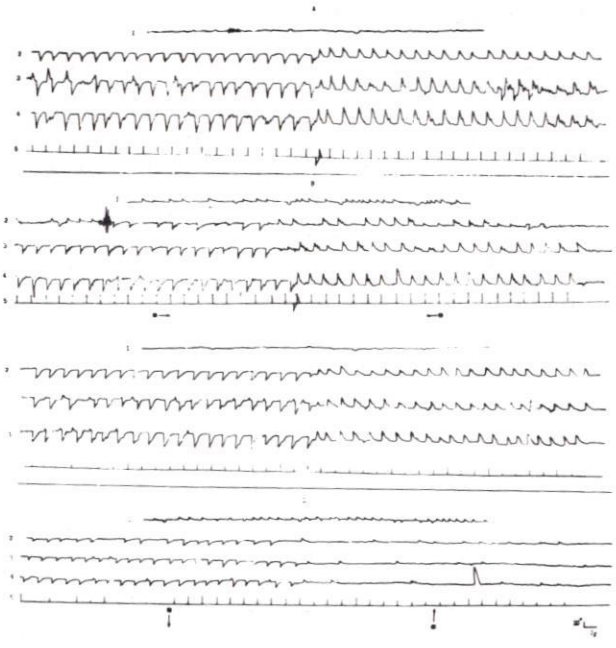


Figure 2. Electrooculograms of spontaneous and evoked eye movements. A,B - light spot moves in the horizontal direction; C,D - light spot moves in the vertical direction (accordingly, horizontal and vertical EOG leads); A,C - EOG before flight; B,D - EOG during flight (flight day 2): 1 - EOG of spontaneous eye movements; 2 - EOG of tracking eye movements with the head in a fixed position; 3 - EOG of tracking eye movements after side-to-side head movements; 4 - EOG of tracking eye movements after rotatory head movements; 5 - light spot. Calibration: 10°, 1 sec.

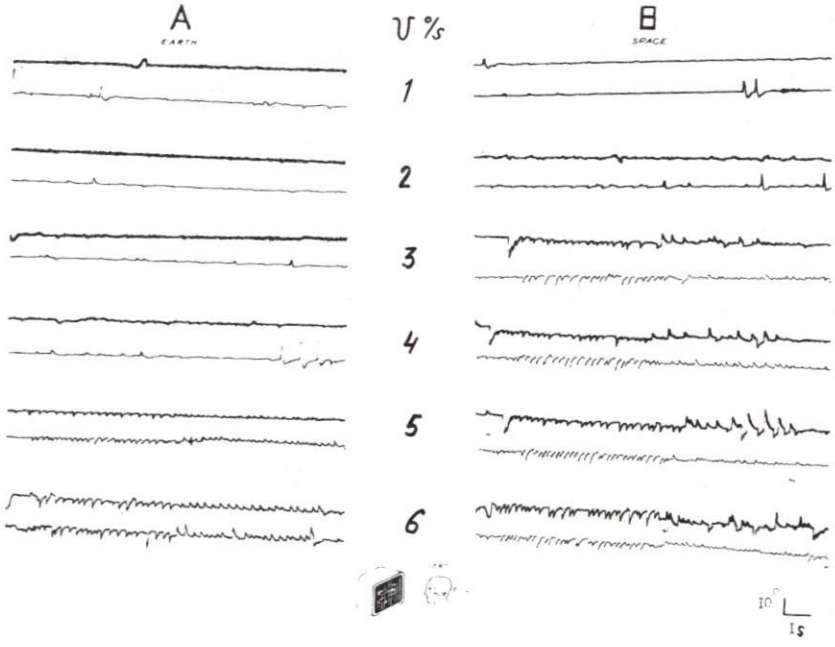


Figure 3. Lower threshold of optokinetic nystagmus on Earth (A) and in space flight (B). V - velocity of optokinetic stimuli (black-and-white strips °/s). Calibration: 10°, 1 sec.

vestigation of both the optokinetic reflex and opto-oculomotor reactions in-flight demonstrated a distinct asymmetry of oculomotor responses to motor stimulation of different direction (decline of the reaction by 18-20% in response to the displacement of the spot from the left to the right).

The oculomotor response to an adequate vestibular stimulation also changed (Fig. 4). During side-to-side movements of the head at a frequency of one movement per second controlled by the metronome with the eyes open or closed a distinct sinusoidal curve was recorded before flight. This curve describes a

frontal plane (from the right to the left shoulder within 90° of arc) at a frequency of one movement per second for one minute;

- continuous head rotation about the vertical axis (from the right to the left within 90° of arc) at a frequency of one rotation per second for one minute.

The protocol of the experiment Optokinesis required that the following parameters be recorded:

1) spontaneous eye movements;

2) tracking eye movements;

3) upper and lower limits of the optokinetic nystagmus;

4) eye movements during predominant otolith stimulation (side-to-side movements);

5) tracking eye movements, then upper and lower threshold of OKS after active head movements;

6) eye movements during predominant canal stimulation (head rotation);

7) tracking eye movements, then upper and lower threshold of OKS after active head rotation).

When analyzing oculograms recorded during optomotor stimulation, the following parameters were measured: coefficient of synchronicity, i.e. ratio of the frequency of oculomotor responses to the frequency of optic stimulation presented; coefficient of phase relations, i.e. ratio of time intervals between input signals and eye reaction intervals; saccadic amplitude, rate of the slow tracking phase, and reaction asymmetry. When evaluating nystagmograms recorded during optokinetic stimulation, the following parameters were also measured: nystagmus frequency and amplitude, reaction asymmetry, velocity of band presentation at which the nystagmus appeared and disappeared.

Oculograms recorded during vestibular stimulation (head turns and rotation) were evaluated with respect to the pattern of the sinusoid curve, i.e. whether it was smooth or had many kinks, whether nystagmic eye movements were present or absent.

The examinations during the Soyuz-T - Salyut-7 flight were performed by Dr. Oleg Y. At'kov, a cosmonaut-physician, on flight days 2 and 5 as well as before and after flight. Oculomotor reactions to optomotor and optokinetic stimulation were recorded when the head was in a fixed position.

This study revealed various changes in the oculomotor function in space flight that were associated with changes in the vestibular apparatus and vestibulo-proprio-oculomotor interactions.

Tracings of eye movements in the absence of stimulation, i.e., with the gaze fixed and in the light-proof goggles with the eyes open) showed destabilization of the eye apple which included an increased spontaneous oculomotor activity of saccadic and floating character in two subjects and in the form of the nystagmic reaction in one subject on flight day 2 (Fig. 2).

Significant changes were also detected in the oculomotor tracking function (Fig. 2). On flight day 1 the changes were seen during the pursuit of the light spots that moved in every direction; however, they were most distinct during the pursuit of the spots that moved in the vertical or diagonal direction.

Before flight the coefficients of synchronicity and phase relations were within 0.9-1.1 and the saccadic amplitudes were stable with the variation scatter 2°. In flight these coefficients decreased significantly to 0.4-0.6 and the saccadic amplitudes diminished and lost their stability (hypometry or hypermetry with the variation scatter 8°). During the slow pursuit phase (compensatory eye deviations towards the spot) additional correction saccades appeared (and the precision of the oculomotor reactions decreased) and in certain cases they were superposed by the nystagmic reaction.

On mission day 5 the pattern of pursuit of a single spot moving in different directions returned to the preflight level in all crewmembers.

In the early period of adaptation to weightlessness oculomotor responses to vestibular stimulation also changed. Before flight vestibular stimulation in the form of rotatory or rocking head movements (which constitute a combination of complex movements) increased the amplitude of the oculomotor response to optomotor stimulation and caused correction saccades. However, on mission day 2 the same responses seemed to make up for the vestibular input deficiency and normalized the oculomotor function in two subjects and completely disorganized it in one subject. On mission day 5 vestibular stimulation did not produce a significant effect on the type of oculomotor responses.

The study of the upper and lower thresholds of the optokinetic response during flight revealed their distinct decline in all subjects: preflight the lower limit of the optokinetic nystagmus corresponded to the stimulation rate 5-6 °/sec and the upper limit, to 10-20 °/sec and in orbital flight the lower limit was 2-3 °/sec and the upper limit was 8-9 °/sec (Fig. 3). The decrease of the optokinetic reflex thresholds was also detected in all subjects on mission day 5. It should be noted that the in-

SENSORY INTERACTION IN WEIGHTLESSNESS

L.N. Kornilova[x], G. Bodo[xx], R.R. Kaspransky[x]

[x]Institute of Biomedical Problems, Moscow, USSR;
[xx]Budapest, Hungary

One of the crucial problems of space medicine related to short-term space flights was and still is space motion sickness. Among several theories advanced to explain its origin the theory of sensory mismatch or sensory conflict has won general recognition.

It is very likely that the major source of sensory conflict is the information transmitted along the vestibular channel because its input is a mechanoreceptor formation which has emerged and developed in the gravity field. Weightlessness modifies seriously the function of the vestibular as well as other afferent systems, particularly the musculoskeletal system, which closely cooperate to provide spatial orientation and motor and autonomic regulation.

Prior to 1984 no studies of the vestibular apparatus or manifestation of vestibular signals in the perceptive, sensory, sensorimotor and autonomic reactions in the weightless state were performed (except for regular measurements of the vestibular function before and after flight).

Recent vestibular studies performed by Soviet investigators (Primate experiment on Cosmos-1514 and -1667 - I.B.Kozlovskaya et al. 1 and Optokinesis experiment on Soyuz-T - Salyut-7 - L.N. Kornilova 2, 3 and by American and West European investigators (Shuttle and Shuttle-Spacelab - W.Thornton, L.Young, M.Reschke, A.Benson, R.Baumgarten, A. Berthoz, J.Dichgans, Ch.Oman et al. 4, 5) have considerably expanded the scope of our knowledge about the function of the vestibular system and its interaction with other afferent inputs in weightlessness.

The present report reviews the data obtained in one of the very first relevant investigations, i.e. the experiment Optokinesis performed in 1984 during the 7-day Soviet-Indian joint flight and the 237-day Salyut-7 flight.

The purpose of this study was to:

- investigate spontaneous oculomotor activity and its dependence on optokinetic stimulation (OKS);

- determine eye tracking movements;

- determine threshold and suprathreshold sensitivity of the oculomotor function to OKS of different direction but of a known magnitude;

- examine cardiovascular responses to prolonged OKS;

- assess vestibulo-oculomotor reactions to predominant otolith (head side-to-side movements in the frontal plane) or predominant canal (head rotation about the long axis) stimulation;

- evaluate the effect of active head movements on optooculomotor reactions;

- investigate adaptation of sensory systems to the weightless state with respect to oculo-motor reactions to vestibular and optokinetic stimulation.

The OKS program is shown in Fig. 1.

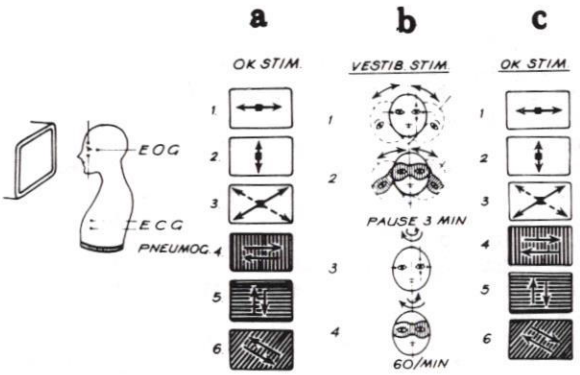


Figure 1. The program of Optokinesis experiment. a - okstim before vestib. stimulus; b - vestib. stimulus; c - okstim after vestib. stimulus.

The OKS program on a video tape (recorded by a Hungarian unit "Oking") provided:

- presentation on a TV screen of a light spot of 0.5° of arc that moved in different directions at a frequency of 1 Hz;

- presentation on a 20° of arc TV screen of black-and-white bands (of about 2° of arc in size) that moved at a velocity of 1 to 20°/sec in the horizontal, vertical and diagonal directions.

Adequate vestibular stimulation included:

- continuous head movements in the

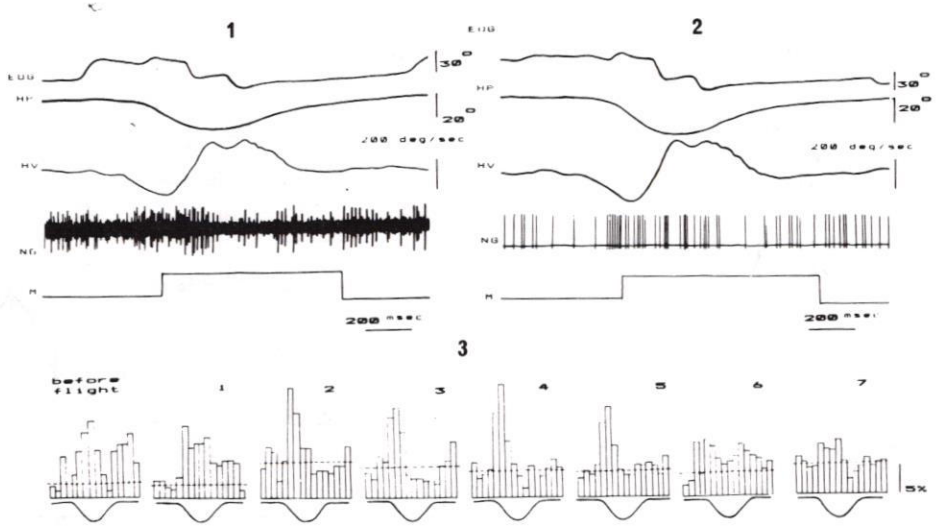


Figure 3. Single unit activity of MVN recorded during horizontal eye movements. 1 - fragment of recording; 2 - single unit activity discriminated by "threshold" procedure; 3 - frequency distribution on preflight and different flight days.

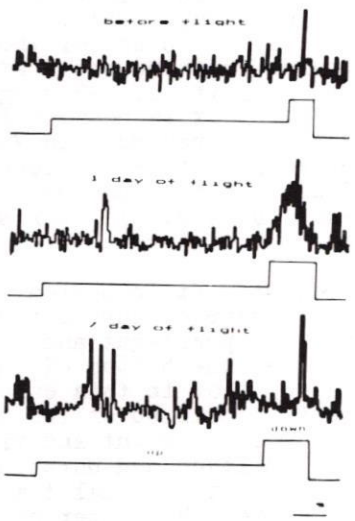


Figure 4. Integrated unit activity of MVN recorded during vertical movement of the chair ("lift" reaction). 1 and 2 - up and down movements correspondingly.

The facilitation of neuronal responses had been revealed also in these experiments in reaction to otolith stimulation. As it is seen in Figure 4, the neuronal populations, identified as canal oriented responded also to otolith signals. On the Fig. 4 examples of mass activity of non population integrated with 30 ms integration time recorded during up and down chair movements are shown. It is clearly seen that on the first day of flight the neuronal response to otolith stimulation is significantly increased. On the following flight days the reaction diminished gradually, so that on the day 7 it reached the preflight value.

Thus, exposition to microgravity in monkeys was followed by the distinct increase of vestibular neurons responses both to canal and otolith stimuli. This hypersensitivity diminished gradually and by the 5-7th days of flight the parameters of dynamic responses of MVN returned to preflight values.

References

1. Barmin V.A., Kreidich Yu.V., Kozlovskaya I.B. Influence of optokinetic stimulation and immersion on eye-head coordination. Physiologist, 26, 6, 1983.

2. Kozlovskaya I.B., Barmin V.A., Kreidich Yu.V., Repin A.A. The effects of real and simulated microgravity on vestibulo-oculomotor interaction. Physiologist, 28, 6, 51-56, 1985.

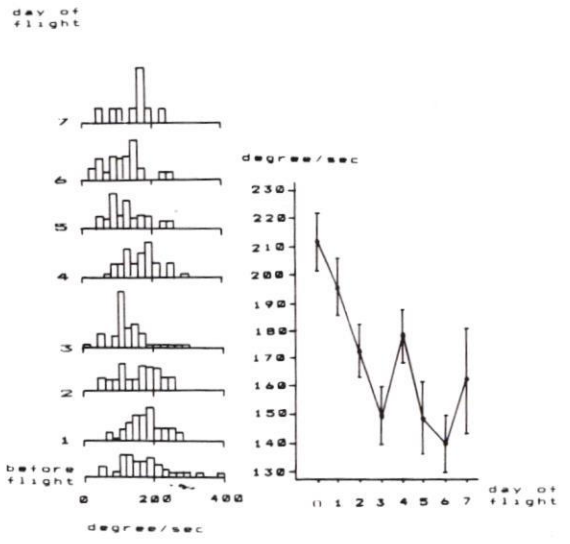


Figure 1. Distribution of head movements velocities causing saccade inhibition during GFR task performance. On the left the distributions histogram for preflight and different flight days are shown; on the right the mean values and SD shown by vertical lines are presented.

close to 1.0 starting the 2nd flight day.

The appearance of K_{vor} asymmetry in weightlessness is also matter of interest. In control the values of K_{vor} in GFR to the right and left targets were equal. In flight it was not so: in monkey "Gordyi" K_{vor} in GFR to the right target increased from the first to the 4th day of flight to 1.5, 1.7, 1.8 and 2.0 correspondingly; but in GFR to the left target the values of K_{vor} was higher reaching 1.8, 2.2, 2.1 and 2.6 accordingly. The asymmetry of K_{vor} was still recorded up to the last day of flight.

The adaptation processes to microgravity were connected in both monkeys with great decrease of head movements amplitudes and velocities: 2 hours after take off the amplitude of head movements, that was normally close to 20 degrees (21.6±1.1) decreased by 30% (15.4±0.7 degrees). On the 5-7th flight days it lowered down to 50%.

On the whole the results of this part of experiment supported and enlarged the previous ones, showing clear, that exposition to microgravity was followed by definite signs of facilitation of canal vestibulo-oculomotor reactions. The processes of adaptation in this case include two mechanisms, that are the early behavioural one, which causes the inhibition of head movements velocities and amplitudes, and the late central one, responsible for the inhibition of the transfer function in the vestibulo-oculomotor reflex arc.

This conclusion was confirmed also by the results of neuronographic studies. Decent recording of 3 neuronalpopulation

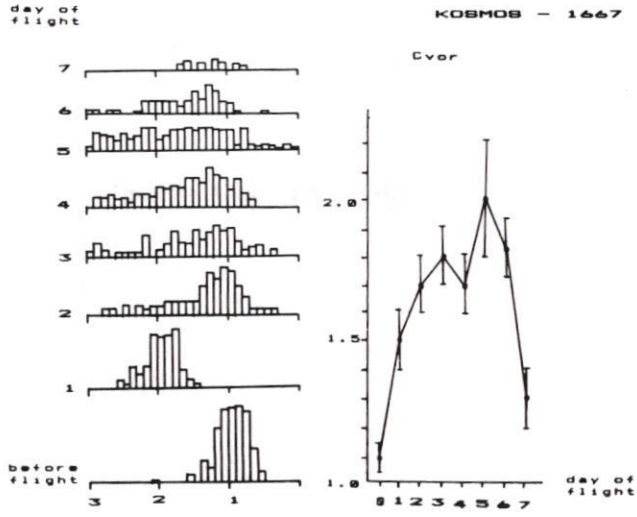


Figure 2. Distribution of K_{vor} in eye-head coordination patterns performed during GFR task on preflight and different flight days.

have been obtained in this experiment that is two in monkey "Vernyi" and one - in monkey "Gordyi". In one of the records (in monkey Vernyi) there was a stable recording of activity of 2-3 single neurons (Fig. 3). As it is seen in Fig. 3, the mass activity, recorded in Vernyi during performance of GFR includes discharges of cells, which can be easily discriminated using simple "threshold" procedures.

The frequency distribution of these single unit discharges during task performance for all preflight and flight days is shown at the bottom of the figure. It is seen, that in this case the head movements consisted of two phases - from the left to the right and vice versa of the same amplitude and duration. Dividing each phase into 4 equal time intervals we calculated the number of impulses in every of them. The number of impulses in 400 ms time interval before the movement start was served as a control. The distribution was averaged by 25 head movement for each day. The dash line on the figure shows the level of activity without head movements.

Under ground conditions the head movements to the right were followed by the frequency increase and to the left - by frequency decrease. Under microgravity the parameters of both reactions were changed starting the day 2 of flight the increase of frequency during movements to the right was accentuated; on the days 6 and 7 the characteristics of response returned to the preflight value. The decrease of frequency during movements to the left on the first records was substituted by an increase, but on the days 2-3 it reappeared and was even accentuated.

CHARACTERISTICS OF VESTIBULAR REACTIONS TO CANAL AND OTOLITH STIMULATION AT AN EARLY STAGE OF EXPOSURE TO MICROGRAVITY

M.G. Sirota, B.M. Babayev, I.B. Belo-ozerova, A.N. Nyrova, S.B. Yakushin, I.B. Kozlovskaya

Institute of Biomedical Problems, Moscow, USSR

The problem of space motion sickness (SMS) has always occupied an important place in space biology and medicine. A detailed study of the complex of symptoms of SMS in manned space flights helped to describe the phenomenology of the disorders and their time-course, to identify the factors initiating and facilitating its manifestations. Nevertheless the data - necessary and sufficient for correct theory of the pathogenesis of SMS can hardly be obtained in manned experiments. In this context the necessity and the advantage of animal studies which provide wide possibilities to standardize all the experimental conditions as well as to record directly the activity of various parts of integrative systems using invasive methods is evident. Therefore the program of experiments carried out on board of biosatellite "Cosmos-1667" included two experiments purposed to investigate the excitation in space of two parts of the vestibular apparatus, namely semicircular canals - on the model of rapid gaze fixation reaction (GFR) and otolith organ - on the model of "lift reaction" (Lift).

Methods

Under conditions of the "Lift" experiment the chair with primate was moving up and down by 50 mm. The ascending movement was slow, it lasted for 8 seconds, the descending one was fast its duration was only 1.4 seconds. So the ascend and descend accelerations in weightlessness were close to 0,0016 and 0,007 g correspondingly.

The parameters of GFR (eye-head coordination pattern) were used for studying the semicircular canals function and characteristics of vestibulooculomotor interaction (1,2).

Horizontal eye and head movements as well as the activity of neurons of medial vestibular nuclei were recorded. The semi-microelectrodes of 0.7-1.0 mOm resistance had been used for neuronal recording during space flight. These electrodes picked up primarily the mass activity of neuronal population, though in some cases the activity of some single close lying units could also be identified and analyzed.

All the date were tape recorded simultaneous recording of input signals, that is amplitudes and velocities of head movements, output characteristics - amplitudes and velocities of eye movements along with neuronal activity of vestibular nuclei provided broad possibilities for not only functional but to some extend also structural analysis of alterations caused by microgravity and adaptive processes in vestibulooculomotor interaction.

The schedule of experiment was uniform for all days of flight and included 12 "lift" stimuli presentation after which monkeys were exposed to GFR task. During each GFR test the animals performed up to 600 eye-head coordination patterns. The records taken in the same conditions 22 hours before flight served as a control.

Results

Before as well as during all days of flight the monkeys were active at working on the experimental program. However the time of its fulfilment exceeded greatly the average values in the first days of flight, reaching 118 minutes in one animal and 96 minutes in the other. Later from day to day the duration of program realization decreased progressively so that to 5-7th days it came to preflight values (25-30 minutes). The results of comparative analysis of GFR "time" characteristics and those of motor reactions allow to assume that the increase in duration of task fulfilment recorded during the first days of flight was due to the alterations of GFR accuracy. The latenies of saccades rose, the number of errors in gaze fixation and penalties in form of extra-time intervals between conditioned signals increased significantly, but the motor reaction latencies at the same time did not change.

The first records of GFR and lift reactions performed 2 hours after launch revealed the definite signs of increase of the dynamic vestibular excitability. That was shown by clear decrease of head movements velocities, causing saccade inhibition (Fig. 1), and significant increase of K_{vor} remained high (2.0, 2.5, and even 3) till 3-5 days of flight. However, along with that some smaller values, close to normal ones, began to appear since 2nd flight day. To the 6th flight day the number of GFR in which K_{vor} exceeded 2 diminished significantly. It can be assumed that variability of K_{vor} characteristic for this time interval reflected the mixture of direct microgravity effects with those of adaptive processes, aimed to normalize the eye-head coordination. It should be pointed out, that the mode of K_{vor} distribution was

CEREBELLAR ADAPTIVE FUNCTION IN ALTERED VESTIBULAR AND VISUAL ENVIRONMENTS

Masao Ito

Department of Physiology
Faculty of Medicine, University of Tokyo
Bunkyo-ku, Tokyo 113, Japan

Roles of the cerebellar flocculus in adaptive control of vestibulo-ocular reflexes are hypthesized on the basis of experimental and theoretical investigations. Neuronal mechanisms of this adaptive function of the cerebellum are explained in terms of a special type of synaptic plasticity found in the cerebellar cortex, i.e., long-term depression at parallel fiber-Purkinje cell synapses. Generalization of the hypothesis to entire problems of adaptive and learning motor control is attempted.

The current view that the cerebellum is an organ dedicated to adaptive and learning control of motor and autonomic functions is based on three lines of evidence: 1) lesion experiments on animals and clinicopathological observations on human patients, 2) structural anaylses of neuronal circuit in and around the cerebellum and discovery of synaptic plasticity in the cerebellar cortex, and 3) recording of signals from cerebellar neurons in alert, behaving animals.

We have been studying roles of the cerebellar flocculus which receives vestibular signals via mossy fiber pathways and visual signals via climbing fiber pathways, while it projects Purkinje cell axons to relay neurons of vestibulo-ocular reflexes. These structural aspects predict that the flocculus adaptively modifies vestibulo-ocular reflexes by referring to retinal errors during inadequate performance of vestibulo-ocular reflexes, represented by visual climbing fiber signals. Remarkable adaptation indeed occurs in the horizontal canal-ocular reflex under sustained visual-vestibular interaction, and this adaptation is abolished by lesion of the flocculus, or of the visual pathway to the flocculus via the inferior olive. Recording from floccular Purkinje cells further demonstrated that vestibular mossy fiber responsiveness of floccular Purkinje cells indeed altered in parallel with adaptation of the horizontal canal-ocular reflex. Thus, the available evidence supports the view that the flocculus is the site of adaptive control of the horizontal canal-ocular reflex.

Paired electrical stimulation of the climbing and mossy fiber pathways to the flocculus indeed causes a sustained depression of the vestibular mossy fiber responsiveness of floccular Purkinje cells. The site of this effect is located at synapses from parallel fibers (axons of cortical granule cells) to Purkinje cells. This long-term depression (LTD) can be induced by paired stimulation of parallel fibers and climbing fibers, or by iontophoretic application of L-glutamate, a putative neurotransmitter of parallel fibers, to Purkinje cells in conjunction with climbing fiber stimulation. LTD appears to be a physiological counterpart of memory in the cerebellum, and mechanisms of this synaptic plasticity have been investigated in both in vivo and in vitro slice preparations. It has been shown that occurrence of LTD depends on Ca influx into Purkinje cell dendrites caused by climbing fiber impulses, and that the depression is due to desensitization of glutamate receptor in parallel fiber-Purkinje cell synapses.

When the horizontal canal-ocular reflex performs inadequately, retinal errors thereby induced may create climbing fiber signals to the flocculus, which would in turn cause LTD in parallel fiber-Purkinje cell synapses active at that moment. Vestibular mossy fiber connections to floccular Purkinje cells, if active at a moment of inadequate reflex performance, would then be disconnected; the reflex performance would be modified toward minimization of retinal errors. Fujita's simulation model of the cerebellar circuit consistent with this view successfully reproduced Gonshor and Melvill Jones' human data of the horizontal canal-ocular reflex adaptation, and so supports the above view.

Similar adaptive mechanisms may apply to vertical and rotatory canal-ocular reflexes, maculo-ocular reflexes and optokinetic eye movements. Even though evidence is less complete, it is probable that the flocculus is also the site of adaptive control of these reflexes. Learning phenomena in more complex motor functions such as locomotion and voluntary limb movements may also be underlaid by similar cerebellar adaptive mechanisms.

Ref. M. Ito The Cerebellum and Neural Control. Raven Press, New York, 1984.

rabbit's horizontal vestibulo-ocular reflex induced by sustained head rotation combined with visual stimulation. **Proc. Japan Acad.** 50: 85-89, 1974
13) Robinson DA: Adaptive gain control of vestibuloocular reflex by the cerebellum. **J. Neurophysiol.** 39: 954-969, 1976
14) Sato Y, Kato I, Kawasaki T, Mizukoshi K, Hayano M: Failure of fixation suppression of caloric nystagmus and ocular motor abnormalities. **Arch. Neurol.** 37: 35-38, 1980
15) Takemori S, Cohen B: Loss of visual suppression of vestibular nystagmus after flocculus lesions. **Brain Res.** 72: 213-224, 1974
16) Sato Y, Kawasaki T, Ikarashi K: Zonal organization of the floccular Purkinje cells projecting to the vestibular nucleus in cats. **Brain Res.** 232: 1-15, 1982
17) Sato Y, Kawasaki T, Ikarashi K: Zonal organization of the floccular Purkinje cells projecting to the group y of the vestibular nuclear complex and the lateral cerebellar nucleus in cats. **Brain Res.** 234: 430-434, 1982
18) Angaut P, Brodal A: The projections of the "vestibulocerebellum" onto the vestibular nuclei in the cat. **Arch. ital. Biol.** 105: 441-479, 1967
19) Haines DE: Cerebellar corticonuclear and corticovestibular fibers of the flocculonodular lobe in a prosimian primate (Galgo senegalensis). **J. Comp. Neurol.** 174: 607-630, 1977
20) Langer T, Fuchs AF, Chubb MC, Scudder CA, Lisberger SG: Floccular efferents in the rhesus macaque as revealed by autoradiography and horseradish peroxidase. **J. Comp. neurol.** 235: 26-37, 1985
21) Carpenter MB, Cowie RJ: Connections and oculomotor projections of the superior vestibular nucleus and cell group 'y'. **Brain Res.** 336: 265-287, 1985
22) Sato Y, Kawasaki T: Functional localization in the three floccular zones related to eye movement control in the cat. **Brain Res.** 290: 25-31, 1984
23) Baker R, Precht W, Llinas R: Cerebellar modulatory action on the vestibulo-trochlear pathway in the cat. **Exptl. Brain Res.** 15: 364-385, 1972
24) Fukuda J, Highstein SM, Ito M: Cerebellar inhibitory control of the vestibulo-ocular reflex investigated in rabbit IIIrd nucleus. **Exptl. Brain Res.** 14: 511-526, 1972
25) Highstein SM: Synaptic linkage in the vestibulo-ocular and cerebello-vestibular pathways to the VIth nucleus in the rabbit. **Exptl. Brain Res.** 17: 301-314, 1973
26) Sato Y, Yamamoto F, Shojaku H, Kawasaki T. Neuronal pathway from the floccular caudal zone contributing to vertical eye movements in cats - role of group y nucleus of vestibular nuclei. **Brain Res.** 294: 375-380, 1984
27) Yamamoto F, Sato Y, Kawasaki T: The neuronal pathway from the flocculus to the oculomotor nucleus: an electrophysiological study of group y nucleus in cats. **Brain Res.** 371: 350-354, 1986
28) Sato Y, Kawasaki T: Target neurons of floccular caudal-zone inhibition in y-group nucleus. **J. Neurophysiol.** (in press).
29) Baker R, Highstein SM: Vestibular projections to medial rectus subdivision of oculomotor nucleus. **J. Neurophysiol.** 41: 1629-1646, 1978
30) Gacek RR: Anatomical demonstration of the vestibulo-ocular projections in the cat. **Acta Oto-laryng.** Suppl. 293: 1-63, 1971
31) Highstein SM: Organization of the inhibitory and excitatory vestibulo-ocular reflex pathways to the third and fourth nuclei in rabbit. **Brain Res.** 32: 218-224, 1971
32) Highstein SM: The organization of the vestibulo-oculomotor and trochlear reflex pathways in the rabbit. **Exptl. Brain Res.** 17: 285-300, 1973
33) Highstein SM, Reisine H: Synaptic and functional organization of vestibulo-oculomotor reflex pathways. **Progr. Brain Res.** 50: 431-442, 1979
34) Tarlov E: Organization of vestibulo-oculomotor projections in the cat. **Brain Res.** 20: 159-179, 1970
35) Kasahara M, Uchino Y: Bilateral senicircular canal inputs to neurons in cat vestibular nuclei. **Exptl. Brain Res.** 20: 285-296, 1974.
36) Wilson VJ, Gacek, RR, Uchino Y, Susswein AJ: Properties of central vestibular neurons fired by stimulation of saccular nerve. **Brain Res.** 143: 251-261, 1978.

to the y-group nucleus (3-6). Polysynaptic inputs to the dorsal-y-group nucleus may also originate not from the semicircular canals but from the otolith organs, since 1) the vestibular nuclear neurons activated by ipsilateral ampullar nerve stimulation were inhibited by contralateral ampullar nerve stimulation (35), while those activated by ipsilateral macular nerve stimulation were also activated by contralateral macular nerve stimulation (36), and 2) target neurons in the dorsal-y-group nucleus activated by stimulation of the ipsilateral vestibular nerve were also activated by stimulation of the contralateral vestibular nerve (28).

Conclusion

These findings strongly suggest that the dorsal-y-group nucleus is functionally different from the ventral-y-group nucleus. The dorsal-y-group nucleus receives floccular caudal-zone inhibition and transmit otolith inputs to the contralateral caudal half of the oculomotor nucleus innervating superior rectus and inferior oblique muscles through the 'crossing ventral tegmental tract'. Maculo-ocular reflex arc through the dorsal-y-group nucleus is composed of, at least, 4 neurons. While the ventral-y-group nucleus is free from floccular inhibition and transmit gravity inputs from the saccule to the other structures of the brain including the flocculus. These conclusions are sumarized in Fig. 3.

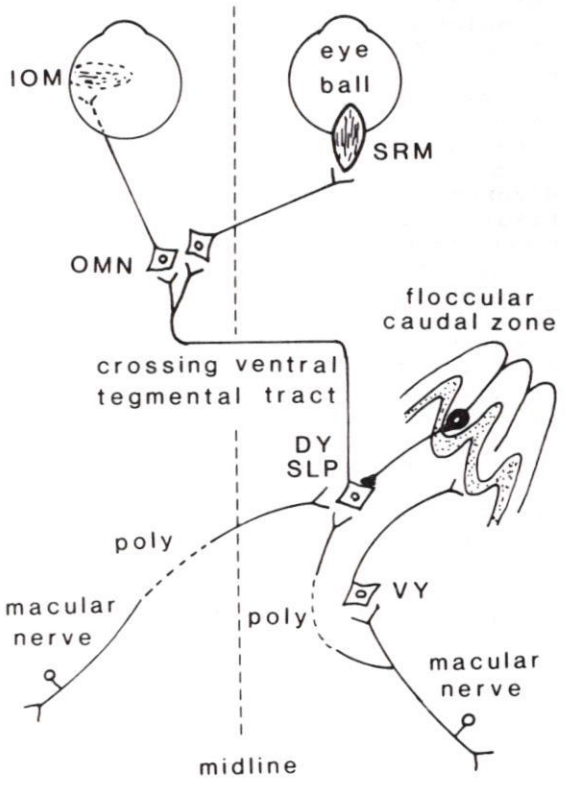


Fig. 3. Summary diagram illustrating organization of maculo-ocular pathways via y-group nucleus and its relevance to cerebellar flocculus. Dotted area in the flocculus stands for a granular layer. Inhibitory Purkinje cell is filled in black. Abbreviations: **IOM**, inferior oblique muscle; **OMN**, oculomotor nucleus; **poly**, polysynaptic; **SRM**, superior rectus muscle; **DY**, **SLP**, and **VY**, see abbreviations in Fig. 2. (Modified from Sato and Kawasaki, J. Neu rophysiol. in press).

References

1) Brodal A. Pompeiano O: The vestibular nuclei in the cat. **J. Anat.** 91: 438- 454, 1957
2) Fuse G: Die innere Abteilung des Kleinhirnstieles (Meynert I, A. K.) und der Deitersche Kern, **Arb. Hirnanat. Inst. (Zurich)** 6: 29-267, 1912
3) Carleton SC, Carpenter MB: Distribution of primary vestibular fibers in the brainstem and cerebellum of the monkey. **Brain Res.** 294: 281-298, 1984
4) Gacek RR: The course and termination of first order neurons supplying vestibular endorgans in the cat. **Acta Oto-laryngol.**, Suppl. 254: 1-66, 1969
5) Hwang JC, Poon WF: An electrophysiological study of the sacculoocular pathways in cats. **Jap. J. Physiol.** 25: 241-251, 1975
6) Kevetter GH, Perachio AA: Central projections of vestibular afferents innervating the macula of the saccule in gerbil. **Neurosci. Lett.** 51: 7-12, 1984
7) Graybiel AM, Hartwieg EA: Some afferent connections of the oculomotor complex in the cat: an experimental study with tracer techniques. **Brain Res.** 81: 543-551, 1974
8) Stanton GB: Afferents to oculomotor nuclei from area "Y" in Macaca mulatta: an anterograde degeneration study. **J. Comp. Neurol.** 192: 377-385, 1980
9) Steiger H-J, Buttner-Enneve JA: Oculomotor nucleus afferents in the monkey demonstrated with horseradish peroxidase. **Brain Res.** 160: 1-15, 1979
10) Yamamoto M, Shimoyama I, Highstein SM: Vestibular nucleus neurons relaying excitation from the anterior canal to the oculomotor nucleus. **Brain Res.** 148: 31-42, 1978
11) Ito M, Jastreboff PJ, Miyashita Y: Specific effects of unilateral lesions in the flocculus upon eye movements in albino rabbits. **Exptl. Brain Res.** 45: 233-242, 1982
12) Ito M, Shiida T, Yagi N, Yamamoto M: The cerebellar modification of

conjugate eye movement, while destruction of the y-group nucleus eliminated the downward eye movement evoked from the floccular caudal-zone (26).

Efferent projections of target neurons of floccular caudal-zone inhibition were then studied (27). Target neurons were identified by observing cessation of spontaneous firings following electrical stimulation of the floccular caudal-zone. The cessation started at 1.0-2.0 ms after floccular caudal-zone stimulation and lasted for 10-40 ms. Target neurons showed antidromic responses to stimulation of the contralateral oculomotor nucleus innervating superior rectus muscles contralateral to the motoneuron and inferior oblique muscles ipsilateral to the motoneuron (27), suggesting efferent projections of target neurons to the oculomotor nucleus innervating superior rectus and inferior oblique muscles. Other investigators also reported projections of the y-group neurons to the oculomotor nucleus (5, 7-9). Therefore, the neuronal pathway responsible for mediation of the downward eye movement evoked by floccular caudal-zone stimulation may be composed of at least three neurons; 1) Purkinje cells in the floccular caudal-zone, 2) target neurons in the y-group nucleus and 3)motoneurons innervating superior rectus and inferior oblique muscles.

We then investigated axonal trajectories of target neurons (28). During extracellular recording of a single target neurons, a glass-insulated tungsten microelectrode was inserted systematically into the brain stem for microstimulation, searching for antidromic responses. Low threshold points for antidromic activation were mapped. The axons of target neurons pass through a region closely ventral to the lateral part of the brachium conjunctivum, continue rostrally in a region between the brachium conjunctivum and the lateral lemniscus, arch medially around the rostral part of the nucleus reticularis tegmenti pontis, cross the midline, continue to the contralateral side by about 1.5 mm lateral from the midline, arch rostrally, run in the central tegmental field on the contralateral side, arch dorsomedially around the caudal pole of the red nucleus, and enters the contralateral oculomotor nucleus from the ventrolateral side. In the caudal half of the contralateral oculomotor nucleus, the axons of target neurons branch out and terminate. This neuronal tract via ventral part of the pontine tegmentum is distinct from classically established vestibulo-oculomotor tract (8, 10, 29-34) via the medial longitudinal fasciculus, the brachium conjunctivum and the ascending tract of Deiters. We call our tract the 'crossing ventral tegmental tract' (28).

Functional differences between dorsal-y-group and ventral-y-group nucleus

On cytoarchitectural grounds the y-group nucleus is divided into two subdivisions; the dorsal subdivision of the y-group (dorsal-y-group) of loosely packed medium sized neurons and the ventral subdivision of the y-group (ventral-y-group) of densely packed fusiform neurons (Fig. 2) (33).

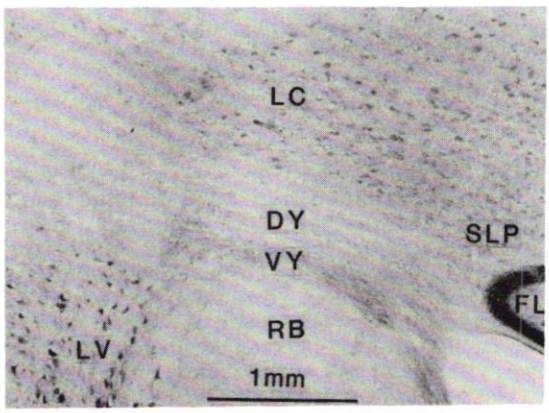


Fig. 2. Photograph of a frontal section through the y-group nucleus showing that the y-group nucleus is located between the lateral cerebellar nucleus (LC) and the restiform body (RB), and that the y-group nucleus is divied into two subdivisions: dorsal-y-group (DY) of loosely packed neurons and ventral-y-group (VY) of densely packed ones. Abbreviations: **LV**, lateral vestibular nucleus; **SLP**, subnucleus lateralis parvocellularis of lateral cerebellar nucleus; **FL**, flocculus.

Differences in neuronal connections between the dorsal-y-group and ventral-y-group nucleus were investigated by observing responses of single dorsal-y-group and ventral-y-group neurons to electrical stimulation of the oculomotor nucleus, the floccular caudal-zone and the primary vestibular nerve (28). Target neurons of floccular caudal-zone inhibition were located in the dorsal-y-group nucleus and the adjacent medial part of the subnucleus lateralis parvocelluralis of lateral cerebellar nucleus. Most neurons in these nuclei project to the contralateral oculomotor nucleus, and about half of these neurons receive polysynaptic inputs from the vestibular nerve on both sides. On the other hand, most neurons in the ventral-y-group nucleus receive monosynaptic inputs from the ipsilateral vestibular nerve, and some of these neurons project to the flocculus. Monosynaptic inputs to the ventral-y-group nucleus may originate from the saccule, since previous anatomical investigations demonstrated saccular nerve projections

ORGANIZATION OF MACULO-OCULAR PATHWAYS VIA Y-GROUP NUCLEUS AND ITS RELEVANCE TO CEREBELLAR FLOCCULUS IN CATS

Yu Sato and Tadashi Kawasaki

Department of Physiology
Faculty of Medicine
Toyama Medical and Pharmaceutical University
Toyama, Toyama 930-01, Japan

The y-group nucleus is a subnucleus of the vestibular nuclear complex, and is situated dorsal to the restiform body and ventral to the lateral cerebellar nucleus (1,2). It receives afferent projections from the saccule (3-6) and projects to the oculomotor nucleus (5, 7-10). Electrical stimulation of the saccule produced upward eye movement (5). Therefore, there is a possibility that the y-group nucleus mediate maculo-ocular reflex originating from the saccule. On the other hand, the cerebellar flocculus is known to modulate vestibulo-ocular reflex (11-15). The y-group nucleus is one of the 3 major target nuclei receiving floccular inhibition (16,17). The present paper reviewed maculo-ocular pathways via y-group nucleus and its relevance to the flocculus.

Neuronal pathway from the flocculus to the oculomotor nucleus via y-group nucleus

Previous anatomical studies have shown that the y-group nucleus receives projections from the cerebellar flocculus (18-20). We studied topographycal localization of floccular Purkinje cells projecting to the y-group nucleus in cats, using the method of retrograde axonal transport of horseradish peroxidase (HRP). Following HRP injection into the y-group nucleus, labeled Purkinje cells were found in the caudal one-third of the ipsilateral flocculus (17). We call this caudal area of the flocculus the caudal-zone (Fig. 1 A and B). An additional experiment in cats by Carpenter and Cowie (21) also supported our view that the y-group nucleus receives projections from the floccular caudal-zone.

The floccular caudal-zone was then electrically stimulated in ketamine-anesthetized cats (22). Slow and smooth downward conjugate eye movement was elicited (Fig. 1C). Since it has been established that the floccular Purkinje cell has the inhibitory effect on the

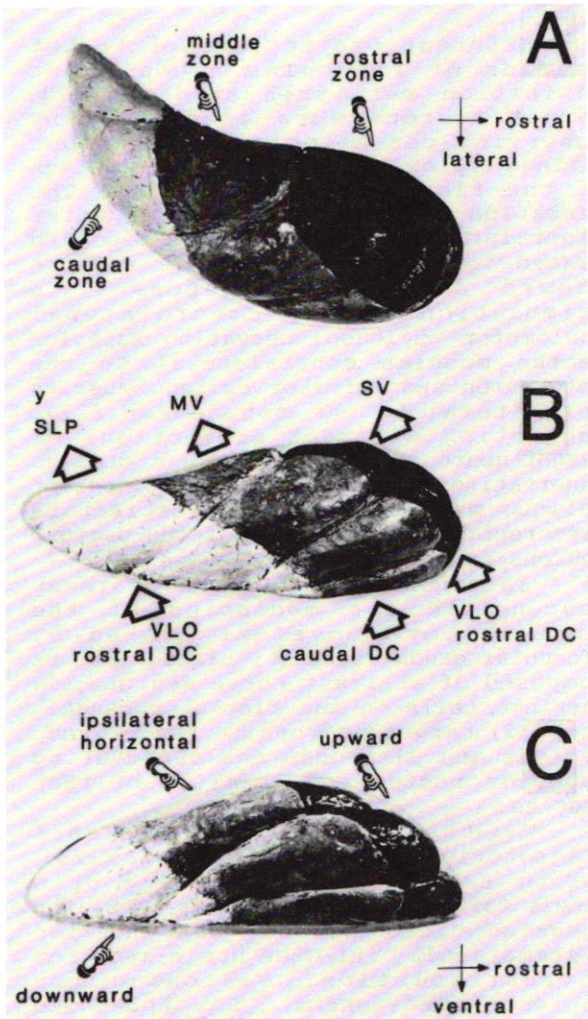


Fig. 1 Photographs of a clay model of the right flocculus (A, top view; B, oblique view; C, side view). The cat's cerebellar flocculus is not a single entity but can be divided into three zones (A). Each zone has different neuronal connections (B). Direction of eye movement elicited by electric stimulation of each zone is different (C). Abbreviations: **DC**, dorsal cap of inferior olive; **MV**, medial vestibular nucleus; **SLP**, subnucleus lateralis parvocellularis of lateral cerebellar nucleus; **SV**, superior vestibular nucleus; **VLO**, ventrolateral outgrouth of inferior olive; **y**, y-group nucleus of vestibular nuclear complex. (Modified from Sato and Kawasaki, Brain Res. 1984).

activities of the vestibular nuclear neurons (23-25), we suggested that the downward eye movement may be elicited by Purkinje cell inhibition on the y-group neurons (22). This view was supported indirectly by our next experiments. Electrical stimulation of the y-group nucleus elicited slow and smooth upward

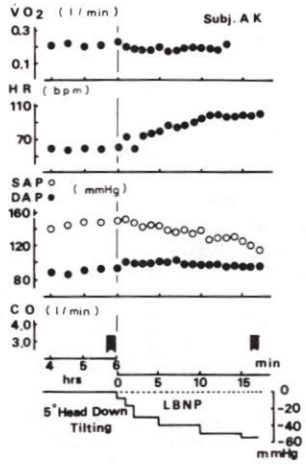


Fig.1, Protocol and Typical time courses of oxgen uptake(VO2), heart rate (HR), systolic arterial pressure(SAP), diastolic arterial pressure(DAP), and cardiac output (CO)in the second experiment in subj. AK

mm Hg of all subjects in HDT resting experiment (HDTR) but the average 53 mm Hg in supine experiment (SR). There was significantly different between the two averages in HDTR and SR (Fig. 2). Tolerable time performed in grade of LBNP load was average 13 minutes of all subjects in HDTR but the average 17 minutes in SR. There was also significantly different between the two averages in HDTR and SR (Fig. 3). These

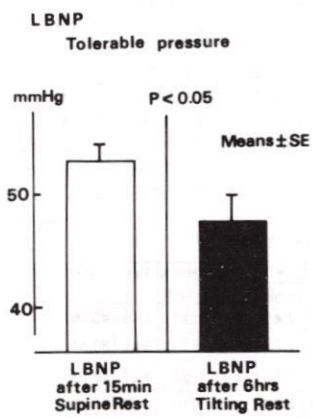


Fig.2, Comparing between the average values of LBNP tolerable pressure in all subjects in the first and second experiments.

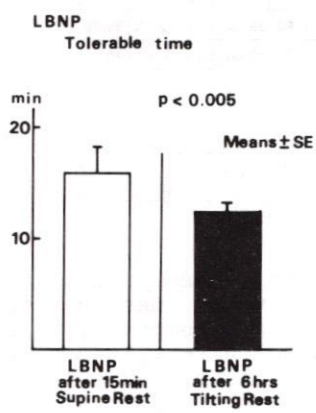


Fig.3, Comparing between the average values of LBNP tolerable time in all subjects in the first and second experiments.

results mean that LBNP tolerance decreases after weightlessness stimulated more than it in SR.

In Fig. 4 , shows the relationships between LBNP tolerable pressure and VO2max, and LBM. The tolerable pressure was siguificantly correlated to VO2max($p<0.05$), but

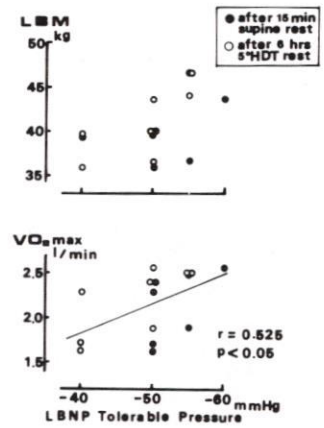


Fig.4, Relationships between LBNP tolerable pressure and lean body mass(LBM), and maximum aerobic power (VO2max), using all values in the two experiments.

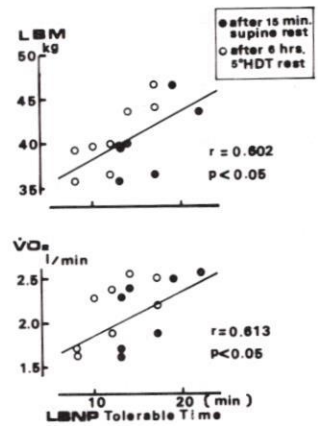


Fig.5, Relationships between LBNP tolerable time and lean body mass(LBM), and maximum aerobic power (VO2max), using all values in the two experiments.

not to LBM. However, LBNP tolerable time was significantly correlated to both LBM and VO2max ($p<0.05$)(Fig.5). Further, LBM was correlated to stroke volume(SV), mean arterial pressure (MAP) and systolic arterial pressure(SAP) given at the final measuring point during LBNP in each subject ($p<0.05$) as well as to VO2max ($P<0.01$).

Discussion

The decrease in LBNP tolerance after the adaptation to weightlessness stimulated is due to increasing sensitivity to sympathetic nervous system, because there was more rapidly reaching to the cardiovascular criterion for LBNP tolerance in HDTR.

LBNP tolerance was significantly correlated to LBM as well as VO2max. The LMB was significantly correlated to SV, MAP, and SAP obtained at the LBNP tolerable time. These facts means that LBM suggested total muscle mass in each subject is a factor of making to decrease the sensitivity of cardiovascular functions to the gravity in woman.

In conclusion, the present results could give so an import evidence that in woman the LBNP tolerance is affected by LBM as well as maximum aerobic power.

Reference

Raven, P.B., et al., J.Appl.Physiol.:Res. En.Ex.Physiol. 56(1):138-144, 1984

EFFECTS OF LEAN BODY MASS AND AEROBIC POWER ON LBNP TOLERANCE IN WOMAN

Shigeyo TORIKOSHI[+], Kikuko YOKOZAWA[+], Miyako INAZAWA[+], Katsuko ITOH[++], Yasuko FUKASE[+++], Junko NAGANO[+], Yoji SUZUKI[++++]

+Lab. of Human Physiol., Tokyo Woman's Christian Univ., 2-6-1, Zenpukuji, Suginami-ku, Tokyo, Japan 105, ++Tsurumi Univ., +++Rikkyo St. Margurite Woman's College, ++++Lab. of Health Adoministration, Faculty of Medicine, Univ. of Tokyo, 3-7-1, Hongo, Bunkyo-ku, Tokyo, Japan 113

The present study has been investigated whether lean body mass (LBM) is a factor of the tolerable capacity against LBNP or not in 8 female students. A LBNP condition was gradually loaded after a 15 min supine rest(SR) and 6 hrs 5° head-down tilting rest(HDTR), respectively. LBM was determined by the body density in a 33 C° water. The criterions for the LBNP tolerance were reaching both over 20 bpm increasing HR form each resting level and below 20 mm Hg decreasing pulse pressure, or having some what bad feeling in subjects. In the experiments, VO2, HR, cardiac output(CO), and arterial blood pressure were measured. Although there was the decrease in the LBNP tolerance in HDTR as comparing with the case in SR, LBM was similarly correlated to VO2max($p<0.01$), and also to LBNP tolerance time and pressure($p<0.05$) as well as to systolic and mean pressure($p<0.05$). The results evidenced that LBM was an important factor of LBNP tolerance as well as VO2max in young woman.

In the previous studies, it has been evidenced that VO2mas is an important factor in tolerance capacities against gravitational stress. The VO2max is inversely correlated to % Fat per body weight. There is so a possiblity that the tolerance against the gravity should be affected by the lean body mass which suggests the total mascle mass in each person, because the mascle mass is a factor supporting venous return with strengthing muscle pump and increasing arterial blood pressure.

In the present study, lean body mass in the body composition was investigated in young woman. Then, the relationships between lean body mass and VO2max, LBNP tolerance, and cardiovascular responses to LBNP stimulated were studied.

Subjects and Methods.

8 female students participated to the present study as subjects. Their age was an average of 22 years old. The averaged body weight in the subjects was 52.0 kg, body hight 158 cm, and VO2max/weight 41.78 ml/kg/min. These characteristics of the subjects were included in Japanese same standard levels of the same age woman.

In their body compositions, the averaged % fat of weight was 21.8 % and thus the lean body mass (LBM) 40.64 kg.

Ahead of the start of the study, the subjects were introduced the purpose and methods of experiments.

The first experiment determined the body composition in each subject by measuring a body density in a 33 C water, by which a % of fat in the body weight could be estimated. The second experiment measured the tolerance against lower body negative pressure(LBNP) in the supine position, in which the subjects rested for 15 minutes.The third experiment also investigated LBNP tolerance, where the subjects were exposured to a -5 head-down tilting (HDT) for 6 hours before LBNP load. In the last two experiments, LBNP was loaded in order to a system, which was giving the subjects -8 mm Hg for one minutes,-16 mm Hg for one minutes,-30 minutes for 3 minutes, -40 mm Hg for 5 minutes, -50 mm Hg for 5 minutes, -55 mm Hg for 3 minutes, and finally -60 mm Hg for 3 minutes, continuously, using a lower body negative pressure box. The criterions for the LBNP tolerance determined in the present study were that increasing HR had reached over 20 beats/min more than a resting level adaped to supine position and the 6 hours HDT and at the same time pulse pressure was decreasing below 20 mm Hg, or that the subjects had maken a sense some what bad feeling. In Figure 1 the experimental protocol and typical time courses of measurements in the 2nd experiment given in subject AK are shown. The measurements were oxygen uptake (VO2), HR, cardiac output (CO), and arterial blood pressure through all experiments. VO2 was determined by a metabolic analysing system which was constructed with a mass-spectrometer, gas flowmeter, and computer. CO was measured by means of an athetylen gas rebreathing, which was analysed by a mass spectrometer. HR was counted from the records of chest leading EKG by a computer. Arterial blood pressure was measured by an auscultation method in the left upper-arm.

SUBJECTS

Subj.	Age yrs	Ht cm	Wt kg	VO_2max l/min	VO_2max ml/kg/min	HRmax bpm	Fat %	LBM kg
M I	24	160.0	51.0	2.49	48.82	193	13.8	43.96
N N	22	152.0	46.5	1.88	40.43	190	21.6	36.46
A M	20	162.0	56.5	2.55	45.13	194	23.0	43.53
A K	22	164.0	59.0	2.50	42.37	196	21.2	46.49
M S	22	161.0	53.0	2.28	43.02	191	25.2	39.64
M A	21	157.0	54.0	1.71	31.67	205	27.2	39.31
H F	21	148.0	46.0	1.62	35.22	194	22.2	35.79
M K	21	159.0	50.0	2.38	47.60	184	20.1	39.93

Table 1, Characteristics of each subjest participated in the present study, who are normal female students.

Results

Tolerable pressure against LBNP which was determined as LBNP value given at reaching a LBNP tolerance criterion was average 47

INCREASED CHOLINERGIC ACTIVITY DURING GRAVITATION-INDUCED PRE-SYNCOPE IN MAN

KÅRE SANDER-JENSEN, JESPER MEHLSEN, CARSTEN STADEAGER, NIELS J. CHRISTENSEN, THUE W. SCHWARTZ, JØRGEN WARBERG, AND PETER BIE

Panum Institute, Hvidovre and Herlev Hospital
University of Copenhagen
Copenhagen, Denmark

The influence of vagal activity on heart rate changes was measured during central hypovolemia induced by lower body negative pressure in six healthy subjects before and after cholinergic blockade with atropine. The results indicate that normotensive central hypovolemia is characterized by increases in indices of sympathetic activity. However, hypotensive central hypovolemia was characterized by a slowing of the heart rate and increases in indices of vagal activity, which was abolished after administration of atropine.

It is generally accepted that gravitation-induced progressive central hypovolemia in man initially is characterized by an increased sympathetic activity (1,3,6). Further decrease in venous return may bring about an abroupt fall in arterial pressure and heart rate (HR) - a vasodepressor syncope is induced. The condition is characterized by arterial hypotension, slowing of the heart, and increases in indices of cholinergic activity (6). Atropine attenuates the decrease in HR and tend to improve the tolerance to central hypovolemia by delaying the onset of the syncope (2). In addition indices of a general increase in vagal, cholinergic activity has been found in emotional (5) as well as tilt-induced syncope in man (6).

The aim of the present study was to evaluate the qualitative changes - especially the increase in cholinergic activity - when the central hypovolemia passes through a normotensive to a hypotensive stage.

Results

The influence of vagal activity on (HR) changes was evaluated during gravitational stress induced by lower body negative pressure in six healthy subjects before and after cholinergic blockade with atropine (0.03 mg per kg body weight). Suction of 55 mmHg resulted intially in an increase in HR (55 ± 4 to 90 ± 5 beats/min), and a decrease in mean arterial pressure (94 ± 4 to 81 ± 5 mmHg), central venous pressure (7 ± 1 to -3 ± 1 mmHg), and cardiac output (6.1 ± 0.5 to 3.7 ± 0.1 l/min). Arterial plasma epinephrine increased from 7 ± 1 to 18 ± 4 pg/ml, and norepinephrine from 27 ± 2 to 55 ± 6 pg/ml.

However, after 8.2 ± 2.3 min mean arterial pressure suddenly dropped to 41 ± 7 mmHg and concomitantly the initially increased HR decreased to 57 ± 3 beats/min. Plasma catecholamines were unchanged, while plasma pancreatic polypeptide increased, indicating an increase in vagal, cholinergic activity. The hypotensive episode could be repeated after atropine injection - although without bradycardia or increase in pancreatic polypeptide. Atropine did not change the time until the onset of syncopal symptoms (8.2 +- 2.3 min), and atropine did not change the degree of hypotension.

Conclusions

The observations support the view that arterial pressure during gravitational stress is maintained by a decrease in pulse pressure stimulating the sympathetic system, resulting in an increase in HR. In addition they show that the subsequent decreased HR associated with severe hypotension is caused by a cholinergic mechanism - presumably increased vagal activity. The observed bradycardia may be evoked, when the left ventricle of the heart - under a high sympathetic activity - is squeezed around an almost empty chamber. Thus the cardiac depressor reflex may serve as a protective mechanism causing a brake on the heart allowing for an improved diastolic filling in situations when venous return is critically reduced (4).

References

1. BJURSTEDT H., G. ROSENHAMER, AND G. TYDEN. Acceleration stress and effects of propranolol on cardiovascular responses. Acta Physiol. Scand. 90: 491-500, 1974.

2. MURRAY R.H, AND S. SHROPSHIRE. Effects of atropine on circulatory responses to lower body negative pressure and vasodepressor syncope. Aerospace Med. 41: 717-722, 1970.

3. MURRAY, R.H., L.J. THOMPSON, J.A. BOWERS, AND C.D. ALBRIGHT. Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. Am. Heart J. 68: 799-811, 1968.

4. OBERG B., AND S. WHITE. The role of vagal cardiac nerves and atrial baroreceptors on the circulatory adjustments to hemorrhage in cat. Acta Physiol. Scand. 80: 395-403, 1970.

5. SANDER-JENSEN K., S. GARNE, AND T.W. SCHWARTZ. Pancreatic polypeptide release during emotionally induced vasovagal syncope. Lancet ii: 1132, 1985.

6. SANDER-JENSEN K., N.H. SECHER, A. ASTRUP, N.J. CHRISTENSEN, J. GIESE, T.W. SCHWARTZ, J. WARBERG, AND P. BIE. Hypotension induced by passive head-up tilt: endocrine and circulatory mechanisms. Am. J. Physiol. (Regulatory, Integrative Comp. Physiol.) 251: R742-R748, 1986.

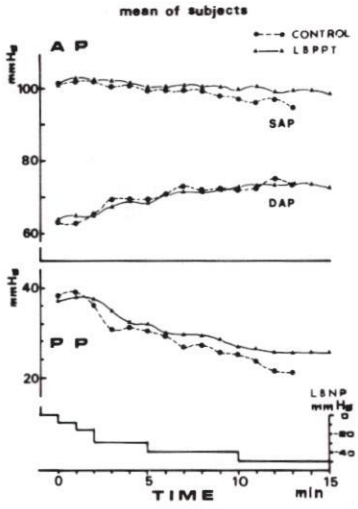


Fig. 1, Protocol of LB NP procedure and time courses of systolic arterial pressure(SAP), diastolic arterial pressure (DAP), and pulse pressure (PP) during LBNP in supine position. Control: no wearing LBPPS LBPPT: wearing LBPPS

ssure(PP) were higher in LBPPS in EX.I.

In Ex.II, VO2, HR, and mean arterial pressure (MAP) at all stages during experiments were not so different between LBPPS and N-LBPPS, but CO,and SV were higher and arteriovenous O2 difference (A-V O2 Diff.) was lower during exercise and recovery in LBPPS than in N-LBPPS (Fig.2). In Fig.3, SV was significantly correlated to CO, MAP and A-V O2 Diff, but not VO2 during exercise, using all values given in all subjects. An importance is the fact that these reglession lines of CO and MAP were shifted to higher position, and the line of A-V O2 Diff was done to lower position in LB

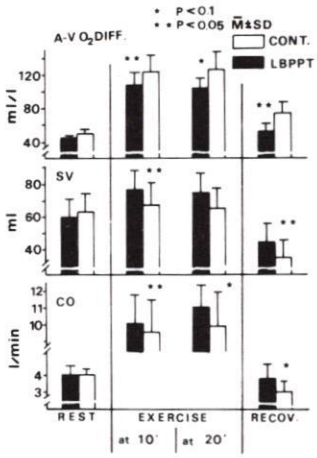


Fig. 2, Mean values of cardiac output (CO), stroke volume (SV),and arteriovenous O2 difference(A-V O2 Diff) given at rest, exercise and recovery in all subjects. Control: no wearing LBPPS LBPPT:wearing LBPPS

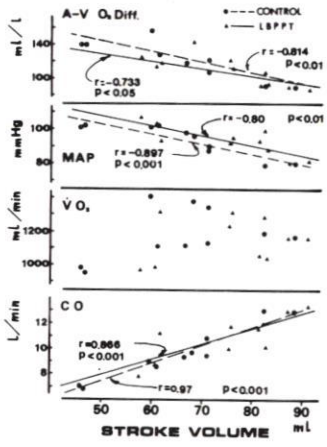


Fig. 3, Relationships between stroke volume(SV) and cardiac output (CO), VO2, mean arterial pressure(MAP) and arteriovenous O2 difference (A-V O2 Diff) during 60 % VO2 max pedalling in all subjects Control: no wearing LBPPS LBPPT: wearing LBPPS

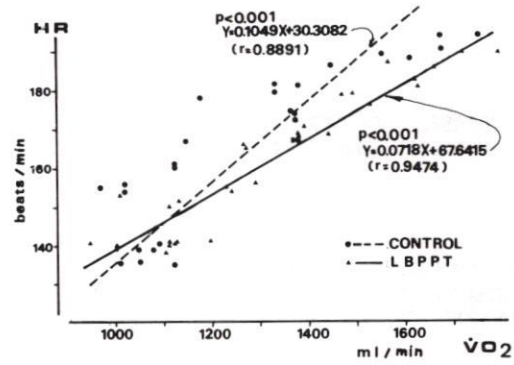


Fig. 4, Relationship between VO2 and heart rate (HR) during running, Control:no wearing LBPPS LBPPT:wearing LBPPS

PPS than in N-LBPPS.

In Ex.III, VO2 during running was not different between LBPPS and N-LBPPS neverthless exercise intensities, but HR was sigunificantly lower in LBPPS(p 0.01). In Fig. 4, the relationship between VO2 and HR during running was significantly correlated, using the values given in the two exercise and in all subjects. An important observation is that the regression line had lower slope and position in LBPPS than in N-LBPPS.

Discussion

The results given in Ex.I shows that wearing LBPPS make HR decrease and PP maintain against gravity stimulated by LBNP. This means that a 20 mm Hg LBPPS is useful to accelerate venous return and thus to keep the prolonged standing position.

Further, the useful LBPPS could applys to defend cardiovascular reflex to gravity during upright exercise and post-exercise, because CO and SV were increased and A-V O2 Diff was decreased during exercise and recovery by wearing LBPPS, and also because despite the same SV during exercise, MAP was higher and A-V O2 Diff was lower at wearing LBPPS.

These facts are also evidenced during running by that despite the same VO2 during moderate or heavy running, HR vs VO2 was lowered by wearing LBPPS in Ex.III. VO2/HR, that is oxygen pulse, suggests SV, so wearing LBPPS could bring the increase in SV during running.

In conclusion, a 20 mm Hg LBPPS gives a useful function to lower the defence reflex of cardiovascular responses to the gravity stimulated. This is carried out by that wearing LBPPS makes to push up blood volume pooled in the lower body part with likely pumping muscle and thus to increase venous return in the upright position in young woman.

Reference

1. Suzuki, Y., Blood pressure related with muscle activity and/or carotid artery compressure during mild supine exercise exposed to LBNP, Supple. to The Physiologist, 27(6):54, 1984
2. Wood.E.H., and E.A. Hoffman, Interserosal forcees, the pressure environment of the central circulation and.., Sup. to Physiogist 26(6):20, 1983

EFFECTS OF LBPP STOCKING ON CARDIOVASCULAR RESPONSES DURING REST AND EXERCISE IN LBNP AND UPRIGHT POSITION IN WOMAN

Junko NAGANO[+], Shigeyo TORIKOSHI[++], Kikuko YOKOZAWA[++], Miyako INAZAWA[++], Katsuko ITOH[+++], Yasuko FUKASE[++++], Yoji SUZUKI[+++++].

+Lab. of Physical Education, Bunka Woman's Univ., 3-22-1, Yoyogi, Shibuya-ku, Tokyo, Japan 151, ++ Tokyo Woman's Christian univ., +++Tsurumi Univ., ++++Rikkyo St. Margurite Woman's College, +++++Lab. of Health Adoministration, Faculty of Medicine, Univ. of Tokyo, 3-7-1, Hongo, Bunkyo-ku, Tokyo, Japan 113

Wearing a lower body positive pressure stocking(LBPPS) with about 20 mm Hg, whether or not the LBPPS is usefull to keep cardiovascular function during upright rest and exercise in 5 female students. Comparing between wearing and no wearing LBPPS,in the lst experiment,the subjects were stimulated by LBNP with NASA procedure. In the 2nd, a 60 % VO2 max pedalling was performed for 20 minutes. In the 3rd, also, 60 and 80 % VO2max treadmill running were performed for 20 minutes. Through the experiments, VO2, cardiac output(CO), HR, and arterial blood pressure(AP) were measured. In all experiments, wearing LBPPS, VO2, and AP were not so different from non-wearing it, but HR was lower, and CO and stroke volume (SV) were higher. Further, HR against VO2 and arteriovinous O2 difference against SV were lower, but mean arterial pressure against SV was higher in wearing LBPPS. Wearing LBPPS could make to be a benefit factor defencing decreasing central blood volume in upright exercise.

A prolonged standing position accelerates the function of the leg's muscle pump to keep venous return and thus heart fulling. Despite the acceleration, however, the central blood volume decreases with decreasing venous return. This brings to decreasing the heart fulling and stroke volume in the prolonged standing. In this case, therfore, myocardial contraction strength and heart rate(HR) are increased to maintain cardiac output(CO). As the results, cardiovascular system could have a overload. These facts suggest that human body is practically week to gravity stimulating, although human life is almost spended in exposuring to gravity. The over stress come from a strong difence reflex of cardiovascular function against gravity should be therefore eliminated as possible as we can. This elimination may be possible by wearing a lower body positive pressure stocking (LBPPS) with about 20 mm Hg, because its pressure is usefull to accelerate venous return with strengthing muscle pump in the legs against gravity.

We have developed a LBPPS, so, in this study, the validity of the LBPPS was investigated focusing cardiovascular responses against gravity in young woman.

Subjects and Methods

5 female students participated to the study as subjects. Their average body weight was 48.8 kg and average body hight was 152 cm. Their average age was 22 years old, so these body sizes were standard in the same age Japanese woman. The maximum aerobic power of an average 38.2 ml/kg/min in all subjects was also ranged in the standard value. The subjects were informed the aim and protocol of the study before the start of experiments.

In the first experiment (Ex.I), the subjects were exposured to LBNP, which was loaded by NASA procedure using LBNP box. In the experiment, heart rate (HR),oxygen uptake (VO2) and arterial blood pressure(AP) were measured in the two cases of wearing lower body positive pressure stocking (LBPPS) and no wearing LBPPS(N-LBPPS). The protocol is shown in Fig.1.

In the second experiment(Ex.II), the subjects performed a 60 % VO2max pedalling for 20 minutes in the upright position, which used a Monark bicycle ergometer. In the experiment, AP, HR, VO2 and cardiac output(CO) were also measured at a 15 min rest,and at 10 min and 20 min during exercise, comparing between the cases of LBPPS and N-LBPPS.

In the third experiment (Ex.III), the subjects performed a 60 % VO2max and a 80 % VO2max of treadmill running for 20 minutes after a 15 min resting on different days. In the experiment, HR was measured at every one minute, and VO2 was done for 5 minutes of 10-15 min period during a 15 min resting before exercise, for every one minute of 15-20 min period during a 20 min exercise, and for 5 minutes of 5-10 min period during recovery in each running, comparing between the two cases of LBPPS and N-LBPPS.

The LBPPS used had about 20 mm Hg positive pressure, which the size was three kinds of small, normal, and large girth and was fixed to each subject. The pressure was calibrated by a wearing positive pressure test machine.

Through all experiments, VO2 was determined by a metabolic analysing system which was constructed with a mass-spectrometer,a gas flow-meter, and a computer. CO was measured by an athetylen gas rebreathing method, in which argon and athetylen gases were contenuously analyses during rebreathing by a msaa spectrometer. HR was counted from the record of the chest leading EKG by a computer. Arterial blood pressure was measured by the auscultation method in the left upper arm.

Results

As shown in Fig.1, changing of AP during LBNP stimulated was clear. That is, systolic arterial pressure (SAP) was gradually decreased and diastolic arterial pressure (DAP) was increasing as LBNP was going up, so pulse pressure became gradually smoller. Although VO2 during LBNP was not so changing, HR was gradually increased. Comparing the changing rates between LBPPS and N-LBPPS, the HR was lower and SAP and pulse pre-

of exercise can readily be explained if the role of the leg muscle pump is taken into consideration. In the resting condition LBNP leads to displacement of blood volume from the intrathoracic space into the distensible capacitance vessels of the legs, causing curtailment of SV. With the onset of pedalling, the leg muscle pump is activated inducing redistribution of blood into the thoracic space with improved cardiac filling. This is in analogy with the course of events when exercise is commenced in the upright position (Bevegård et at., 1960) and in hypergravity (Rosenhamer, 1967).

Relation between blood redistribution and hyperpnea. - It has been claimed that exercise-induced translocations of blood towards the heart may be responsible for the abrupt initial phase of exercise hyperpnea (Weiler-Ravell et al., 1983). Despite the considerable increase in SV following commencement of exercise in our LBNP experiments, the ventilatory response was similar to that in the control condition. This observation is not compatible with a causal relationship between exercise-dependent blood-flow and ventilatory transients.

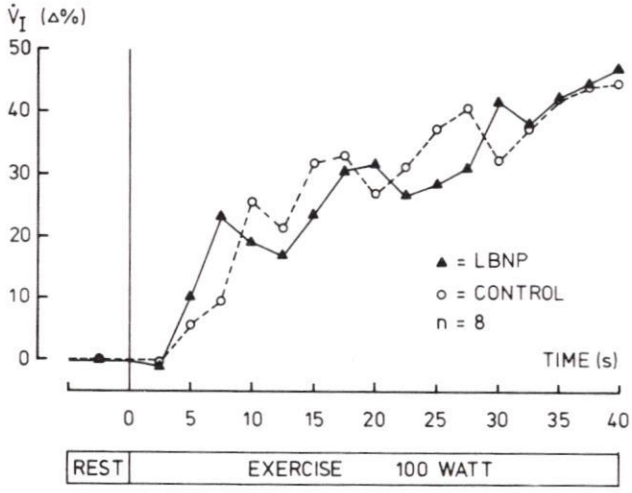


Figure 2. Responses of inspired minute volume ($\dot{V}_I$) to transition from rest to 100 W exercise in the control condition and during LBNP. Values in per cent of respective final responses are weighted means calculated on a 2.5s basis (from Acta Physiol. Scand. 1986, 127:507-512).

Magnitude of ventilatory steady-state responses. - The finding that ventilation and respiratory drive in terms of $P_{0.1}$ were considerably reduced in steady-state exercise during LBNP is interpreted in terms of diminished humoral and/or locally induced (in the working muscles) chemical drive. It seems likely that such mechanisms may have originated in an improved blood perfusion of the working muscles, since LBNP would tend to induce subatmospheric pressure in the leg veins during the phasic relaxation periods. In this way the stroke volume of the leg muscle pump is augmented and consequently the mean flow in the working muscles is accelerated.

References

Bevegård, S., A. Holmgren and B. Jonsson. 1960. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. Acta Physiol. Scand. 49:279-298.

Rosenhamer, G. 1967. Influence of increased gravitational stress on the adaptation of cardiovascular and pulmonary function to exercise. Acta Physiol. Scand. (Suppl 276) 68.

Weiler-Ravell, D., D.M. Cooper, B.J. Whipp and K. Wasserman. 1983. Control of breathing at the start of exercise as influenced by posture. J. Appl. Physiol. (REEP) 55:1460-1466.

Table 1. Responses of adult rats to whole body suspension.

Day of Suspension	Body Weight (g)	Food Intake (g/100g/d)	Water Intake (ml/100g/d)	Urine Volume (ml/100g/d)
0	465	7	10	4
1	430	2	3	3
7	385	6	8	5
14	390	9	12	7

REFERENCES

1. Deavers, D. R., X. J. Musacchia and G. A. Meininger. Model for antiorthostatic hypokinesia: head-down tilt effects on water and salt excretion. J. Appl. Physiol. 49:576-582, 1980.

2. Doty, S. B. and E. Morey-Holton. Alterations in bone forming cells due to reduced weight bearing. The Physiologist 27:S-81 - S-82, 1984.

3. Dunn, C. D. R., P. C. Johnson, R. D. Lange, L. Perez and R. Nessel. Regulation of hematopoiesis in rats exposed to antiorthostatic hypokinetic/hypodynamia: I. Model description, Aviat. Space Environ. Med. 56:419-426, 1985.

4. Musacchia, X. J., D. R. Deavers, G. A. Meininger and T. P. Davis. A model for hypokinesia: effects on muscle atrophy in the rat. J. Appl. Physiol. 48:479-486, 1980.

5. Musacchia, X. J. and J. M. Steffen. Cardiovascular and hormonal responses in a rat model which mimics responses to weightlessness. The Physiologist 27:S-41 - S-42, 1984.

6. Musacchia, X. J., J. M. Steffen and D. R. Deavers. Rat hindlimb muscle responses to suspension hypokinesia/hypodynamia. Aviat. Space Environ. Med. 54:1015-1020, 1983.

7. Rose, A., J. M. Steffen, X. J. Musacchia, A. D. Mandel and G. Sonnenfeld. Effect of antiorthostatic suspension on interferon α/β production by the mouse. Proc. Soc. Exptl. Biol. Med. 177:253-256, 1984.

INFLUENCE OF SIMULATED WEIGHTLESSNESS ON MAXIMAL $\dot{V}O_2$ OF UNTRAINED RATS

J. Michael Overton and

Charles M. Tipton

Exercise Physiology Laboratory
Department of Exercise and Sport Sciences
University of Arizona
Tucson, Arizona 85721, USA

ABSTRACT

The purpose of this study was to determine the effect of hindlimb suspension on maximal oxygen uptake ($\dot{V}O_2$ max) of rodents. Male Sprague-Dawley rats (300-350 g) were assigned to head-down (HD) suspension (N=8), horizontal (HOZ) suspension (N=12), or cage (C) control (N=9) for 6-9 days. Rats were tested for $\dot{V}O_2$ max before and after surgical instrumentation (Doppler flow probes, carotid and jugular cannulae), and after suspension. Body weight was significantly decreased after suspension in both HD and HOZ groups, but was significantly increased in the C group. Absolute $\dot{V}O_2$ max ($ml \cdot min^{-1}$) was not different in the C group. However, because of their increased weight, relative $\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$) was significantly reduced. In contrast, both relative and absolute $\dot{V}O_2$ max were significantly lower following suspension for the HD and HOZ groups. These preliminary results support the use of hindlimb suspension as an effective model to study the mechanism(s) of cardiovascular deconditioning.

INTRODUCTION

The head-down suspension rodent model (4,10) is associated with transient elevations in central venous pressure (12) and neck interstitial pressure (6), diuresis and natriuresis (4), hindlimb muscle atrophy (11), and bone loss (10), all of which are features of actual or simulated weightlessness. However, there is no information available as to its value in studying cardiovascular deconditioning, defined as a reduced exercise capacity and impaired cardiovascular response to an orthostatic challenge (9). Therefore, the purpose of the current study was to determine the effect of head-down and horizontal suspension on maximal oxygen uptake (VO_2 max) of adult rodents.

METHODS

Male Sprague-Dawley rats weighing 300-350 grams were assigned to one of three treatment groups for a six- to nine-day period: 1) 30° head-down (HD) suspension (N=8), 2) horizontal (HOZ) suspension (N=12), and 3) cage (C) control (N=9). The HD group was suspended using a modification of the Musacchia method (4). Animals were confined within a semicircular plexiglass harness using velcro straps. The tail of the animal was passed through a small opening in a plexiglass attachment to the harness and secured by taping a 2 cm portion of the flanged end of a 5 ml syringe barrel to the tail. The HOZ suspension was identical to the HD suspension with the exception of body position. C animals were housed in metal cages 14cm X 19cm X 14cm. All animals were provided tap water and rat chow ad libitum in two forms. In addition to pellets, a paste consisting of chow and tap water containing 2cc each of parsnips extract, cherry extract, and apple cider per gallon in a 1:2 (weight:volume) ratio was also provided in an attempt to encourage eating by the suspended rats (12).

After familiarization with treadmill running, animals were tested for $\dot{V}O_2$ max using methods described previously (1). Briefly, animals performed a graded exercise protocol to exhaustion in a plexiglass-enclosed treadmill which utilizes a flow-through design for analysis of expired oxygen and carbon dioxide fractions allowing calculation of $\dot{V}O_2$ max using standard equations. Each animal performed three $\dot{V}O_2$ max tests: 1) pre-surgery control, 2) pre-treatment, and 3) post-treatment. Surgery consisted of implantation of Doppler flow probes (8) followed by cannulation of the right carotid artery and external jugular vein four days later. Pre-treatment $\dot{V}O_2$ max was conducted one-two days following cannulation. Apparent efficiency was calculated as the inverse of the regression of the caloric equivalents of metabolism against external work performed (3). Body weight, $\dot{V}O_2$ max, run time and apparent efficiency were analyzed using 3x3 mixed ANOVA and Duncans test.

RESULTS

The results of this study are shown in Table 1. There were no differences between groups prior to surgery; however, differences did develop following surgery as the absolute $\dot{V}O_2$ max was lower in the HOZ and HD groups while body weight was lower following surgery in the HD group. After the treatment period, the C group demonstrated significant weight gains while both suspended groups exhibited significant weight losses. As a result, the C animals exhibited a significant reduction in relative $\dot{V}O_2$ max (absolute $\dot{V}O_2$ max was unchanged). While both suspended groups demonstrated significant reductions in absolute $\dot{V}O_2$ max from pre-treatment levels, only the HD group had significantly lower relative $\dot{V}O_2$ max compared to pre-treatment values. Running efficiency was not affected by suspension. Total run time during the graded exercise protocol was comparably reduced in all groups.

DISCUSSION

The interpretation of the $\dot{V}O_2$ max data is confounded by the changes in body weight observed in this study (and in other suspension studies using adult animals reported at the 8th IUPS meeting). While the HD and HOZ rats lost weight despite providing the paste diet, the C animals gained weight. The reduction in relative $\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$) in the C group is probably associated with the increased body weight of the animals. Conversely, the reductions in relative $\dot{V}O_2$ max in the HOZ and HD groups were offset by reductions in body weight. Additional experiments are currently being conducted to determine the direct effects of acute weight changes on relative and absolute $\dot{V}O_2$ max in adult rats.

The potential mechanism(s) responsible for the reduction in $\dot{V}O_2$ max following head-down suspension appear to involve the hypokinesia and hindlimb unloading present in both suspension groups, as well as the additional effects of the head-down posture. The apparent efficiency of running was not significantly altered, indicating that mechanical aspects of running were not a consideration. A lowered $\dot{V}O_2$ max must be due to either reduced delivery or reduced extraction

of oxygen. Delivery is typically considered to be the limiting factor for $\dot{V}O_2$ max. Unfortunately, cardiac output measurements are not available. A reduction in blood volume, which has been observed in the suspension model by others (5), could compromise delivery. The hemodynamic response of suspended animals to graded exercise using Doppler flow probes is being examined. This will allow measurement of iliac blood flow during exercise which, if compromised, could contribute to the reduced $\dot{V}O_2$ max observed in this study. A decreased lean body mass, as well as a reduction in extraction per unit of muscle, could contribute to decreased oxygen extraction. Data indicating hindlimb muscle atrophy (11) and reduced (2) or unchanged (7) mitochondrial enzyme levels provide evidence that reduced extraction must be considered as a possible mechanism for our observations. In conclusion, these preliminary results support the use of hindlimb suspension as an effective model to study the mechanism(s) of cardiovascular deconditioning. (Supported in part by NIH-HL 33782-02 and NASA-NAG 2-392.)

REFERENCES

1. Bedford, T.G., C.M. Tipton, N.C. Wilson, R.A. Oppliger, and C.V. Gisolfi. Maximum oxygen consumption of rats and its changes with various experimental procedures. **J. Appl. Physiol.** 47:1278-1283, 1979.
2. Bello, M.A., R.R. Roy, and V.R. Edgerton. Hindlimb suspension effects on the morphologic and metabolic properties of rat medial gastrocnemius. **Physiologist** 28:315, 1985.
3. Brooks, G.A., C.M. Donovan, and T.P. White. Estimation of anaerobic energy production and efficiency in rats during exercise. **J. Appl. Physiol.** 56:520-525, 1984.
4. Deavers, D.R., X.J. Musacchia, and G.A. Meininger. Model for antiorthostatic hypokinesia: Head-down tilt effects on water and salt excretion. **J. Appl. Physiol.** 49:576-582, 1980.
5. Dunn, C.D.R., P.C. Johnson, R.D. Lange, and C.S. Leach. A comparison of hematological data from various "models" with those obtained from actual space flight. **Aviat. Space Environ. Med.** 55:444, 1984.
6. Hargens, A.R., J. Steskal, C. Johansson, and C.M. Tipton. Tissue fluid shift, forelimb loading, and tail tension in tail-suspended rats. **Physiologist** 27(6):S37-S38, 1984.
7. Hauschka, E., R.R. Roy, and V.R. Edgerton. Hindlimb suspension effects on the morphologic and metabolic properties of the rat soleus. **Physiologist** 28:315, 1985.
8. Haywood, J.R., R.A. Shaffer, C. Fastenow, G.D. Fink, and M.J. Brody. Regional blood flow measurement with pulsed Doppler flowmeter in the conscious rat. **Am. J. Physiol.** 241:H273-H278, 1981.
9. Levy, M.N., and J.M. Talbot. **Research Opportunities in Cardiovascular Deconditioning.** NASA Contractor Report 3707 , 1983, 72 p.
10. Morey, E.R. Spaceflight and bone turnover: Correlation with a new rat model of weightlessness. **Bioscience** 29:168-172, 1979.
11. Musacchia, X.J., J.M. Steffen, and D.R. Deavers. Rat hindlimb muscle responses to suspension hypokinesia/hypodynamia. **Aviat. Space Environ. Med.** 54:1015-1020, 1983.
12. Popovic, V. Antiorthostatic hypokinesia and circulation in the rat. **Physiologist** 24(6):S15-S16, 1981.
13. Wunder, C.C., C.M. Tipton, and K.M. Cook. Femur-bending properties as influenced by gravity: IV. Limits after high and low weight-bearing. **Aviat. Space Environ. Med.** 51:902-907, 1980.

Table 1. Body weight, maximal oxygen uptake, efficiency and run time (mean and SE)

	Cage	Horizontal	Head-down
Control			
Body weight (grams)	323 ± 4	322 ± 5	319 ± 6
$\dot{V}O_2$ max ($ml \cdot min^{-1}$)	30.6 ± 1.1	30.7 ± 0.6	29.9 ± 1.3
$\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$)	94.0 ± 3.0	94.9 ± 2.3	93.2 ± 4.1
Apparent efficiency (%)	5.0 ± 0.2	5.9 ± 0.5	5.3 ± 0.4
Run time (min)	18.4 ± 0.2	18.8 ± 0.3	17.7 ± 0.5
Pre-treatment			
Body weight (grams)	324 ± 3	317 ± 4	308 ± 8^{ac}
$\dot{V}O_2$ max ($ml \cdot min^{-1}$)	30.0 ± 0.9	28.3 ± 0.7^{a}	27.7 ± 1.1^{ac}
$\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$)	93.0 ± 2.6	91.0 ± 2.2	89.9 ± 2.4
Apparent efficiency (%)	4.4 ± 0.2	5.3 ± 0.4	5.6 ± 0.5
Run time (min)	17 ± 0.5^{a}	17.3 ± 0.5^{a}	17.6 ± 0.6
Post-treatment			
Body weight (grams)	340 ± 5^{ab}	300 ± 6^{abc}	296 ± 5^{abc}
$\dot{V}O_2$ max ($ml \cdot min^{-1}$)	28.8 ± 0.8	25.3 ± 0.6^{abc}	24.7 ± 0.5^{abc}
$\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$)	85.9 ± 1.8^{ab}	87.2 ± 1.7^{a}	84.5 ± 0.9^{ab}
Apparent efficiency (%)	5.1 ± 0.5	5.0 ± 0.4	5.3 ± 0.2
Run time (min)	15.8 ± 0.5^{ab}	15.1 ± 0.3^{ab}	15.6 ± 0.4^{ab}

[a]Significant intragroup difference from control. [b]Significant intragroup difference from pre-treatment. [c]Significant intergroup difference from cage.

CONTINUOUS DETERMINATION OF BLOOD VOLUME AND BLOOD SODIUM CONCENTRATION ON CONSCIOUS RATS: A POTENTIAL TOOL FOR THE ANALYSIS OF WATER BALANCE DURING WEIGHTLESSNESS

T. MORIMOTO, E. SUGIMOTO, H. NOSE,
T. OKUNO, T. NATSUYAMA, and M. MORITA

Department of Physiology,
Kyoto Prefectural University of Medicine,
Kamigyoku, Kyoto 602, Japan.

A new system to measure blood volume (BV) and plasma sodium concentration [Na] in conscious rats was developed, and the method was applied to measure the transient changes in BV and [Na] during head down suspension in rats.

A small extracorporeal circulation was made with chronic catheters in aorta and jugular vein and the blood was passed through a γ-counter and a sodium sensitive glass electrode with flow through type. Determination of BV is based on the dilution method of red cell labeled with radioactive Cr. The accuracy of the BV determination on a known volume of rat's blood in a flask was whithin 1% and the coefficient of deviation over 10 min was within 0.2%. The accuracy of sodium sensitive glass electrode was within the error of flame photometry. The method was used for head-down suspension of rats, and BV showed a transient decrease at the beginning of the suspension and recovered to the pre-suspension value, while [Na] showed steady increase. After the suspension, BV showed steady increase with no change in [Na]. These results suggest different responses between head-out water immersion and head-down suspension.

To simulate weightlessness, head-out water immersion and head-down tilt have been commonly used for human subjects and also for animal experiments. Using dogs as experimental animal, Miki et al. (1) showed that BV is increased by about 3.5% during head-out water immersion. Recently, we developed a new method to measure circulating blood volume and blood sodium concentration in conscious rats continuously (2, 3), and an attempt was made to determine whether BV is increased during head-down suspension or not.

At least 5 days prior to the experiment, rats were splenectomized and cannulated into descending aorta and jugular vein. The other ends of catheters were pulled out through an interscapular incision and threaded through a flanged and coiled stainless steel spring. The rats were bonded on the back with plaster mesh cast for the head-down suspension. On study days, the catheters were connected with the extracorporeal shunt circuit, which contains a glass coil placed in a well type γ-counter and a sodium sensitive glass electrode with flow through type as shown in Fig. 1.

Circulating blood volume was determined with the dilution method of erythrocyte labeled with radioactive chromium.

The accuracy of the BV obtained from this system was checked by measuring a known volume of rat's blood. Twenty ml of blood with the labeled erythrocyte was pooled in a flask, and the volume was measured continuously using the circuit. Saline was infused into the flask, and the amount of infused saline was estimated. As the results, the deviation of the reading from the known amount was less than 0.2%, and the coefficient of variation of the BV obtained over 10 min was about 1% when at least 40 μCi of Cr was used for 20 ml of BV.

The system used to measure sodium concentration consists of a sodium sensitive glass electrode and a reference electrode with flow through type. In the commercially available analyzer (SERA-230, Horiba, Kyoto), a flow junction of KCl solution is used to obtained stable junction potential. However, in our system, the liquid junction was replaced by 3.3 M KCl agar bridge to minimize contamination of blood with KCl. The junction potential was most stable when the agar bridge was prepared with 5% agar powder, 3.3 M KCl, 140 mM NaCl adjusting pH to about 7.4 with Tris-HCl buffer solution.
The electromotive force of the glass electrode was read with a high input-impedance amplifier, and the output was recorded with a desk top computer after analog-digital conversion, together with the out-put of rate meter for blood volume determination.

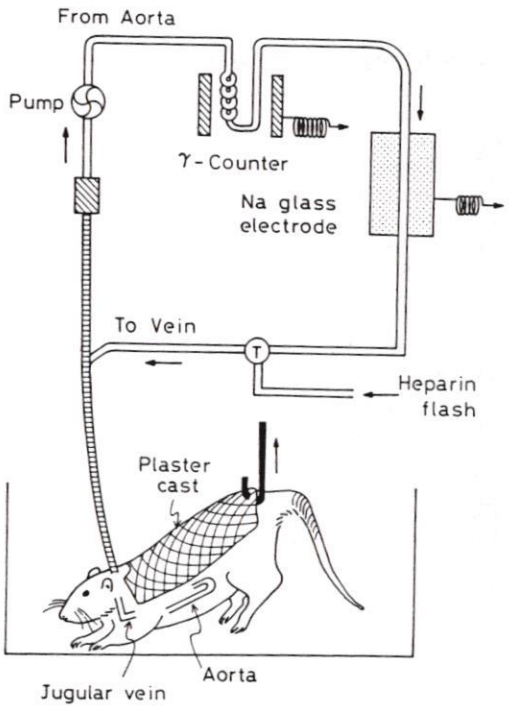


Fig 1. The system used for continuous determination of circulating blood volume and plasma sodium concentration in rats during head-down suspension.

The accuracy of the system was determined using human serum samples and buffer solutions, and the relationship between plasma sodium concentrations or Tris−HCl buffer solutions as determined with a flame photometer and the electromotive force of the sodium glass electrode showed high correlation and the 95% confidence limit of the regression line was 0.3 mV which was equivalent to about 1.5 meq/l of sodium concentration within this range. The effect of erythrocytes on the electromotive force was also checked using pooled blood in a flask. The pooled blood was pumped to the electrode system, and the sodium conentration was determined as infusing dilute or concentrated NaCl solution into the flask. Blood samples were obtained at equilibrium stages, and the concentration of plasma Na was determined by flame photometry, and the values obtained with these methods coincided within the accuracy of flame photometry.

On the study days, catheters were connected with a pump to the system and at least 2 h were allowed for the equilibrium of infused tracer. After the equilibrium of BV and [Na], rats were suspended for 1 h and then the recovery was followed for another 1 h. Head−down suspension was induced attaching the plaster mesh cast bonded to the rat to a overhanging beam by a freely rotating swivel as developed by Morey (4). This experiment was repeated on 6 rats, and mean and standard errors of the changes in BV and [Na] are shown in Fig. 2. The fall in BV at the initial stage was consistent and the fall was observed up to 10th min, and then BV increased to the original level. [Na] was constant at the initial stage, and then showed gradual rise. Because the fall of BV started with the handling of rat, loss of blood with the increase in sympathetic vasoconstriciton is suggested. In about 15 min after the end of the suspension, increase in [Na] was ceased, and gradual increase in BV was observed, which suggest inflow of isotonic interstitial fluid into vascular space. To account the change in blood volume observed in this experiment, further information on urine volume and cardiovascular and hormonal variables are needed.

The results obtained in this experiment suggest that the response of BV to head down suspension differ from that observed during water immersion.

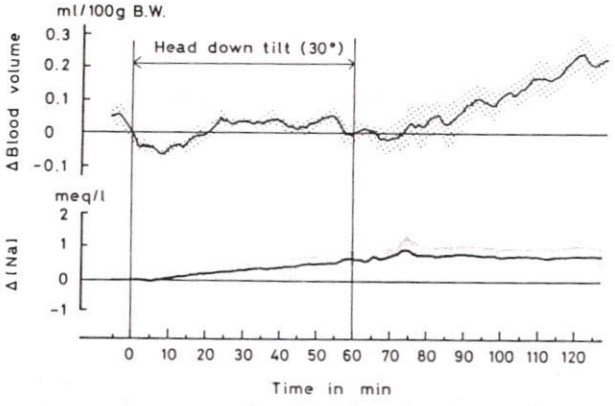


Fig. 2 Changes in circulating blood volume and plasma sodium concentration during and after head−down suspension. Values are shown as mean and SE of 6 observations.

Rererences

1. Miki, K., G. Hajduczok, S.K. Hong and J.A. Krasney. Plasma volume changes during head−out water immersion in conscious dogs. Am. J. Physiol. 251 (Regulatory Integrative Comp. Physiol. 20): R582−R590, 1986
2. Nose, H., M. Morita, T. Yawata and T. Morimoto. Continuous determination of blood volume on conscious rats during water and food intake. Jpn. J. Physiol. 36: 215−218, 1986.
3. Nose, H., E. Sugimoto, T. Morimoto, S. Usui and T. Aomi. Continuous recording of plasma sodium concentration and blood volume in awake rats. Jpn. J. Physiol. 36: 607−611, 1986.
4. Morey, E.R. Speceflight and bone turnover: Correlation with a new rat model of weightlessness. Bioscience 29: 168−172, 1979.

MECHANISM OF THE INCREASE IN PLASMA VOLUME DURING HEAD-OUT WATER IMMERSION (WI) IN DOGS

Kenju Miki, Suk Ki Hong* and John A. Krasney*

Department of Physiology, School of Medicine, University of Occupational & Environmental Health, Kitakyushu 807, Japan, *State University of New York at Buffalo, Buffalo, NY 14214 USA

The present study was undertaken to determine the mechanism underlying the alteration of transcapillary fluid movement during WI. Systemic arterial (Pa), central venous (Pv), plasma oncotic, interstitial fluid hydrostatic (Pif) pressures were measured. Mean capillary pressure, which was calculated from Pa, Pv and an estimated pre-to-postcapillary resistance ratio of 5-12, increased by 27 mmHg while Pif increased by 27 mmHg at lower forelimb. A greater increase in Pif than mean capillary pressure during WI would create a negative hydrostatic pressure gradient across the capillary wall. The oncotic pressure gradient across the capillary wall was estimated to be < 1.2 mmHg during WI. Thus, it is probable that the negative hydrostatic pressure gradient for fluid movement across the capillary wall plays a major role in the increase in plasma volume which occurs during WI.

We have reported that WI (37°C) causes an increase in plasma volume, which precedes the onset of a diuresis in awake dogs (3). Plasma volume increased by 7.2% of initial plasma volume at 35 min of WI and then it decreased slightly from the peak level during the period of WI in splenectomized dogs (3). In splenectomized and acutely nephrectomized dogs, plasma volume increased linearly during WI by 33% above the control level by 120 min of WI (4). We observed also that thoracic duct lymph flow did not change significantly during WI (5). We concluded from these studies that WI leads to a sustained fluid movement from the extravascular into the intravascular space across the capillary wall.

The present study was designed to determine the mechanisms involved in the fluid shift across the capillary wall during WI. To achieve this aim, intravascular hydrostatic, plasma oncotic, and interstitial hydrostatic pressures were measured continuously in conscious dogs.

METHODS

Six mongrel female dogs were utilized. Five weeks before the experiment, the dogs were anesthetized with thiamylal sodium (35 mg/kg iv). Subsequently, perforated capsules (cylinder type measuring 15 mm in diameter and 8 mm in length) were implanted in the subcutaneous space of the lower forelimb. The capsules were constructed of porous polytehylene (pore size 70 μm). The catheters exiting from the capsule were routed subcutaneously to the interscapular region, and the tips were left beneath the skin. The dogs received either ampicillin (5-10 mg/kg) or gentamicin sulfate (5-10 mg/kg) prophylactically for 5 weeks to prevent infection of the capsules. Two weeks before the experiment, the dogs were reanesthetized and catheters were positioned with their tips in the abdominal aorta and the inferior vena cava via the right femoral artery and vein for measurement of systemic arterial and central venous pressures, respectively. Catheters were also placed in the left femoral artery and vein for the subsequent establishment of an extracorporeal circuit to measure blood volume. These catheters were routed also to the interscapular space, and all the catheters were exteriorized at this time. The catheters were capped and protected by a fitted jacket.

Arterial (Pa), central venous (Pv), and interstitial fluid hydrostatic (using both Guyton's capsule (Pcps) and wick catheter (Pwick) methods) pressures were measured with Statham strain gauge transducers. The zero reference level for the vascular pressures was taken to be the level of the tricuspid valve and was kept constant throughout the experiment as the strain gauges were mounted on an outrigger bar that kept the transducers at the same reference level as the dogs were lowered into the tank. Plasma oncotic pressure was measured with a needle-type colloid osmometer that uses a hollow fiber as a semipermeable membrane using the extracorporeal circuit (3). The range of the physiological changes in mean capillary pressure (Pc) was calculated indirectly from Pa and Pv using the following equation:

$$Pc = Pa/(1+Ra/Rv) + (Ra/Rv) \times Pv/(1+Ra/Rv)$$

where Ra/Rv is the pre-to-postcapillary resistance ratio. We assumed a value of 5-12 for the Ra/Rv ratio in order to estimate the range of the physiological changes in Pc according to previous reports (2,3).

The WI experiments consisted of an 80 min control period in the air, 100 min of water immersion, and then an 80 min recovery period in the air. The dogs were immersed to the midcervical level after the control period in the air. The water in the immersion tank was held at a temperature of 37°C to keep the dogs at the thermoneutral condition (1). Comparisons between experimental values and individual control values were made by the Friedman multiple comparison test.

RESULTS

The interstitial fluid hydrostatic pressure measured by both wick and capsule methods increased immediately after the start of WI to 25 mmHg and 23 mmHg respectively at 2 min of WI and these levels were maintained during WI. The external reference pressure (Pref) was 30 mmHg in WI (Fig. 1).

Pa increased immediately after the start of WI by 24 mmHg above the control level at 30 min of Wi and this level was maintained throughout the immersion period (Table 1). There was also a step increase in Pv by 14-15 mm Hg. Therefore, the estimated increase in Pc from the control level

ranged from 15 (Ra/Rv=12) to 16 mmHg (Ra/Rv=5) at 30 min of WI. This increment of Pc was maintained throughout WI. The Pcps increased by 27 mmHg above the control level. Plasma oncotic pressure decreased by 1.3 mmHg at 30 min of WI because of hemodilution (3).

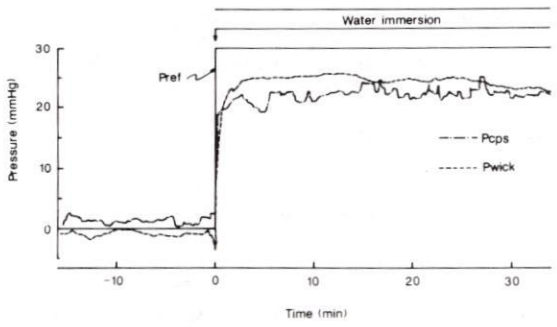


Fig. 1. Typical recording of interstitial fluid hydrostatic pressure measured by widk (Pwick) and capsule (Ppcs) methods in response to the increase in external hydrostatic pressure (Pref) due to WI.

Table 1. Changes in hydrostatic and oncotic pressures of intravascular and interstitial spaces during WI.

	Control	WI		
(mmHg)		30min	60min	90min
Pa	111±4	135±5*	132±3*	133±4*
Pv	1±1	15±1*	16±1*	15±1*
Pc				
(Ra/Rv=5)	19±1	35±1*	35±1*	35±1*
(Ra/Rv=12)	9±1	24±1*	25±1*	25±1*
πpl	16.0±1.0	14.7±1.0*	15.1±1.0*	15.3±1.0
Pcps	1±2	28±2*	27±2*	27.2±2*

Values are mean ± SE of 6 experiments.
*Significantly different from the control level.
See detail in text.

DISCUSSION

We have reported that WI causes a sustained fluid movement from extravascular to intravascular space immediately after the start of WI. Plasma volume increases during the early phase of WI and this response precedes the onset of the diuresis (3,4). We also reported that this fluid shift following WI was caused by an increase in net fluid absorption across the capillary wall, not by the increase in lymph flow rate (5). Transcapillary fluid movement (Jv) is governed by balancing the hydrostatic and oncotic pressures of the intravascular and interstitial fluid spaces and capillary filtration coefficient (Kf), and it can be described as follows:

$$Jv = Kf[(Pc-Pif)-\sigma(\pi pl-\pi if)]$$

where σ is the osmotic reflection coefficient for total protein. The observed increase in net fluid absorption (negative Jv) is likely caused by the negative transcapillary pressure gradient.

It is noteworthy that both the mean capillary and interstitial fluid hydrostatic pressures increased immediately after the start of WI with elevated levels maintained thoughout WI. However, the magnitude of the increase in Pcps caused by WI exceeds the increase of mean capillary pressure. The changes in hydrostatic pressure gradient (Pc-Pif) from the control level was -11 to -12 mmHg at 30 min of WI, which is in favor of fluid reabsorption.

The plasma oncotic pressure decreased by -1.3 mmHg at 30 min of WI. We have estimated the change in interstitial fluid oncotic pressure to be < 0.1 mmHg based on the observed change in interstitial fluid volume during 120 min of WI (4). Therefore, the magnitude of the changes in oncotic pressure gradient ($\pi pl-\pi if$) is within 1.2 mmHg.

The estimated range of the net pressure gradient for fluid movement was -9.8 to -10.8 mmHg. This level of negative pressure gradient might be sustained during the course of WI since both mean capillary and interstitial fluid hydrostatic pressure were at high levels throughout WI. Therefore, the development of a sustained negative pressure gradient seems to be the major cause of the continuous fluid movement from extravascular to intravascular spaces observed during WI.

In summarizing the above discussion, WI causes an increase in both capillary and tissue fluid hydrostatic pressure. However, the fact that the magnitude of the increase in tissue fluid pressure exceeds the increase in capillary pressure, might create the negative pressure gradient for fluid movement which, in turn, elicits an increase in plasma volume. The diuresis acts to minimize the increase in plasma volume.

REFERENCES

1. Krasney, J.A., G. Hajduczok, C. Akiba, B.W. McDonald, D.R. Pendergast and S.K. Hong. Cardiovascular and renal responses to head-out water immersion in canine model. Undersea Biomed. Res. 11:169-183, 1984.
2. Miki, K. Dynamics of the plasma-interstitial fluid distribution and transcapillary pressure differences. Jpn. J. Physiol. 31:917-929, 1981.
3. Miki, K., G. Hajduczok, S.K. Hong and J.A. Krasney. Plasma volume changes during head-out water immersion in conscious dogs. Am. J. Physiol. (Regulatory Integrative Comp. Physiol.) 251:R582-R590, 1986.
4. Miki, K., G. Hajduczok, S.K. Hong and J.A. Krasney. Extracellular fluid and plasma volume responses to head-out water immersion in anesthetized, nephrectomized dogs. Physiologist 28:318, 1985.
5. Miki, K., M.M. Pazik, E. Krasney, S.K. Hong and J.A. Krasney. Lymph flow of the thoracic duct during head-out water immersion (WI) in conscious dogs. Physiologist 29:138, 1986.

PHYSIOLOGICAL COMPARISON OF RAT MUSCLE IN BODY SUSPENSION AND WEIGHTLESSNESS

X. J. Musacchia, J. M. Steffen, R. D. Fell and J. Dombrowski

Dept Physiol. and Biophys., Dept Biol., Exer. Physiol. Lab., Univ. Louisville, Louisville, KY 40292

Hind limb unloading is achieved with whole body suspension (WBS) and with tail suspension (TS). Comparable levels of muscle mass loss and decreases in protein levels result during one to three weeks of exposure to microgravity (uG), WBS and TS. Losses are most apparent in soleus (S), intermediate in gastrocnemius (G) and least in extensor digigorum longus (EDL). Comparison of S and EDL type I and II fiber changes (numbers and area) after seven days of uG flight (SL-3) and WBS showed, in S, an increase in Type I and Type II fiber density and a decrease in area. Except for a decrease in Type I fiber density in EDL, all other parameters remained comparable. The general conclusions were that the S under uG and WBS responds in a similar manner. The EDL, for the most part, shows little change under both conditions.

Animal models for research in gravitational physiology adress two questions: how do animal systems adapt to conditions of microgravity? and, can experiments with earthside animal models be developed to simulate responses comparable to those evoked during exposures to microgravity?

The first question addresses general features of physiological adaptation to a stressful environment. In the processes of evolution animals have adapted to conditions of 1G relative to genetic and physiologic limitations. Studies that test animal responses to a specific stressful environment (microgravity) are valuable in assessing these limitations. The second question addresses the development of animal models used for comparisons with subjects exposed to conditions of microgravity.

During the last two decades many pathophysiologic responses of animal and human exposure to uG have been documented but are far from complete. It is widely accepted that exposure to uG for periods of one to three weeks results in atrophy of skeletal muscle in rats. This atrophy results from disuse associated with hypokinesia and hypodynamia. Our discussion will focus on earthside experiments that have been used for comparison with microgravity in both the U.S.S.R. COSMOS series of biosatellites and the U.S. Space Lab 3 project in 1985. Specifically, this brief review will speak to questions associated with the effects of hypokinesia and hypodynamia on skeletal muscle.

Several animal systems have been used as models for skeletal muscle disuse atrophy in the rat. Two variations of the unloaded hindlimb model most frequently used are the whole body suspension (WBS) system and the tail suspension (TS) system. The question has been, do these models produce results that are comparable to those seen when rats are exposed to microgravity?

Our work has focused on the development and use of the WBS and recently we have had the opportunity to compare skeletal muscle changes using WBS and (SL-3) seven day uG exposed rats.

MATERIALS AND METHODS

Male Sprague Dawley rats, 350-400 gm, were suspended in a harness for a period of seven days as previously described in detail (12, 13). Appropriate weight matched control rats were maintained in metabolic cages. These subjects were compared with 360-410 gm rats exposed to seven days of uG ($\simeq$ weightlessness) during the SL-3 flight in 1985. Ground control subjects for the SL-3 rats were maintained in a holding facility comparable to that in the Spacelab. For tissue samples, WBS animals were sacrificed with pentobarbital sodium 65mg/100gm, and SL-3 rats were anesthesized with halothane and decapitated. Hindlimb muscles, (S, G and EDL) were excised and frozen in liquid N_2. Tissues were placed in OCT compound, and frozen sections were treated with an ATPase stain, adjusted to pH 9.4. The method is a modification of Dubowitz et al (1973). Numbers of muscle fibers and fiber areas were recorded using a computerized image analysis system.

RESULTS AND DISCUSSION

Comparison of models with uG experiments: Loss of muscle mass and protein content have been used as measures for evaluation of disuse atrophy in hindlimb unloading due to WBS and TS. Examples of such data from the literature are presented for S, G and EDL in Table I. These selected references are not intended to represent a complete review of the literature. For example, there is additional data of muscle mass and protein loss when the hindlimbs are casted. Booth (1977) reported a 21% and 45%, respectively, loss of S and G mass after 21 days of casting. Almon and Dubois (1983) also reported that after six days of limb casting there are losses in muscle mass, 40% in S and 14% in EDL. Szoor et al (1981) using 8 and 14 day periods of limb casting, reported progressive loss in S, G and EDL mass.

The data in Table 1 clearly illustrates that S shows the most consistent and dramatic loss of mass following space flight and during WBS and TS unloading. In addition, prolonged TS unloading, i.e. after 14 days, does not appear to greatly enhance the process of muscle mass loss (11). During recovery from WBS muscle mass increase in S, G, and EDL (13).

The muscle mass changes during WBS and microgravity parallel total protein levels (14, 15). Those authors showed that the disuse atrophy can be attributed to loss of cellular protein. Through studies of relationships between protein, RNA and DNA, they predicted that exposure to microgravity should result in decrease cell mass but no loss in fiber numbers. This concept was experimentally tested and is reported below.

The data from the reports cited in Table I does not distinguish between ages, weights, sex and strains of rats. In the Russian COSMOS series the rats were Wistar strain (Bratislava) and generally young adults, both males and females. The SL-3 subjects used by Steffen and Musacchia (15) are Sprague Dawley adult males weighing about 400 gm. In contrast, most other rats in WBS and TS unloading experiments have been juvenile or young growing rats ranging in weight from less than 100 gm to about 250 gm. In earlier experiments (12) using Sprague Dawley males, 170-200gm, we reported not only muscle mass loss but also an initial loss in body weight that was corrected within a few days to renewed weight gain. The weight loss in young growing animals is related to lessened food intake. Older animals show significant and sustained weight loss during seven days of exposure to microgravity (Figure 1) (16) and WBS unloading.

From the literature review, one can conclude that hindlimb unloading and exposure to microgravity result in significant loss in muscle mass and total protein in S, a predominately slow twitch, antigravity muscle. In G, a mixed fiber muscle, there is also a significant loss of mass and protein in response to both WBS or microgravity. In contrast, the least change in mass and protein content ocurs in the EDL. Thus, despite the variation in experimental approaches under conditions of hypokinesia and hypodynamia, disuse muscle atrophy is apparent and differs in accordance with muscle antigravity functions.

In an effort to develop more precise experimental protocols comparisons were made between seven day microgravity exposed rats (SL-3) and seven day WBS hindlimb unloaded rats. Rats were of the same sex (males) and body weight. Figure 1 shows that body weight loss occurs under both conditions. Figure 2 shows significant parallel losses in soleus mass.

The EDL (Figure 3) showed a significant loss of mass in the seven day flight subjects but not in response to seven days of WBS. We have no specific explanation for these differences at this time, although there may be a clue in the fact that WBS subjects often exhibit a plantarflexed limb for extended periods. These are random observations and as yet there has been no attempt at quantification. It is possible that this form of muscle positioning may cause some attentuation in the disuse atrophy.

CONCLUSIONS

Comparisons of model systems (WBS and TS) with uG show that they are highly comparable for periods of one to three weeks of hindlimb unloading. The sensitivity of muscles are greatest in the slow twitch (predominant type I fiber) soleus, greater than the gastrocnemius a mixed fiber (type I and II) muscle and least effected, the mixed fiber (predominantly type II fiber) EDL. The loss in muscle mass, in response to unloading in WBS and TS and uG exposures (COSMOS and SL-3) during space flight is explained in terms of protein loss. A specific experiment dealing with changes in fiber numbers and fiber areas confirmed earlier reports that muscle mass loss was the result of cellular content rather than fiber number.

Supported in part by NASA grant NAG2-386.

TABLE I Comparison of muscle mass and total protein change, loss (-) or gain (+), in response to microgravity (space flight) and hindlimb unloading using whole body (WBS) or tail suspension (TS) systems. Sources are cited.

SOLEUS

Conditions & Days	Percent Change Mass	Protein	Ref.
MICRO G			
COSMOS 605 22	32(-)		(8)
COSMOS 690 20.5	25(-)		(9)
COSMOS 605 22		46(-)	(5)
COSMOS 1129 18.5	40(-)		(18)
SL-3 7&.5R*	34&24(-)	34&40(-)	(7)
SL-3 7	24(-)	16(-)	(15)
UNLOADED			
WBS 7&7R*	29&11(-)		(13)
14&7R*	42&24(-)		(13)
WBS 7&14		30&41(-)	(14)
(Back Harness) 7	46(-)		(4)
TS 7&14	34&52(-)		(5)
TS 14→90	45→54(-)		(11)
TS 6	25(-)		(10)
TS 14	48(-)		(20)

GASTROCNEMIUS

MICRO G			
COSMOS 690 20.5	19(-)		(9)
SL-3 7&7.5R*	15&14(-)	13(-)	(7)
SL-3 7	14(-)	9(-)	(15)
UNLOADED			
WBS 7&7R*	19&1(-)		(13)
14&7R*	10&6(+)		(13)
WBS 7&14		23&14(-)	(14)
WBS 14	10(-)		(19)
TS 6	3(-)		(10)
TS 14→90	21→16(-)		(11)

(cont) **EXTENSOR DIGITORUM LONGUS**

MICRO G			
COSMOS 605			
22	12(-)		(8)
COSMOS 690			
20.5	No Change		(9)
COSMOS 1129			
18.5	29(-)		(18)
SL-3			
7	10(-)	9(-)	(15)
UNLOADED			
WBS			
7&14	7.5(-)&17(+)		(14)
WBS			
7&7R	4&9(+)		(13)
14&7R	4&7(+)		(13)
TS			
7&14	No Change &9(-)		(5)

*R=Recovery

TABLE II Comparisons of type I and II fibers in the predominately slow twitch soleus and fast twitch extensor digitorum longus (EDL) muscles from seven day space flight (Micro G) and WBS rats. Values expressed as percentage of appropriate controls for uG or WBS cage rats.

	Type I		Type II	
	I/mm^2	Area/uM^2	II/mm^2	Area/uM^2
SOLEUS				
Micro G	+29	-38*	+69	-37
WBS	+15	-14*	+10	-21*
EDL				
Micro G	+59	-10	+63	-10
WBS	+12	-24*	+30	-14

*Significantly different from controls = P<0.05

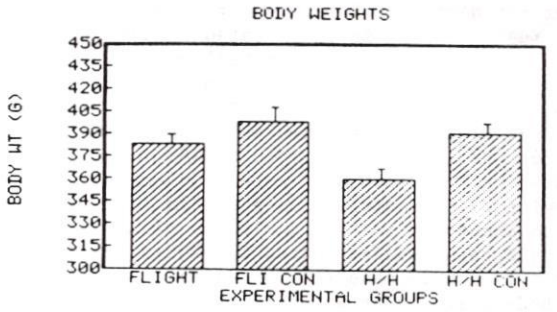


Figure 1. Body weights, significant differences ($P < 0.05$) between flight and flight controls, and H/H and H/H controls

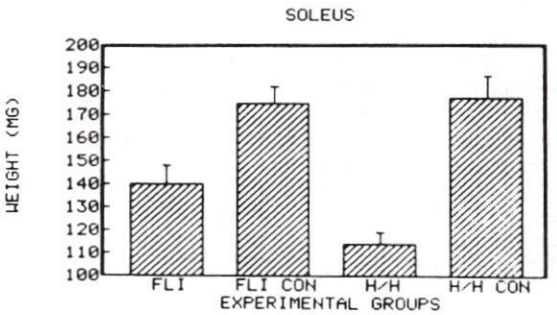


Figure 2. Soleus weights, significant differences ($P < 0.05$) between flight and flight controls, and H/H and H/H controls

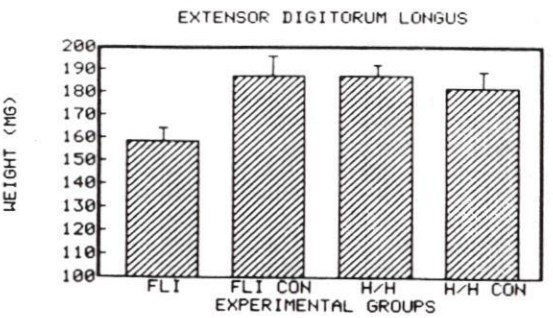


Figure 3. EDL weights, significant differences ($P < 0.05$) between flight and flight controls

REFERENCES

1. Almon, R. R., D. C. DuBois. Glucocorticoid Sensitivity, Disuse, and the Regulation of Muscle Mass. Physiologist, Vol. 26. No. 6, Suppl. 1983. pp. 92-93.

2. Booth, F. W. Time Course of Muscular Atrophy During Immobilization of Hindlimbs in Rats. J. Appl. Physiol.: Respirat. Environ Exercise Physiol. 43(4): 656-661, 1977.

3. Dubowitz, V. and M. H. Brook. Muscle Biopsy: A Modern Approach. W.B. Sanders, Co., Ltd. London pp5-33, 1973.

4. Feller, D. D., H. S. Ginoza, E. R. Morey. Atrophy of Rat Skeletal Muscles in Simulated Weightlessness. The Physiologist, Vol. 24, No. 6, Suppl. 1981

5. Fitts, R. H., J. M. Metzger, D. A. Riley, B. R. Unsworth. Models of Disuse: A Comparison of Hindlimb Suspension and Immobilization. J. Appl. Physiol. 60(6): 1946-1953, 1986.

6. Gayevskaya, M.S., N.A. Veresotskaya, N. S. Kolgonova, Ye. V. Kolchina, L. M. Kurkina and Ye. A. Nosova. Changes in Metabolism of Soleus Muscle Tissues in Rats Following Flight aboard the KOSMOS-690 Biosatellite. Kosmich. Biol. I Aviakosmich. Med., Vol. 13, pp. 16-19, 1979.

7. Henriksen, E.J., M.E. Tischler, S. Jacob and P.H. Cook. Muscle Protein and Glycogen Responses to Recovery from Hypogravity and Unloading by Tail-cast Suspension. The Physiologist 28: No. 6, Suppl S-193-194, 1985

8. Ilyina-Kakueva, E., V. V. Portugalov. Combined Effect of Space Flight and Radiation on Skeletal Muscles of Rats. Aviat. Space Environ. Med. 48(2): 115-119, 1977.

9. Ilyina-Kakueva, E., V. V. Portugalov, N. P. Krivenkova. Space Flight Effects on the Skeletal Muscles of Rats. Aviat. Space Environ. Med. 47(7): 700-703, 1976.

10. Jaspers, S. R., J. M. Fagan, M. E. Tischler. Biochemical Response to Chronic Shortening in Unloaded Soleus Muscles. J. Appl. Physiol. 59(4): 1159-1163, 1985.

11. LeBlanc, A., C. March, H. Evans, P. Johnson, V. Schneider, S. Jhingran. Bone and Muscle Atrophy with Suspension of the Rat. J. Appl. Physiol. 58(5): 1669-1675, 1985.

12. Musacchia, X. J., D. R. Deavers, J. A. Meininger, T. P. Davis. A Model for Hypokinesia: Effects on Muscle Atrophy in the Rat. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48(3): 479-486, 1980.

13. Musacchia, X. J., J. M. Steffen, and D. R. Deavers. Rat Hindlimb Muscle Responses to Suspension Hypokinesia/Hypodynamia. Aviat. Space Environ. Med. 54: 1015-1020, 1983.

14. Steffen, J. M. and X. J. Musacchia. Effects of Hypokinesia and Hypodynamia on Protein, RNA and DNA in Rat Hindlimb Muscles. Am. J. Physiol 247 (Regulatory Integrative Comp. Physiol. 16): R728-732, 1984.

15. Steffen, J. M., X. J. Musacchia. Spaceflight Effects on Adult Rat Muscle Protein, Nucleic Acids, and Amino Acids. Am. J. Physiol. 251 (Regulatory Integrative Comp. Physiol. 1986. (in press)

16. Steffen, J.M., R. D. Fell and X. J. Musacchia. Physiological Responses During Whole Body Suspension of Adult Rats. The Physiologist. 1986. (in press)

17. Szöőr, Á., M. Rapcsák, G. Hollósi. Experiemtnal Invesigations on the Hypokinesis of Skeletal Muscles with Different Functions, VIII. Acta Bio. Acad. Sci. Hung. 32 (2), 129-135, 1981.

18. Rapcsák, M., V. S. Oganov, A. Szöőr, S.A. Skuratove, T. Szilágyi, Ő. Takács. Effect of Weightlessness on the Function of Rat Skeletal Muscles on the Biosatellite "COSMOS-1129." Acta Physiol. Hung., Volume 62 (3-4), pp. 225-228 (1983).

19. Templeton, G. H., M. Padalino, J. Manton, T. LeConey, H. Hagler, . The Influence of Rat Suspension-Hypokinesia on the Gastrocnemius Muscle. Aviat. Space Environ. Med. 1984; 55:381-6.

20. Templeton, G. H., M. Padalino, J. Manton, M. Glasberg, C. J. Silver, P. Silver, G. DeMartino, T. LeConey, G. Klub, H. Hagler, J. L. Sutko. Influence of Suspension Hypokinesia on Rat Soleus Muscle. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 56(2): 278-286, 1984.

NEUROPHYSIOLOGICAL RESPONSES IN SUSPENDED ANIMAL MODELS

Yutaka Oomura and Toshihiko Katafuchi

Department of Physiology
Faculty of Medicine
Kyushu University
Fukuoka 812, Japan

In unanesthetized rats, single neuron activity in the lateral hypothalamic area (LHA) and paraventricular nucleus (PVN) was recorded during horizontal and head-down tilt suspension. When the rat was raised in the horizontally suspended position, 21 of 44 neurons in the LHA changed activity as follows: immediate increase (7/21, Type I), immediate decrease (3/21, Type II), and gradual decrease (11/21, Type III). The responses were suppressed on raising with a head-down tilt in about half of the neurons tested. Eight of 34 neurons in the PVN changed activity with horizontal suspension; gradual decrease (6/8) and gradual increase (2/8). Seven of the 8 neurons showed a greater response by head-down tilting. Among the remaining neurons, 5 exhibited a gradual decrease in activity during head-down tilt without any change during horizontal suspension. In addition, four of 5 neurons that showed a decrease in activity during head-down tilt increased their activity by hyperosmotic stimuli. Possible signals which induce the changes in the neuronal activity and an involvement of the hypothalamus in regulation of autonomic nervous and endocrine system under simulative hypogravic condition are discussed.

INTRODUCTION

Weightlessness and simulated weightlessness cause a variety of changes in metabolic, cardivascular and body fluid homeostasis (10,15). It is well known that the hypothalamus is involved in regulation of these functions through the endocrine and autonomic nervous system. To understand the central mechanism of these reactions, we investigated the effects of simulative hypogravic condition induced by horizontal or head-down suspension on single neuron activity in the lateral hypothalamic area (LHA) and paraventricular neucleus (PVN). A portion of this study has been previously reported (5).

METHOD

Wistar rats weighing 300-350 g were used. The suspension with or without a head-down tilt method as a low G simulation was applied (11,12,15,16). Under ketamine (100 mg/kg) anesthesia, a bundle of recording electrodes consisting of five flexible teflon coated platinum-iridium wires (Medwire, New York, 25 μm o.d.) was implanted into the LHA (A, 2.3 posteror to the bregma; L, 1.5; H. 7.5-8.5 mm down from the cortex surface), or PVN (A, 1.5 posterior to the bregma; L, 0.6; H, 7.5 mm down from the cortex surface). Each electrode was exposed at the cut end and cemented with polyethylene glycol. After recovery, 2 wires were selected and single neuronal activity was differentially amplified through a dual type FET (2SK18A, Toshiba) placed on the skull (6). Rats wore a denim harness which had four openings to extend the legs and had a bar attached for suspension. Long-term recording was performed under unaesthetized conditions during the series of trials as follows; standing on the floor, horizontal suspension, and suspension with a 45° head-down tilt. In some of the PVN neurons, hypertonic saline (2% NaCl) administered intraperitoneally (0.5 ml/rat) or intra-third-cerebroventricularlly (2 μl/rat). After the experiments were completed, recording sites were verified histologically.

RESULTS

1) Responses of LHA neurons

Twenty one of 44 LHA neurons (48%) displayed changes in discharge frequency by the horizontal suspension. Among these 21 neurons, 7 (33%) responded with an increase in their activity immediately on raising the animal from the ground level (Type I), 3 (14%) with an immediate decrease (Type II), and 11 (53%) with a gradual decrease (Type III).

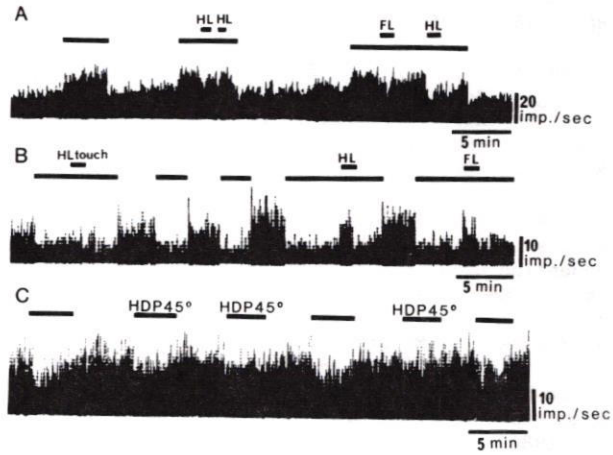


Figure 1. Effects of body suspension and partial landing on LHA neuronal activity. A, B and C, different neurons. _____, horizontal suspension; HL, FL, partial landing of hind limbs (HL) or forelimbs (FL) during suspension. HL touch; light touch of hind-limbs with a board. HDP 45°, head-down position at 45°. A: immediate increase in activity on horizontally raising of the rat (Type I), and immediate decrease by partial landing. B: immediate decrease in activity (Type II), and immediate increase by partial landing. Light touching of hind-limbs with a board caused no change in single neuron activity. C: gradual decrease in activity to horizontal suspension (Type III) and suppression of the decrease at a 45° head-down tilt position.

Fig. 1 shows Type I (A), Type II (B) and Type III (C) neurons respectively. These neuronal activities returned to the base line level as soon as the fore-limbs or hind-limbs of the rats were

supported by a board landing. Only touching of the limbs on the board without flexions of joints during suspension resulted in no change in neuronal activity (Fig. 1B, left). Therefore, changes in the LHA neuronal activity caused by suspension are probably attributed to changes in signals coming from proprioreceptors, e.g., muscle receptors in extensor muscles or antigravity muscles, tendon organs, and joint receptors. The neuronal activity of Type III neurons showed a slower response than that of Type I or Type II neurons by the horizontal suspension (Fig. 1C). The decrease sometimes began to recover gradually before landing. On the basis of these results, it could be assumed that Type I and Type II neurons were more directly influenced by proprioreceptive signals than Type III neurons. The slow response of Type III neurons may result from the modulation or integration of proprioreceptive stimuli on their way to the LHA or in the LHA itself.

We examined the effects of head-down tilt suspension on the LHA neuronal activity which showed the changes in response to horizontal suspension. Of the 10 neurons tested, 3 were determined to be Type I neurons and 7 were Type III neurons. Seven of 10 neurons exhibited suppression of the response to horizontal suspension on raising with head-down position from the ground level. Fig. 1C showed an example of such neurons (Type III). The responses of the other 3 neurons were not different from those to horizontal suspension. These changes in the response would be induced by tilting the animal's body itself, because other experimental procedures were the same as those of the horizontal suspension method. This would indicate that signals coming from sources other than proprioreceptors, for example from the vestibular organ, baroreceptors or volume receptors in the thoracic cavity might contribute to this attenuation of the responses.

2) Responses of PVN neurons

Eight of 34 PVN neurons (24%) changed their activity by the horizontal suspension; 6 (75%) exhibited a gradual decrease (Fig. 2A) and 2 (25%), a gradual increase in activity (Fig. 2C). There were no neurons that showed immediate changes in activity as did LHA neurons (Type I and Type II). Only touching of the limbs on the board caused no change in neuronal activity (Fig. 2C). These neurons exhibited a greater response to head-down tilt than to horizontal suspension (Fig. 2A,C). Among the remaining neurons, 5 showed a gradual decrease by head-down tilt without any change in activity during horizontal suspension (Fig. 2B).

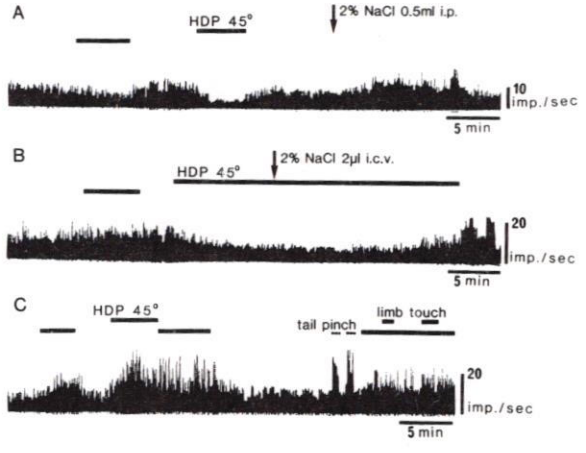


Figure 2. Effects of body suspension and osmotic stimuli on PVN neuronal activity. A, B and C different neurons. _____, horizontal suspension; HDP 45°, head-down position at 45°. A: gradual decrease in activity on horizontally raising of the rat, and greater response by head-down tilt. Intraperitoneal injection of hypertonic saline caused an increase in activity. B: no change in activity during horizontal suspension and decrease by head-down tilting. Intracerebroventricular injection of hypertonic saline during the suppressed period had no effect. C: gradual increase in activity by horizontal suspension with a greater response by head-down tilt. Tail pinching caused an immediate increase in activity. Light touching of limbs with a board, no change.

Eleven neurons showed gradual decrease in activity during head-down tilting, of which 6 showed smaller response by horizontal suspension. Since activation of baroreceptors has been shown to inhibit PVN neurosecretory cells (4,9) and conversely, antiduretic hormone is released in response to head-up tilt in quadriplegic subjects (19), the decrease in activity during head-down tilt might be caused by information from baroreceptors in the thoracic cavity. Most of these neurons (4 of 5 neurons tested) increased their activity by intracerebroventricularlly or intraperitoneally administered hypertonic saline (Fig. 2A). Thus, this suggested that baroreceptors and osmotic stimuli converge onto the same neuron in the PVN. However, information from baroreceptors was more effective than that of osmotic stimuli because hyperosmotic stimuli had no effect on PVN activity during the suppressed period induced by head-down tilt (Fig. 2B). Administration of hypertonic saline had no effect in a neuron showing a gradual increase during horizontal suspension (not shown). Neuronal activity of this neuron was increased by noxious stimulii such as tail pinching (Fig. 2C).

DISCUSSION

It has been shown that hypothalamic neurons were affected by stimulation of muscle afferent nerve, as well as visceral stimulation (1,3,13,18). Among the possible pathways by which these different modalities affect the hypothalamic neurons, it has been suggested that somatosensory inputs reach the hypothalamus multisynaptically via the mesencephalic reticular formation (RF) (2). Namely, degeneration studies have showed the existence of the reticulo- hypothalamic pathway that is related to the so-called extralemniscal sensory system (20). Proprioreceptive information which was suggested to alter the hypothalamic neuronal activity in the present experiments, might pass through this pathway. Since the signals coming from muscle spindles have a strong association with the vestibulo-cerebellar system, there is another possibility, i.e., these signals and vestibular information itself are conveyed via the cerebellar nuclei, including the vestibular and fastigial nuclei. Electrophysiological studies have shown that the lateral vestibular nucleus (Deiters') has polysynaptic connections with the LHA (7). In addition, a recent anatomical study showed a direct projection from the cerebellar nuclei to the hypothalamus (3). Information from thoracic baroreceptors which perceived changes in blood redistribution was thought to be carried by the pathway from the nucleus of the solitary tract to the LHA directly or via the parabrachial nucleus (8,14).

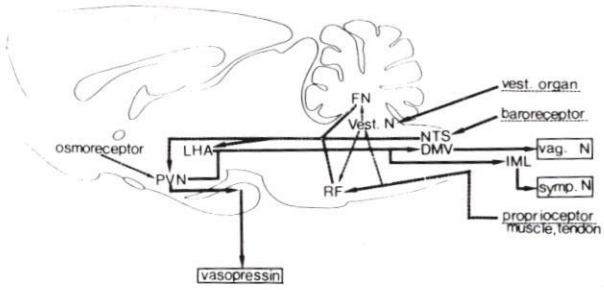


Figure 3. Input-output organization of the LHA and PVN during body suspension. LHA, lateral hypothalamic area; PVN, paraventricular nucleus; NTS, nucleus tractus solitarius; DMV, dorsomotor nucleus of the vagus; IML, intermediolateral cell column of the spinal cord; Vest. N, vestibular nuclei; FN, fastigial nucleus; RF, mesencephalic reticular formation; Vag. N, vagus nerve; Symp. N, sympathetic nerve.

Our results show the possibility that proprioreceptive, vestibular, and/or baroreceptor information induce changes in hypothalamic neuronal acitivty. Monosynaptic projections originating from LHA and PVN reach preganglionic neurons of the sympathetic and parasympathetic systems, intermediolateral cell column of the spinal cord and dorsomotor nucleus of the vagus (17). It was also demonstrated that the LHA and PVN were involved in the modulation of efferent autonomic nerve activity (13). Therefore, it is possible that the LHA and PVN, receiving the signals discussed above, influence these autonomic nuclei and neurosecretory cells in the PVN and modulate the autonomic responses and release of vasopressin. Fig. 3 shows possible input-output organization during body suspension. This hypothesis may account for the autonomic and endocrine disorders in weightlessness.

REFERENCES

1. Brooks, C.McC., J. Ushiyama, G. Lange, Reactions of neurons in or near the supraoptic nuclei, Am. J. Physiol. 202, 487-490, 1962.
2. Feldman, S., Effects of reticular formation leisons on afferent projections to the hypothalamus, electroencephalogr. Neurophysiol. 15, 672-682, 1963.
3. Haines, D.E., E. Dietrichs, T.E. Sowa, Hypothalamo-cerebellar and cerebello-hypothalamic pathways: a review and hypothesis concerning cerebellar circuits which may influence autonomic centers and affective behavior, Brain Behav. Evol. 24: 198-220, 1984.
4. Kannan, H. and Yamashita, H., Electrophysiological study of paraventicular nucleus neurons projecting to the dorsomedial medulla and their response to baroreceptor stimulation in rats, Brain Research, 279: 31-40, 1983.
5. Katafuchi, T., H. Yoshimatsu, Y. Oomura, Responses of lateral hypothalamic neurons to simulative hypogravic condition induced by body suspension, Brain Res. Bull. 12, 29-31, 1984.
6. Katafuchi, T., Y. Oomura, H. Yoshimatsu, Single neuron activity in the rat lateral hypothalamus during 2-deoxy-D-glucose induced and natural feeding behavior, Brain Res. 359, 1-9, 1985.
7. Katafuchi, T., K.P. Puthuraya, H. Yoshimatsu, Y. Oomura, Responses of rat lateral hypothalamic neuron activity to vestibular nuclei stimulation, Brain Res., 1987, in press.
8. Koh, E.T., J.A. Ricardo, Afferents and Efferents of the parabrachial region in the rat: evidence for parallel ascending gustatory versus visceroceptive systems arising from the nucleus of the solitary tract, Anat. Rec. 190, 449, 1975.
9. Koizumi, K. and Yamashita, H., Influence of atrial stretch receptors on hypothalamic neurosecretory neurons, J. Physiol. (Lond.) 285: 341-358, 1978.
10. Kozerenko, O.P., A.I. Grigoriev, A.D. Egorov, Results of investigations of weightlessness effects during prolonged manned space flights onboard salyut-6, Physiologist, Suppl. 24, S49-54, 1981.
11. Morey, E.R., E.E. Sabelman, R.T. Turner, D.J. Baylink, A new rat model simulating some aspects of space flight, Physiologist 22, S23-24, 1979.
12. Musacchia, X.J., D.R. Deavers, G.A. Meininger, T.P. Davis, A model for hypokinesia: effects on muscle atrophy in the rat, J. Appl. Physiol. 48, 479-486, 1980.
13. Oomura, Y., H. Yoshimatsu, Neural network of glucose monitoring system, J. Auton. Nerv. Syst. 10: 359-372, 1984.
14. Ricardo, J.A., E.T. Koh, Anatomical evidence of direct projections form the nucleus of the solitary tract to the hypothalamus, amygdala, and other forbrain structures in the rat, Brain Res. 153, 1-26, 1978.
15. Saiki, H., M. Nakaya, Y. Sugita, M. Kamachi, Metabolic and hormonal mechanisms of mineral metabolic adaptation to induced hypokinetics in rats, Aviat. Space Environ. Med. 47, 846-852, 1976.
16. Sandler, H., Low-G simulation in mammalian research, Physiologist 22, S19-S22, 1979.
17. Saper, C.B., A.D. Loewy, L.W. Swanson and W.M. Cowan, Direct hypothalamo-autonomic connections, Brain Res. 117: 305-312, 1976.
18. Spyer, K.M., Baroreceptor sensitive neurones in the anterior hypothalamus of the cat, J. Physiol. (Lond.) 224, 245-257, 1972.
19. Sved, A.F., F.H. McDowell and W.W. Blessing, Release of antidiuretic hormone in quadriplegic subjects in response to head-up tilt, Neurology 35: 78-82, 1985.
20. Wolf, G., L.V. DiCara, A third ascending hypothalamopetal pathway, Exp. Neurol. 33, 69-77, 1971.

EFFECTS OF GRAVITY ON RHYTHMIC ACTIVITIES IN THE PHRENIC AND SYMPATHETIC NERVE DISCHARGES

Takehiko Hukuhara, Naofumi Kimura,
Kazuo Takano and Fusao Kato

Department of Pharmacology II
The Jikei University School of Medicine
Nishishinbashi, Minato-ku, Tokyo 105

Abstract

Effects of passive postural changes on the cardiac-related sympathetic nerve activity and high frequency oscillation in the phrenic nerve discharge were quantitatively analyzed by spectral analyses. Experiments were performed on vagotomized rabbits with intact sinus nerves, anesthetized with ether, paralyzed and artificially ventilated. In the power spectrum of renal sympathetic nerve discharge, cardiac-related component was decreased by head-up tilting (30°) and was increased by head-down tilting (30°). Coherence between sympathetic nerve discharge and arterial pulse at the frequency of cardiac rhythm was decreased by head-up tilting and was increased by head-down tilting. In the power spectrum for phrenic nerve discharge, the peak-area corresponding to the high frequency oscillation, which was estimated by non-linear least-squares method, was increased by both the head-up and head-down tiltings.

Introduction

Changes in the sympathetic nerve discharge (SND) produced by postural changes have been analyzed by means of integration or pulse count in respect of the overall activity of the nerve discharge (12). Therefore, the changes in the rhythmic components of SND produced by postural changes are presently unknown except a part of them. Previous works (8, 9) from our department have demonstrated that the overall activity of the renal SND is markedly increased by head-up tilting, and that both the head-up and head-down tilting procedures cause an increase in the total activity of phrenic nerve discharge (PND) and a prolongation of the respiratory cycle of PND, in vagotomized rabbits with intact carotid sinus nerves. In addition, the cross-correlation analysis has revealed that the head-up tilting is accompanied by a shift in the phase relation between respiratory volleys in the SND and PND and an increase in the cross-correlation coefficient of the two nerve discharges (9). It still remains, however, to be established whether the other rhythmic components in SND and PND are influenced by tilting procedures. Spontaneous efferent discharges recorded from sympathetic nerve bundles usually are synchronized into bursts that are locked in a 1:1 relation to the cardiac cycle by the baroreceptor reflexes (2). However, it was demonstrated that the 1:1 relationship between bursts of SND and the cardiac cycle was disrupted when heart rate was markedly decreased (5) or arterial blood pressure was lowered (6). In the first part of the present study, we have investigated the changes in the relationship between cardiac-related activity in SND and arterial pulse caused by tilting procedures. For this purpose, we employed the analytical method of coherence spectra and evaluated the changes in the height of the spectral peak at the frequency of cardiac rhythm in the coherence spectra between SND and arterial pulse wave (11). A coherence function indicates the linear relationship between two signals at a given frequency (1). In the second part of the study, we have undertaken detailed quantitative analyses of the effects of postural changes on the high frequency oscillation (HFO) which is the 60- to 100-Hz component observed in the inspiratory phase of PND (4, 13). According to the previous studies (3, 4, 13) and recent our studies (10), it is probably considered that HFO originates in the brain stem and is a characteristic component in the efferent nerve activities which innervate skeletal muscles associated with respiratory movement.

Methods

Experiments were performed on 6 rabbits of either sex, weighing between 2.2 and 3.6kg. The animals were anesthetized with diethyl ether, immobilized with gallamine triethiodide (5mg/kg, i v) and artificially ventilated. The tidal volume of artificial ventilation was adjusted to maintain the end-tidal CO_2 level at 4.1±0.7% (NEC San-ei 1H21 expired gas analyzer). Rectal temperature was maintained between 37 and 38° C with a heat pad. Bilateral cervical vagus nerves were cut in all experiments. The carotid sinus nerves were remained intact and aortic depressor nerves were also remained intact in a part of experiments. Spontaneous efferent discharges were recorded from the right phrenic and renal sympathetic nerve bundles. Electrical recording-artefacts accompanied with the experimental postural changes were possibly minimized by using implanted bipolar platinum electrodes insulated with silicon rubber. Capacity-coupled preamplification with a band pass of 0.5-1,000Hz for renal SND and 16-1,000Hz for PND was used (NEC San-ei Type 1205D preamplifier). Femoral arterial blood pressure and the electrocardiogram were recorded using standard techniques. The animal was placed in the supine position on a tilting table and was tilted for 2 to 10 min to the head-up position (at 30°) or the head-down position (at 30°). Data before and after tiltings were stored on magnetic tape and were analyzed using a NEC San-ei 7T17 computer after passing these signals through the adequate low-pass filters for preventing aliasing (1). First, the power spectra of SND and arterial pulse and coherence spectra between the arterial pulse and SND were computed (120s data, 0 to 50 Hz; ensemble average of 30 segments). To estimate the degree of the linear relation between arterial pulse and cardiac-related activity in SND, the height of the spectral peak at the frequency of cardiac rhythm was calculated in the coherence spectra (1, 11). If the coherence is large close to 1.0 at a given frequency, it can be interpreted that components of two signals at the given frequency are synchronized and coherent. Second, according to the standard procedure (1), we calculated the power spectral density function of PND (0 to 200Hz, 0.25Hz/bin; ensemble average of 30 segments) from consecutive 120s data. Our preliminary survey (10) based on the non-linear least-squares method has revealed that the Cauchy distribution could be regarded as one of the fittest approximation of the peak corresponding to HFO in the power spectrum. By using this "curve fitting" estimation method, the peak-area and peak-frequency of the spectral peak corresponding to HFO in PND were estimated. Statistical analysis was performed with Student's t-test for paired data. Probability levels less than 0.05 were considered significant. Values are expressed as means ± standard deviations (SD).

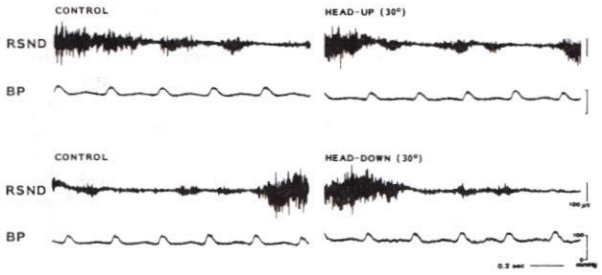


Figure 1. Effects of postural changes on cardiac-related activity in the renal sympathetic nerve discharge. Top: control (horizontal supine) and head-up position 2 min after the tilting. Bottom: control (horizontal supine) and head-down position 2min after the tilting. RSND, renal sympathetic nerve discharge; BP, arterial blood pressure. Horizontal calibration is 0.2s. Vertical calibration for nerve discharge is 100 μV.

Results

Effect of postural changes on renal sympathetic nerve discharge.

Spontaneous efferent discharges recorded from the renal sympathetic nerve were synchronized into burst discharges that were locked in a 1:1 relation to the arterial pulse cycle at the horizontal supine (control in Figure 1) before tiltings. After tilting to the head-up position, the cardiac-related activity in SND was dissociated from pulse cycle and was no longer locked in a 1:1 relation to the cardiac cycle (Figure 1). The mean arterial pressure (control; 96±22mmHg) was lowered to 83±29mmHg by head-up tilting. When the animal was tilted to the head-down position, cardiac-related sympathetic nerve activity was more closely locked to the cardiac cycle (Figure 1). The mean arterial pressure (control; 98±16mmHg) was increased to 105±16mmHg by head-down tilting.

Power spectral analysis of renal sympathetic nerve discharge

Figure 2 shows the power spectra ranging from 2 to 10Hz of the renal SND before and after tiltings. Power spectrum of the renal SND had a major peak corresponding to the cardiac-related activity in SND at about 4Hz (indicated with arrow, Figure 2, I). The height of the peak corresponding to the cardiac-related activity in SND decreased after tilting to the head-up position (Figure 2,IB). In contrast, the head-down tilting procedure markedly raised the spectral peak corresponding to the cardiac-related activity in the power spectra of SND (Figure 2, IIB).

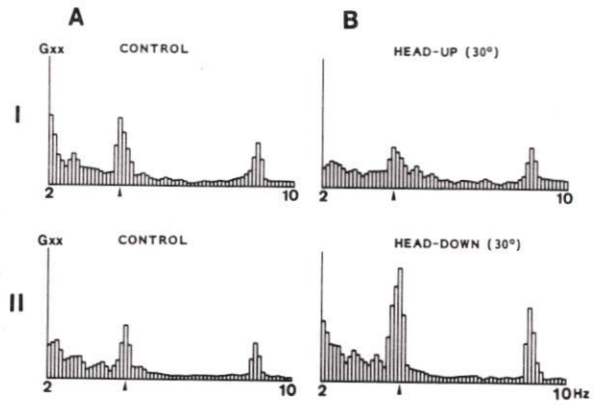


Figure 2. Power spectra for renal sympathetic nerve discharge. IA: horizontal supine (control). IB: 2min after head-up tilting. II: horizontal supine (IIA, control) and 2min after head-down tilting (IIB). I and II are from same rabbit. Ordinate is power spectral density. Abscissa is frequency. Resolution was 0.125Hz. Arrow under each spectrum indicates the frequency of the cardiac rhythm.

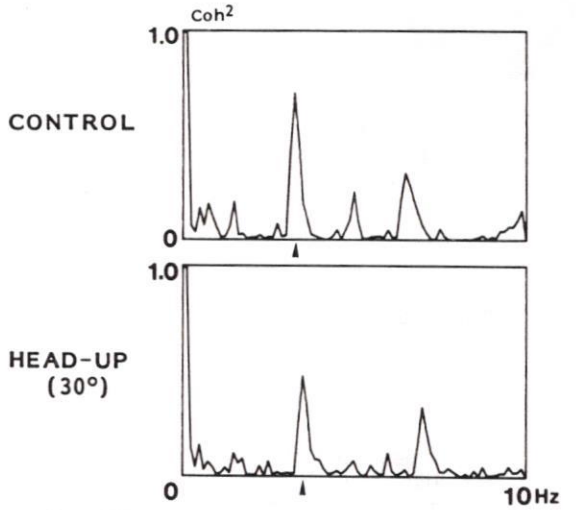


Figure 3. Effect of head-up tilting on coherence spectra between renal sympathetic nerve activity and arterial pulse wave. Squared coherence spectra between renal sympathetic nerve activity and arterial pulse wave at horizontal position (top) and head-up position (bottom). Arrow under each spectrum points the frequency of cardiac rhythm. Vagotomized rabbit with intact bilateral carotid sinus nerves. Ordinate is squared coherence (Coh^2) and abscissa is frequency. Each coherence spectrum was averaged 30 times. Resolution was 0.125Hz. The data analyses were performed 2min after the tiltings.

Coherence spectra between arterial pulse and sympathetic nerve discharge

Coherence spectra between SND and arterial pulse wave had spectral peaks corresponding to the cardiac rhythm and its harmonics (Figure 3 and 4).

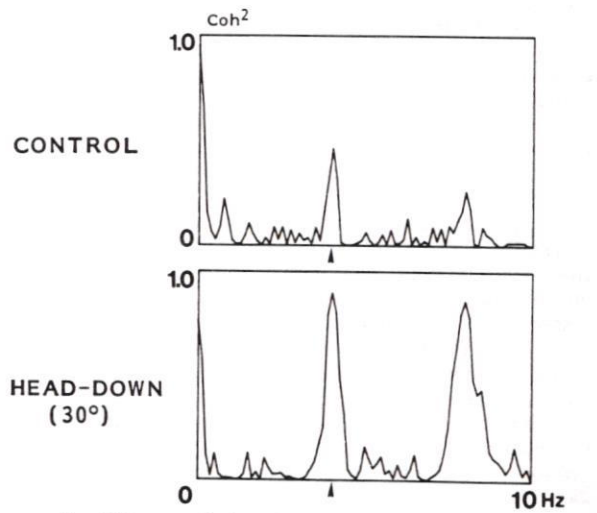


Figure 4. Effect of head-down tilting on coherence spectra between renal sympathetic nerve activity and arterial pulse wave. Squared coherence spectra between renal sympathetic nerve activity and arterial pulse wave at horizontal position (top) and head-down position (bottom). Arrow under each spectrum indicates the frequency of cardiac rhythm. Vagotomized rabbit with intact bilateral carotid sinus nerves. Ordinate is squared coherence (Coh^2) and abscissa is frequency. Each coherence spectrum was averaged 30 times. Resolution was 0.125Hz. The data analyses were performed 2min after the tiltings.

Table I. Effects of postural changes on coherence between SND and arterial pulse.

	n	Control	Tilting
Head-up 30°	7	0.59±0.17	0.41±0.20*
Head-down 30°	8	0.57±0.14	0.77±0.18*

Each value is the coherence between renal SND and arterial pulse at the frequency of cardiac rhythm (mean±SD). n: number of trials. *Significantly different from the control value ($P<0.05$).

The height of the peak at the frequency of the cardiac rhythm (about 4Hz) was decreased by head-up tilting (Figure 3). While, the tilting to the head-down position caused a rise of the peak corresponding to the cardiac rhythm (Figure 4). The mean values of coherence of the peak corresponding to the cardiac rhythm before and after tilting procedures are shown in Figure 5 and Table I. Before tilting to the head-up position, the mean coherence of the peak corresponding to the cardiac rhythm was 0.59±0.17 (n=7). The coherence significantly decreased to 0.41±0.20 (n=7) after tilting to the head-down position. The mean value of the coherence was 0.57±0.14 before the head-down tilting, and significantly increased to 0.77±0.18 after head-down tilting (n=8).

Effect of postural changes on phrenic nerve discharge

Typical recordings of the spontaneous efferent discharge of the phrenic nerve were shown in Figure 6. High frequency oscillation (HFO) with about 100Hz rhythm was observed in the inspiratory phase of PND. Under the condition that the end-tidal CO_2 was controlled not so as to change, the amplitude of the wave of HFO increased after tilting to the head-up position. In the head-down tilting procedure, an increase in the end-tidal CO_2 was unavoidable. The amplitude of PND increased accompanied with an elevation of the end-tidal CO_2.

Effect of postural changes on the spectral peak of high frequency oscillation

A sharp peak corresponding to the high frequency oscillation (HFO) was found near 100Hz in the power spectrum of the PND. This spectral peak

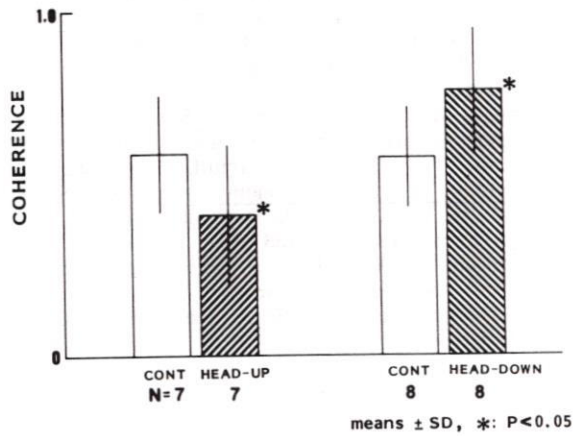


Figure 5. Coherence at the frequency of cardiac rhythm. Height of each column shows the mean value of the squared coherence between renal SND and pulse wave at the frequency of cardiac rhythm. Vertical bar shows SD. Shaded column is head-up or head-down position. Open column is the control (horizontal supine) of each. N: Number of experiments. *Significantly different from the control value ($P<0.05$).

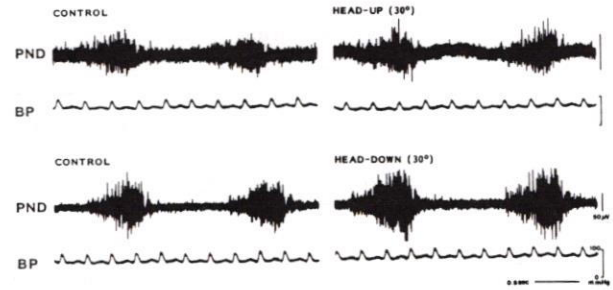


Figure 6. Effect of postural changes on the phrenic nerve discharge. Top: horizontal supine (control) and 2min after head-up tilting. Bottom: horizontal supine (control) and 2min after head-down tilting. Top and bottom tracings are from different rabbits. PND, phrenic nerve discharge. BP, arterial blood pressure. Horizontal calibration is 0.5s. Vertical calibrations for nerve activities are 50 μV.

was fitted to the Cauchy distribution by non-linear least-squares method. The head-up tilting procedure caused a rise of the peak corresponding to the HFO in the power spectrum (Figure 7).

The mean values of the peak-area and peak-frequency estimated by the curve fitting method based on the non-linear least-squares method are shown in Table II. Under the condition that the tidal volume of artificial ventilation was adjusted to maintain the mean value of end-tidal CO_2 level at 4.1% (Table II), the peak-area corresponding to the HFO significantly increased after tilting to the head-up position. The peak-frequency was not significantly changed by the head-up tilting. In the head-down tilting position, the peak-area corresponding to the HFO increased depending on the elevation of end-tidal CO_2 and the peak-frequency was elevated.

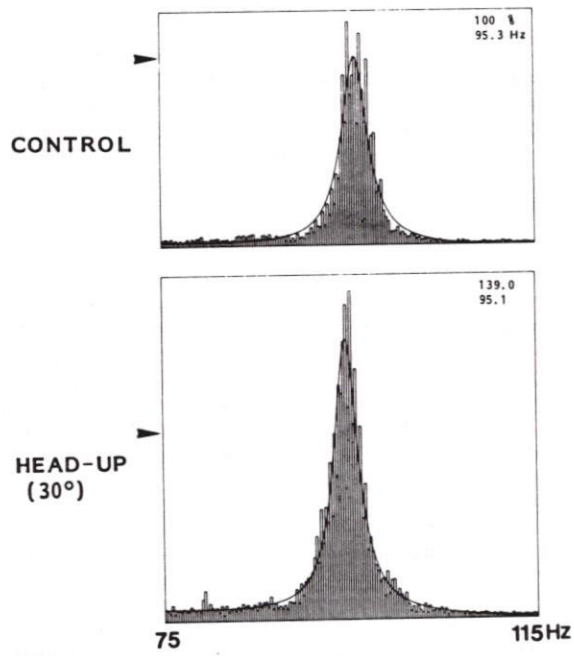


Figure 7. Effect of head-up tilting on the spectral peak of the high frequency oscillation. Power spectra for high frequency oscillation in PND. Horizontal position (top) and 2min after head-up at 30° (bottom). Ordinate represents power spectral density. Arrows indicate the peak-height of the control. Abscissa is frequency. Bin width was 0.25Hz. The curve drawn with a solid line indicates Cauchy distribution fitted by non-linear least-squares method.

Table II. Effect of head-up tilting on the spectral peak of high frequency oscillation in PND.

	n	Control	Head-up
Peak-area (%)	8	100	133±19*
Peak-frequency (Hz)	8	105±16	104±16
End-tidal CO_2 (%)	8	4.1±0.7	4.1±0.8

Peak-area and peak-frequency were estimated by curve fitting method. Values are expressed as means±SD. n: number of trials. *Significantly different from the control value ($P<0.05$).

Discussion

One of the major findings of the present study is that the head-up tilting procedure causes a disruption of the 1:1 relationship between cardiac-related sympathetic nerve activity and arterial pulse. In addition, the head-down tilting procedure intensified the relationship between arterial pulse and cardiac-related sympathetic nerve activity. These results are consistent with a recent description by Gebber and Barman (6). They presented that the 1:1 relationship between bursts of SND and the cardiac cycle was disrupted under the condition of reduced blood pressure. When the inputs from the arterial baroreceptors are decreased by lowering blood pressure, baroreflex mechanisms may be no longer able to maintain the 1:1 locking of bursts of SND to the cardiac cycle. In some cases of the present experiments, the spectral peak corresponding to the cardiac rhythm was eliminated from the coherence spectrum between arterial pulse and SND when the blood pressure was markedly lowered by prolonged head-up tilting. As well as this, the spectral peak corresponding to the cardiac rhythm was eliminated from the coherence spectrum between SND and arterial pulse after complete section of the carotid sinus and aortic depressor nerves (11). It is considered that the baroreflex mechanism of rabbit is not enough to compensate the fall in arterial pressure caused by head-up tilting under the tested experimental condition, because the arterial blood pressure was actually decreased by head-up tilting. In a previous report (7), it is described that in the vertical head-up position the rabbits died in the course of 15 minutes to 2 hours.

Another finding of the present study is that head-up tilting procedure causes an increase in the peak-area of high frequency oscillation (HFO) estimated by the curve fitting method based on the non-linear least-squares method. Since the end-tidal CO_2 was unchanged before and after the head-up tilting procedure, this increase in the peak-area was probably mediated by baroreceptor reflex mechanisms rather than peripheral chemoreceptor reflex or central chemosensitivity. In addition, the peak-frequency was not significantly changed by passive head-up tilting. As presented in a recent report (10) from our department, The increase in the peak-area corresponding to HFO produced by hypoventilation is accompanied by an elevation in the peak-frequency. In the head-down position, an increase in the end-tidal CO_2 was unavoidable. The peak-area corresponding to the HFO increased depending on the elevation of end-tidal CO_2. This increase in the peak-area of HFO was accompanied by a shift of the peak to the higher side as well as the response to hypercapnea.

In conclusion, the 1:1 relationship between the bursts in SND and arterial pulse was disrupted by head-up tilting, and was intensified by head-down tilting. The component of high frequency oscillation in neural outflow from respiratory center was increased by both the tilting procedures.

Acknowledgements

This study was partly supported by the Ministry of Education, Science, and Culture, Japan, Grant-in-Aid No. 57480137 and 00437003.

References

1. Bendat, J. S., and A. G. Piersol. In: Random Data: Analysis and Measurement Procedures, New-York: Wiley-Interscience, 1971.
2. Bronk, D. W., L. K. Ferguson, R. Margaria, and D. Y. Solandt. The activity of the cardiac sympathetic centers. Am. J. Physiol. 117: 237-249, 1936.
3. Cohen, M. I. Synchronization of discharges, spontaneous and evoked, between inspiratory neurons. Acta. Neurobiol. Exp. 33: 189-218, 1973.
4. Dittler, R., and S. Garten. Die zeitliche Folge der Aktionsstroeme in Phrenicus und Zwerchfell bei der natuerlichen Innervation. Z. Biol. 58: 420-450. 1912.
5. Gebber, G. L. Basis for phase relations between baroreceptor and sympathetic nervous discharge. Am. J. Physiol. 230: 263-270, 1976.
6. Gebber, G. L., and S. M. Barman. Lateral tegmental field neurons of cat medulla: A potential source of basal sympathetic nerve discharge. J. Neurophysiol. 54: 1498-1512, 1985.
7. Hill, L. The influence of the force of gravity on the circulation of the blood. J. Physiol. London 18: 15-53, 1895.
8. Hukuhara, T., Jr., N. Kimura, K. Takano. Effects of gravity on the phrenic and renal sympathetic nerve activities in the rabbit. Proceedings of the 13th International Symposium on Space Technology and Science 1615-1620, 1982.
9. Hukuhara, T., Jr., N. Kimura, K. Takano. Effect of gravity on neural outflow from the central respiratory and vasomotor control mechanisms in the rabbit. The Physiologist 27: S17-S20, 1984.
10. Kato, F., N. Kimura and K. Takano and T. Hukuhara Jr. Quantitative spectral analysis of high frequency oscillations in efferent nerve activities with respiratory rhythm. In: Respiratory Muscles and Their Neuromotor Control, edited by G. Sieck et al., New-York: Alan R. Liss, Inc. (in press).
11. Kimura, N., F. Kato, K. Takano, and T. Hukuhara Jr. Spectral analysis of cardiac-related sympathetic nerve activity in rabbits. In: Brain and Blood Pressure Control, edited by K. Nakamura, Amsterdam: Elsevier Science Publishers B.V., 1986, pp.153-162.
12. Ninomiya, I., and Y. Yonezawa. Sympathetic nerve activity, aortic pressure and heart rate in response to behavioral stimuli. In: Integrative Functions of the Autonomic Nervous System, edited by McC. Brooks et al., Tokyo: Univ. Tokyo Press, 1979, pp.433-442.
13. Richardson, C. A, and R. A. Mitchell. Power spectral analysis of inspiratory nerve activity in the decerebrate cat. Brain Res. 233: 317-336. 1982.

COMPARATIVE ASPECTS OF HEMATOLOGICAL RESPONSES IN ANIMAL AND HUMAN MODELS IN SIMULATIONS OF WEIGHTLESSNESS AND SPACE FLIGHT

R.D. Lange[1], J.B. Jones[2], and P.C. Johnson, Jr.[3]

[1]Department of Medical Biology, Knoxville Unit of University of Tennessee College of Medicine, 1924 Alcoa Highway, Knoxville, Tennessee 37920
[2]Department of Environmental Practice, University of Tennessee College of Veterinary Medicine, Knoxville, Tennessee 37916
[3]NASA/Johnson Space Center, Houston, Texas 77058

This paper reviews some human and animal responses to space flight as well as in control models in simulations of weightlessness. Astronauts after space flight have been found to have a decreased red blood cell mass and plasma volume. The reason for these changes is unknown but appears to be caused primarily by a decrease in the need of red blood cells in the weightless condition. Similar though more moderate changes have been found in human subjects subjected to prolonged bed rest or water immersion. What happens to the red cell mass of laboratory rats flown in microgravity is not known but rats have shown an increase in the rate of random red cell loss in flight suggesting a probable decrease. Rat models subjected to either head-down suspension or restraint alone have shown a decrease in red blood cell masses and a decrease in their plasma volume.

I. Introduction

Numerous studies have shown that astronauts after flights have a reduction in their ^{51}Cr red cell mass and ^{125}I HSA plasma volume and consequently a decreased blood volume (6,26). Similar changes have occurred in human subjects in simulations of weightlessness produced by bed rest with or without head-down tilt (1,8,10,13, 14,17,19,24). Far fewer studies have been carried out on animals flown in microgravity and it is not known whether the laboratory rat is a valid model for the changes which occur in humans during space flight (4,5,9,11,12,15,16,21-23). However, rats subjected to either antiorthostatic or orthostatic hypokinesia/hypodynamia exhibit some of the same changes in red cell mass and plasma volume found in astronauts after space flight (2,3).

We have compared the hematological changes found after space flight with changes found in simulated weightlessness. Because of limitations in space, we concentrate on the studies of human astronauts and their simulated controls on Spacelab 1 (SL-1). The focus on animal studies was on the results from animals flown on Spacelab 3 (SL-3) together with ground-based simulation experiments. The results of these studies have been previously published separately (2,3,11,12, 14). Results of other investigators will be discussed as space permits.

II. Human Studies

Although some of the red blood cell changes found in early flights of NASA spacecraft were undoubtedly due to hyperoxic damage to red blood cells caused by the utilization of an increased partial pressure of oxygen, the Russian experience plus the results of Skylab and shuttle studies effectively rule out hyperoxia as a cause of the decrease in red cell mass (6,26).

The results of Skylab reticulocyte studies pointed towards a decreased production of red blood cells. This was investigated in personnel who flew on SL-1 and in simulation subjects who were selected on the basis of similarity of age, weight, sex (male), physical condition and overall health status (14). During the simulation of the inflight period, the control subjects were placed at -6° head-down bed rest for a period equal to the flight period. The following table shows the changes in red cell mass and plasma volume in SL-1 flight personnel, and control subjects.

Table 1. Percent decrease in red cell mass (RCM) and plasma volume (PV)

	RCM		PV		
	Mean	S.E.	Mean	S.E.	N
SL-1, 10 days	9.3*	1.6	6.0	4.3	4
Bedrest, 10 days	4.6*	1.2	5.4	4.4	5

*Significantly ($p<.05$) different from preflight measurement.

The changes in reticulocyte numbers are shown in Table 2.

Table 2. Reticulocyte numbers x 10^9/L

	Preflight	MD-1	L+0	L+8
Flight	64±5	49±15	24±8*	48±5
Bedrest	35±6	36±4	38±6	32±9

*Significantly different ($p<.05$) from preflight measurement. MD = mission day; L = landing day.

As shown in Table 2 the reticulocyte number decreased in the astronauts, indicating a probable decrease in production of red blood cells. However, this was certainly not complete and as shown in Table 3 incorporation of radioactive iron injected preflight was quite similar in control and flight subjects. The post-flight decrease in the calculated red blood cell iron incorporation suggests an increased red blood cell production in crew members.

Table 3. RBC iron incorporation SL-1 and bedrest simulation (% in RBC)

	MD-1	MD-7	L+0	L+1	L+8	L+12
Flight	19	85	88	93	85	86
Bedrest	21	86	91	92	91	92

MD = mission day; L = landing day.

Also mitigating a complete shutdown of bone marrow production is the fact that the levels of serum iron and iron-binding capacity were unchanged. This also shows that iron stores are replete. Serum ferritin is a measure of iron stores and on SL-1, as shown in Table 4, there were significant increases seen on MD-7, L+0, and L+1. This could indicate that the iron from red blood cells lost early in flight was being

reutilized and also that the inflight loss of red blood cells was not the result of external hemorrhage.

Table 4. Ferritin changes SL-1 and bedrest simulation (percent change).

	MD-1	MD-7	L+0	L+1	L+8	L+12
SL-1	1.5	53*	62*	63*	1.9	-15
Bedrest	1.3	-13.9	-11.6	-11.9	-34.2*	-33.0*

*Significantly different ($p<.05$) from preflight measurements. MD = mission day; L = landing day.

The other major cause for a loss of red blood cell mass would be increased red blood cell destruction. However, radioactive tracer studies on SL-1 crew members showed that the percentage of red blood cells remaining at 8 days was the same as it was for simulation subjects and was normal. Intravascular hemolysis should lead to decreased serum haptoglobin, but haptoglobin increased slightly but not significantly.

III. Animal Studies

Simulation studies for SL-3 flight animal studies were carried out using rats suspended in a jacket and harness arrangement. In the first study the head-down angle was approximately 20° and by use of fore limbs the rats were able to move through 360° (2).

The results in the suspended rats showed:

A. Reduction in red blood cell mass,
B. Suppression of erythropoiesis,
C. A transient increase in hematocrit due to a reduction in plasma volume,
D. A post-exposure hematocrit decrease,
E. A weight loss (or failure to thrive),
F. A reduction in food and water consumption.

Similar results are observed in man so at least in a gross sense, the rat "model" seemed to reproduce many of the known hematological effects found during and after space flight.

The studies were expanded to evaluate the effect of restraint alone as opposed to head-down tilt and many of the same changes were found (3). Changes in red blood cell clearance were thought to be unique to the head-down posture. This is currently being reevaluated and preliminary results have shown no change in red blood cells remaining in the circulating red blood cell mass. Thus, survival was normal (R. Nachman, unpublished observations).

While the changes in red cell parameters have been conclusively shown in astronauts, to our knowledge no isotope studies of red cell mass have been performed on rats flown in space so it is not known if the rat is indeed a potential model for "space anemia."

On SL-3, 24 rats were flown on the 8-day flight. The hematology studies performed after the flight showed (11,12):

A. Hematocrits, red blood cell counts, and hemoglobin determinations were increased in flight animals. The number of reticulocytes were slightly decreased in the large rats and slightly increased in small rats but the differences were not significant.

B. There were no significant differences from control animals in spleen cell differentials or erythropoietin determinations for control and flight animals.

C. The bone marrow cells of flight animals demonstrated an increased sensitivity to erythropoietin when grown in methylcellulose cultures.

IV. Discussion

A comparison of the results of changes in red blood cell parameters in the human and rat studies are shown in Tables 5 and 6.

Table 5. Human studies

	SL-1			Bedrest Simulation 6° Head Down		
	L+0	L+8	L+13	L+0	L+8	L+13
RCM	↓*	↓	--	↓*	↓*	--
Plasma Vol	↓	↑	--	↓	NC	--
Blood Vol	↓*	NC	--	↓	↓	--
HCT	↓	↓*	↓*	↑	↓	--
RBCC	↓	↓*	↓*	↑	↓	↓
Hgb	↑*	↓*	↓*	↑	↓	↓
MCV	↑	↑	↑	NC	NC	NC
MCH	↑*	NC	NC	NC	NC	NC
MCHC	↑*	↓	↓	↑	↑	↑*
RBC Shape						
Discocyte %	↓	↓	NC	--	--	--
Echinocyte %	↑	↑*	↑	--	--	--
BM Ery.	--	--	--	--	--	--
Retics	↓	--	NC	↑	↓	↑
Fe Inc.	88%	--	--	91%	--	--
Serum Fe	NC	↓	↓	↓	↓	↓
Ferritin	↑*	NC	↓	↓	↓*	↓*
Haptoglobin	↑	↑	↑	↑	NC	NC
Epo	↓	↓	↓	↑	NC	NC
RBC Surv.	NC	--	--	NC	--	--

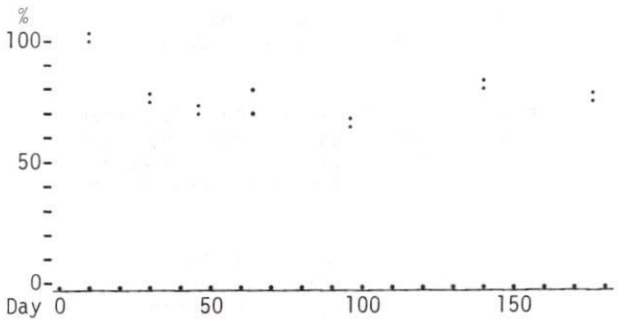
NC = Unchanged
* = Sig. <0.05.

Table 6. Rat studies

	SL-3 L+0		Head Down Suspended Rats		
	Sm. Rats	Lg. Rats	L+0	L+8	L+28
RCM	--	--	↓*	↓	NC
Plasma Vol	--	--	↓*	↓	NC
Blood Vol	--	--	↓*	↓*	NC
Hct	↑*	↑	↓*	↓*	↑
RBCC	↑*	↑	NC	↓	--
Hgb	↑*	↑	↓*	↓	--
MCV	↓	↓	↓*	↓	
MCH	↓	NC	--	--	--
MCHC	↓	↑	--	--	--
RBC Shape					
Discocytes	--	--	NC	NC	NC
Echinocytes	--	--	NC	NC	NC
Retics	↑	↓	↓*	↑	↓
BM Ery.	↓	↓	NC	NC	NC
Fe Inc.	--	--	↓*	NC	NC
RBC Surv.	--	--	↓*	--	--
Epo	↓	--	↑	--	--

NC = not changed from control.
-- = not performed.
* = Sig. <0.05

U.S.S.R. studies have also shown a decrease in hemoglobin mass of cosmanauts as shown in Figure 1.



Redrawn from Balakovskii et al. (1).
X axis, duration of (days).
Y axis, hemoglobin mass (% of base value).

The loss appears to level off so that after flights of 140 and 175 days mean decreases in hemoglobin mass (CO method) of -16 and -18 percent were found. Simulations by means of bedrest or immersion hypokinesia have shown a loss of red cell mass and plasma volume (10,13,14,17,20,24). The results of one study are shown in Table 7.

Table 7. Studies involving 30-day hypokinesia.

	HH[1]		AH[3]		Control	
	Hgb M[4] g/m^2	Retic[5] %	Hgb M g/m^2	Retic %	Hgb M g/m^2	Retic %
Before	432	5.7	420	6.9	418	7.8
After 30 days	343[6]		350[6]		---	
14-17 d read pt.	---	13.0[7]	404	12.6[7]	420	9.4

From Balakovskii et al. (1).
[1] = horizontal hypokinesia
[3] = antiorthostatic hypokinesia
[4] = hemoglobin mass
[5] = reticulocyte count
[6] = $p = <0.02$
[7] = $p = <0.001$

It is of interest that Kakurin et al. (7) found that antiorthostatic hypokinesia at -12° reproduced more closely the physiological responses shown in space crew members than did horizontal bed rest alone or head-down tilt at other angles.

In flight animals flown in space on Cosmos flights, Gazenko and Ilyin et al. found no differences in the values of hemoglobin, hematocrit and red blood cell counts (4,5). Gazenko et al. (4) and Leon et al. (16) found evidence for a hemolytic component in flight animals. However, in later studies, Leon et al. (15) found that when the animals were centrifuged in flight to produce the effect of gravity, the hemolysis was prevented indicating that the hemolysis results from the lack of gravity rather than other factors in the flight enfironment. Similar to the results of SL-3 rats, LeBlanc (unpublished observations) found that in flight animals there was an early post-flight significant increase in red blood cell counts, hemoglobin, hematocrit and mean corpuscular volume. Some observers have found a decrease in bone marrow red blood cell precursors in flight animals (4,5,21,23) though no changes were found in the SL-3 rats. It is apparent that findings for animal studies have varied from one study to the other and point up the need for isotopic studies of plasma volume and red cell mass to determine if the changes mimic those observed in humans participating in microgravity flights.

We still do not know the cause of the reduction in red blood cell mass in astronauts 19 years after the first description of this phenomena by Fischer, Johnson and Berry (6) and whether the rat is a proper model for "space anemia." Lists of possible causes for the anemia have been published (6,26). The anemia may be caused and maintained by decreased production of red blood cells which could be multifactorial. Some of the accumulated data suggests that after an initial decrease in the circulating red cells, the "erythrostat" appears to be reset at a lower level due to a decreased demand brought on by weightlessness. This is analogous to the atrophy of disuse seen in muscles and other tissues and the body's setting of ideal points for organ weights. The need to perform isotope studies of red cell mass and plasma volume to determine if these values decrease as do those of human astronauts is inferred from the animal studies. The needs for future studies were pointed out by a working group of the life sciences research office of the Federation of American Societies of Experimental Biology and are given in Table 8 (25).

Table 8. Baseline data for analysis of erythrokinetics of space flights*

	Settings and Subjects			
	Ground-Based**		Inflight***	
Parameter	Animal	Human	Animal	Human
Red cell count	+	+	+	+
Hemoglobin	+	+	+	+
Hematocrit	+	+	+	+
Red cell mass	+	+	+	+
Blood volume	+	+	+	+
Plasma volume	+	+	+	+
Reticulocyte count	+	+	+	+
Erythropoietin	+	+	+	+
Plasma or serum haptoglobin	+	+	+	+
Platelets	+	+	+	+
Red cell shape	+	+	+	+
Red cell size	+	+	+	+
Blood P_{50}	+	+	+	+
Blood PCO_2	+	+	+	+
Red cell ATP	+	+	+	+
Red cell 2,3-DPG	+	+	+	+
Red cell sodium	+	+	+	+
Skin petechiae	-	-	+	+
Subcutaneous, subserosal oozing of RBC	-	-	+	-
Bone marrow smear	+	-	+	-

*When feasible, measure sequentially for temporal aspects.
**Examples: Biological laboratories, hospitals, space simulation facilities (bed rest, water immersion, etc.), spacecraft simulators.
***Include pre-, in-, and postflight phases.

V. Bibliography

1. Balakhovskii, I.S., V.I. Legen'kov and R.K. Kiselev. Changes in hemoglobin mass during space flight and simulations. Kosm. Biol. Aviakosm. Med. 14:14-20, 1980.

2. Dunn, C.D.R., P.C. Johnson, R.D. Lange, L. Perez and R. Nessel. Regulation of hematopoiesis in rats exposed to antiorthostatic,

hypokinetic/hypodynamia. I. Model description. Aviat. Space Environ. Med. 56:419-426, 1985.

3. Dunn, C.D.R., P.C. Johnson and R.D. Lange. Regulation of hematopoiesis in rats exposed to antiorthostatic hypokinetic/hypodynamia. II. Mechanisms of the "anemia." Aviat. Space Environ. Med. 57:36-44, 1986.

4. Gazenko, O.G., A.M. Genin, E.A. Ilyin, V.S. Oganov and L.V. Serova. Adaptation to weightlessness and its physiological mechanisms (results of animal experiments aboard biosatellites). Physiologist 23 (Suppl. 6):S11-S15, 1980.

5. Ilyin, E.A., L.V. Serova, V.V. Portugalov, R.A. Tigranyan, E.A. Savina, M.S. Gayevskaya, Y.I. Kondratyev, A.D. Noskin, V.I. Milyavsky and B.N. Yurov. Preliminary results of examinations of rats after a 22-day flight aboard the Cosmos 605 biosatellite. Aviat. Space Environ. Med. 46:319-321, 1975.

6. Johnson, P.C. The erythropoietic effects of weightlessness. In Current Concepts of Erythropoiesis edited by C.D.R. Dunn, New York: John Wiley, 1983, pp. 279-300.

7. Kakurin, L.I., V.I. Lobachik, V.M. Mikhailov and Yu A. Senkevich. Antiorthostatic hypokinesia as a method of weightlessness simulation. Aviat. Space Environ. Med. 47:1083-1086, 1976.

8. Kiselev, R.K., I.S. Balakhovskii and O.A. Virovets. Change in hemoglobin mass during prolonged hypokinesia. Kosm. Biol. Aviakosm. Med. 9:80-84, 1975.

9. Kozinets, G.I., V.I. Korol'kob, I.I. Britvan, I.A. Bykova and N.E. Spitsyna. Morpho-functional properties of the peripheral blood and bone marrow cells of rats following a flight on board the Kosmos-936 biosatellite. Kosm. Biol. Aviakosm. Med. 17:61-65, 1983.

10. Kozinets, G.I., M.S. Belakovskii, A.S. Ushakov, I.A. Bykova and V.P. Matvenko. Structural and functional changes in human erythrocytes and leukocytes during a seven-day immersion hypokinesia. Kosm. Biol. Aviakosm. Med. 17:48-51, 1983.

11. Lange, R.D., R.B. Andrews, L.A. Gibson, C.C. Congdon, P. Wright, C.D.R. Dunn and J.B. Jones. Hematologic measurements in rats flown on Spacelab shuttle mission SL-3. Am. J. Physiol. in press.

12. Lange, R.D., R.B. Andrews, L.A. Gibson, P. Wright, C.D.R. Dunn and J.B. Jones. Hematologic parameters of astrorats flown on SL-3. Physiologist 28(Suppl. 6):S195-S196, 1985.

13. Lamb, L.E., R.L. Johnson, P.M. Stevens and B.E. Welch. Cardiovascular deconditioning from space cabin simulator confinement. Aerospace Med. 35:420-428, 1964.

14. Leach, C.S., J.P. Chen, W. Crosby, P.C. Johnson, R.D. Lange, E. Larkin and M. Tavassoli. Spacelab 1 hematology experiment (INS103): Influence of spaceflight on erythrokinetics in man. NASA technical Memorandum 58268, Houston: Johnson Space Center, 1985.

15. Leon, H.A., L.V. Serova and S.A. Landaw. Effect of weightlessness and centrifugation on red cell survival in rats subjected to space flight. Aviat. Space Environ. Med. 51:1091-1094, 1980.

16. Leon, H.A., L.V. Serova. J. Cummins and S.A. Landaw. Alterations in erythrocyte survival parameters in rats after 19.5 days aboard Cosmos 782. Aviat. Space Environ. Med. 49:66-69, 1978.

17. Miller, P.B., R.L. Johnson and L.E. Lamb. Effects of moderate physical exercise during four weeks of bed rest on circulatory functions in man. Aerospace Med. 36:1077-1082, 1965.

18. Musacchia, X.J., J.M. Steffan and D.R. Deavers. Rat hindlimb muscle responses to suspension hypokinesia/hypodynamia. Aviat. Space Environ. Med. 54:1015-1020, 1983.

19. Nixon, J.V., R.G. Murray, C. Bryant, R.L. Johnson, JR., J.H. Mitchell, O.B. Holland, C. Gomez-Sanchez, P. Vergne-Marini and C.B. Blomqvist. Early cardiovascular adaptation to simulated zero gravity. J. Appl. Physiol. 46:541-548, 1979.

20. Rakova, I.A. and V.N. Shvets. Morphologic study of the hematopoietic organs of rats during hypokinesia. Kosm. Biol. Aviakosm. Med. 12:64-68, 1978.

21. Shvets, V.N. and N.P. Krivenkova. Morphology of the bone marrow cells of rats on the Kosmos 690 biosatellite. Kosm. Biol. Aviakosm. Med. 11:75-78, 1977.

22. Shvets, V.N. and V.V. Portugalov. Space flight effects on the hemopoietic function of bone marrow of the rat. Aviat. Space Environ. Med. 47:746-749, 1976.

23. Shvets, V.N., A. Vatsek, G.I. Kozinets, I.I. Britvan and V.I. Karol'kov. Hemopoietic status of rats exposed to weightlessness. Kosm. Biol. Aviakosm. Med. 18:12-16, 1984.

24. Stevens, P.M., T.N. Lynch, R.L. Johnson and L.E. lamb. Effects of 9-alphafluorohydrocortisone and venous occlusive cuffs on orthostatic deconditioning of prolonged bed rest. Aerospace Med. 37:1049-1056, 1966.

25. Talbot, J.M. and K.D. Fisher. Research opportunities in loss of red blood cell mass in space flight. Bethesda, MD. Publication of: List Sciences Research Office, Federation of American Societies for Experimental Biology, 1985.

26. Tavassoli, M. Anemia of spaceflight. Blood 60:1059-1067, 1982.

Acknowledgement

The use of funds provided by the U. S. National Aeronautics and Space Administration for the publication of this paper is gratefully acknowledged. The authors greatly appreciate the editorial review by F. J. Miller.

LOCAL FLUID SHIFTS IN HUMANS AND RATS: COMPARISON OF SIMULATION MODELS WITH ACTUAL WEIGHTLESSNESS

Charles M. Tipton, J. Michael Overton,
Michael J. Joyner and Alan R. Hargens

Department of Exercise and Sport Sciences
University of Arizona, Tucson, Arizona, and
Division of Orthopaedics and Rehabilitation
University of California, San Diego, California

INTRODUCTION

In the years that have elapsed since the first human was sent into space, enormous advances have been made in our understanding of the anatomical, biochemical, physiological, and psychological adjustments that transpire before, during, and after flight. Despite these advances, much remains unknown about a variety of processes, including fluid shifts and their consequences. Most authorities would agree that the transition from earth's gravity to a microgravity environment is the primary stimulus for the fluid shifts and their cascading effects on bodily appearances and functions.

The repeated demonstrations of head and facial puffiness with nasal congestion, engorged neck veins, and the sensation of blood rushing to the head with space flight has given credence to the existing models that have evolved over the years that are available for testing and evaluation purposes (25). Expected with the models would be an increase in central venous pressure (CVP). However, published (17) and recent (16) reports from space experiments do not support such a concept nor do recent human data concerned with head-down tilt or water immersion in a seven-day period (14). The issue becomes even more complicated and confusing because there are published space flight results from Russian cosmonauts which show elevated venous pressures, when compared to preflight, after ten days or longer (32).

For transcapillary fluid shifts to occur, changes are needed between the hydrostatic and colloid osmotic forces at the capillary level (8,9). Unfortunately, there are no flight data available on these important matters. It is repeatedly documented that most astronauts and cosmonauts lose body mass during space flight with the majority of this loss being body water (20). Because these changes can be coupled with girth decreases of the thigh and calf regions (25), further credence is given to the concept that the local tissue fluid shifts are occurring with fluid movement from the legs to the thorax and cephalic regions. According to Leach and Johnson (19), approximately a liter of fluid is lost from each leg during space flight. In the recent D1 flight, impedance results from four subjects indicated a fluid loss of approximately three liters in a seven-day period (1). Even with incomplete information, it appears that the loss in body water is predominantly extracellular in nature. This impression is supported by pre- and post-flight data that show decreases in plasma volume (1,13,19,25). Part of the decrease in total body water is related to a decrease in water intake, a reduction in the amount of metabolic water being formed, and to sweating (7). Contrary to the prediction models for microgravity, there is a paucity of inflight data that demonstrates a diuresis had occurred. Of course, this could be explained by anorexia and hypohydration (7).

As noted by Leach and Johnson (19) and listed by Halstead and Dufour (2), the urinary electrolyte profiles of astronauts beginning with Gemini and continuing through the space shuttle program have not been uniformly consistent. The most recent shuttle flights show that the excretion rates of sodium, chloride and potassium reached their minimum on the second day after which they returned to the preflight value by the seventh day (19). Urinary aldosterone levels, which were increased in the Gemini experiments, were not significantly altered in the Apollo studies, were increased in the Skylab, and showed a delayed elevation in the shuttle experiments (19). Plasma aldosterone concentrations decreased in the Skylab studies and, unfortunately, the space shuttle results are incomplete at this time (19). A hormone of interest to this topic, antidiuretic hormone (ADH), showed a decrease with urinary measurement during the Skylab experiments, and an increase during the shuttle. Since plasma and urinary cortisol concentrations are increased with space flight, the element of anxiety compounds interpretation and prevents the invoking of cause and effect relationships. It is speculated that the atrial natriuretic factor in plasma is increased during the early stages of flight (discussions at 8th IUPS meeting). If confirmed in flights, this finding would help to explain urinary sodium and potassium changes (7,19).

The lack of completeness in fluid shift data is due to many factors, e.g., the differences in conditions, responsibilities, exercise and eating habits, methodologies, anxieties, subject adaptability, duration of flight, nature of the mission, and combinations thereof. Consequently, it has become the responsibility of the scientific community to develop animal and human models for simulated weightlessness in order to better control and to better standardize the experimental conditions, subjects, and variables so that continuous and accurate measurements can be made on the responsible mechanisms.

HUMAN SIMULATION MODELS

Of the human models being used, we recommend the head-down bed rest over the horizontal bed rest approach. As discussed at the 1986 IUPS meeting, the consensus was that a -5° angle should be used by researchers. Not only does head-down tilting produce the facial puffiness, vein enlargement, nasal congestion, and headaches (11,26) observed during flight (25), it retains the hypokinesia component of the horizontal bed rest method. Even though water immersion will usually initiate a transcent increase in central venous pressure, a diuresis, decreased plasma volume, decreased interstitial pressure (15), and possibly decreased antidiuretic hormone levels (14,33), we favor the head-down tilt approach over water immersion because it facilitates direct measurement of local fluid shifts without exaggerated physiological responses, the risks of high blood pressure, or the issue of water compression on the chest (7,14).

Hargens and co-workers inserted wick catheters (11) into subcutaneous and intramuscular tissues of the leg and measured interstitial and colloid osmotic pressures of subjects participating in a -5° eight-hour head-down tilt study (Table 1). The interstitial fluid pressures declined significantly with a non-significant decline in its colloid osmotic pressure. Because of difficulties, capillary hydrostatic pressures were not measured. However, extrapolating from the results of others (21), we can assume that capillary hydrostatic pressure in the toes would decrease from 90 mmHg

to approximately 30 mmHg. This change could be the initial mechanism for the tissue fluid shift when the head-down position is taken. Of interest is a new technique that measures lip mucosal capillary blood flow (28). When used with head-down tilt, flow was decreased while systolic blood pressure was elevated. It was hypothesized that the facial edema observed in actual and simulated weightlessness was related to the less regulated pre-capillary sphincters in the face than in the legs (28).

Associated with the central shifts of interstitial fluid, which represent 15% of the fluid reservoir volume of muscle and 50% of the subcutaneous volume (8,11), are girth decreases in the calf and thigh, lower leg displacement volumes, decreases in plasma volume, and transient increases in central venous pressure (5,11,26). Select measurements of cardiac dimensions also show transient increases (5,26) which would be associated with an increased filling pressure. Most of the changes noted become stabilized and revert to either pre-tilt or lower values after 24 hours or less, indicating that other regulatory mechanisms have been invoked.

Head-down tilt elicits a diuresis that is generally associated with decreases in ADH, renin and aldosterone with elevations in the excretion of sodium and potassium (Table 1). However these changes are not consistent with the resultss noted in the early stages of space flight (19). These composite changes would likely be associated, in part, with increases in the plasma level of the atrial natriuretic factor (ANF) (6,7,19,25). Recent reports at the 1986 IUPS meeting (6) confirm that ANF values are increased during the early stages of simulated weightlessness. Surprisingly, there are limited data available on renal function during these experiments. Using creatinine measurements as a rough index of the glomerular filtration rate, we noted a brief decrease during their eight-hour period (11).

One structure that has received little attention in the area of fluid balance are the lungs. When estimates of lung tissue volumes were made (3), head-down tilt was associated with a transient increase that returned to base line values within two hours. Recent reports on segmental volume changes with impedance plethysmography indicate that the head-down tilt markedly elevates the torso segment volume for several days (22). Such a change would be expected to influence lung tissue water content and possibly respiratory water loss (20). To our knowledge, direct measurements of this important parameter have not been reported for either space flight or simulated weightless conditions.

ANIMAL MODELS

We believe that many of the animal models used for simulation purposes have been more concerned with hypokinesia and cardiac deconditioning than with fluid shifts and their physiological consequences. Even though researchers have been using a variety of species to study space-related problems, it is highly probable that financial, political, and technical constraints will result in only primates and rodents being flown in future flights. Although promising primate models for fluid shifts have been developed by Sandler at NASA-Ames and Moore-Ede at Harvard University, this manuscript will pertain only to rodents.

The development of a head-down suspension model with "unloaded" hind legs, first by Morey-Holton (23) and then by Musacchia and co-workers (24), has provided scientists with a simulation animal model to study many facets of weightlessness. However, we recommend that a 30° angle be used in order for the front legs to support 50% of their body mass (10). Reports from rats flown on Cosmos 1129 for 18.5 days showed significant decreases in carcass (-6.6%) and skin (-17.2%) water mass, and a -36% decrease in extracellular water mass (31). Rats (astrorats) flown on Spacelab 3 exhibited indirect evidence for a decrease in plasma volume and the presence of dehydration (18).

Similar to humans, our suspended rats show signs of head and neck puffiness. Hargens and associates (10) inserted wick catheters into the subcutaneous tissues of the necks of suspended rats and found that interstitial pressures were increased by 6 cm H_2O at 48 hours. Unfortunately, similar experiments have not been performed with their hind limbs. Popovic (27) was the first to demonstrate in unanesthetized animals that head-down suspension would elevate right atrial pressure to 4-5 mmHg before returning to baseline values after two days. Similar trends have been confirmed by others (29, Figure 1). Shellock's studies (29) are interesting because he demonstrated that the angle of suspension (45° vs. 20°) significantly increased the CVP value obtained (8 mmHg vs. 4 mmHg) after one hour. At 24 hours, the values were similar to pre-suspension ones. Although preliminary in nature, our Doppler iliac artery blood flow data to the hind limbs and to the mesentery vascular bed (Figure 1) indicates a gradual decrease with suspension. Whether this is a reflection of changes in the activity of the sympathetic nervous system or the reflex adjustments from unloaded muscles or both remains to be determined. Popovic found an increase in cardiac output (27) but later felt it was more of a stress response than a preloading effect. Early studies (4) by the Louisville group indicated that suspension had minimal effects on urine volume during the first two days after which it remained increased with suspension for as long as two weeks without marked changes in water intake. However, their recent studies reported at the 8th IUPS meeting in Japan exhibited an initial diuresis that we and others have observed in suspended rats. Urinary sodium and potassium excretion values remained lower than control rats (1-2 days) after which these specific electrolytes were markedly higher than the controls (4). In the Louisville simulation studies (4), plasma osmolarity did not change while serum aldosterone concentrations increased approximately twofold by the seventh day. The natriuresis and kaliuresis observed in these and related simulation studies suggest that other mechanisms must be involved, e.g., the atrial natriuretic factor (ANF) (6,7,19). When attempts were made to measure atrial and plasma ANF levels in Spacelab 3 rats (13) as well as renin (PRA) (12), negative results were obtained, presumably because of the time factor between measurements (13). Interestingly, there is also a paucity of animal stimulation data on changes in arginine vasopressin concentrations.

Tucker and co-workers (30) subjected rats to seven days of suspension and measured serum sodium and plasma renin activity (PRA). In addition, nephron filtration rate and proximal tubular fluid reabsorption rate were recorded. They noted a significant decrease in PRA which is in contrast to the negative results on this topic from Spacelab 3 (12). Tucker et al. (30) also reported a significant reduction in nephron filtration rate which was due to an increase in efferent arteriolar resistance. No changes were noted in hydrostatic or colloid osmotic forces or in the glomerular permeability coefficient. Urine flow was 75% of the value found for the cage control animals. These interesting but preliminary results dramatize the need for additional and more controlled studies concerned with renal functions and mechanisms.

CONCLUSION

From the information presented it is evident that more information is needed and that additional investiga-

tions are required to understand the time courses of fluid shifts and their responsible mechanisms. For simulation models to be helpful, more standardization of procedures and protocols is needed. For reasons described earlier, we feel the -5° head-down tilt should be adopted for human stimulation studies and a -30° head-down tilt for rodents (10). Both populations need a zero-degree unloaded horizontal control, and a caged control group (4) is recommended for investigations with rats. Finally, more direct measurements are necessary for many of the parameters associated with fluid shifts, and prudent approaches to secure this information should be considered.

REFERENCES

1. Baisch, F., L. Beck, A. Samel, and L.D. Montgomery. Early adaptation of body fluid and cardiac performance to changes in G-level during space flight. First presentation of scientific results of the German Spacelab Mission D1. Norderney, 1986.

2. **Biological and Medical Experiments on the Space Shuttle, 1981-1985.** Edited by T.W. Halstead and P.A. Dufour. Life Science Division, NASA Headquarters, 1986, 176 p.

3. Bonde-Petersen, F., N.J. Christensen, O. Henriksen, et al. Aspects of cardiovascular adaptation to gravitational stresses. **Physiologist** 23(suppl):S7-S10, 1980.

4. Deavers, D.R., X.J. Musacchia, and G.A. Meininger. Model for antiorthostatic hypokinesia: Head-down tilt effects on water and salt excretion. **J. Appl. Physiol.** 49:576-582, 1980.

5. Gaffney, F.A., J.V. Nixon, E.S. Karlsson, et al. Cardiovascular deconditioning produced by 20 hours of bedrest with head-down tilt (-5°) in middle-aged healthy men. **Am. J. Cardiol.** 56:634-638, 1985.

6. Gharib, C., G. Gauquelin, A.M. Allevard. Plasma atrial natriuretic factor (αhANF) during 4 hr head down tilt at -6°. Proceedings of Eighth Annual Meeting IUPS Commission on Gravitational Physiology, Tokyo, Japan, Nov. 1986, p. 63.

7. Greenleaf, J.E. Mechanism for negative water balance during weightlessness: An hypothesis. **J. Appl. Physiol.** 60:60-62, 1986.

8. Hargens, A.R. Interstitial osmotic pressure associated with Donnan equilibria. In: **Tissue Fluid Pressure and Composition**, edited by A.R. Hargens. Baltimore: Williams and Wilkins, 1981, pp. 43-61.

9. Hargens, A.R., J.B. Cologne, F.J. Menninger, et al. Normal transcapillary pressure in human skeletal muscle and subcutaneous tissues. **Microvascular Research** 22:177-189, 1981.

10. Hargens, A.R., J. Steskai, C. Johansson, and C.M. Tipton. Tissue fluid shift, forelimb loading, and tail tension in tail-suspended rats. **Physiologist** 27(suppl):S37-S38, 1984.

11. Hargens, A.R., C.M. Tipton, P.D. Gollnick, et al. Fluid shifts and muscle function in humans during acute simulated weightlessness. **J. Appl. Physiol.** 54:1003-1009, 1983.

12. Hartle, D.K. and W.J. Inge. Plasma renin concentrations (PRA) of rats orbited for seven days aboard NASA Spacelab 3. **Physiologist** 28(suppl)S233-S234, 1985.

13. Inge, W.H. and D.K. Hartle. Atriopeptin (AP-3) in atria and plasma of rats orbited aboard NASA Spacelab 3 (SL3) for seven days. **Physiologist** 28(suppl): S231-S232, 1985.

14. Katkov, V.E., L.I. Kakurin, V.V. Chestukhin and K. Kirsch. Central circulation during 7-day space flights and ground-based studies. Presentation at Eighth Annual Meeting IUPS Commission on Gravitational Physiology, Tokyo, Japan, 11-5-86.

15. Khosla, S.S. and A.B. DuBois. Osmoregulation and interstitial fluid pressure changes in humans during water immersion. **J. Appl. Physiol.** 51:686-692, 1981.

16. Kirsch, K. Venous pressures in weightlessness: Results from the Spacelab 1 and D-1 missions. Presentation at Eighth Annual Meeting IUPS Commission on Gravitational Physiology, Japan, 11-5-86.

17. Kirsch, K., F. Haenel and L. Röcker. Venous pressure in microgravity. **Naturwissenschaften** 73:447-449, 1986.

18. Lange, R.D., R.B. Andrews, L.A. Gibson, et al. Hematological parameters of astrorats flown on SL-3. **Physiologist** 28(suppl):S195-S196, 1985.

19. Leach, C.S. and P.C. Johnson, Jr. Fluid and electrolyte control in simulated and actual spaceflight. **Physiologist** 28(suppl):S34-S37, 1985.

20. Leach, C.S., J.I. Leonard, P.C. Rambaut and P.C. Johnson. Evaporative water loss in man in a gravity-free environment. **J. Appl. Physiol.** 45:430-436, 1978.

21. Levick, J.R. and C.C. Michel. The effects of position and skin temperature on the capillary pressure in the fingers and toes. **J. Physiol.** (London) 274:97-109, 1978.

22. Montgomery, L.D. Body volume changes during simulated weightlessness: An overview. Report presented at the 7th Man in Space Symposium, Houston, Texas, February 1986.

23. Morey, E.R. Space flight and bone turnover: Correlation with a new rat model of weightlessness. **BioScience** 29:168-172, 1979.

24. Musacchia, X.J., D.R Deavers, G.A. Meininger, and T.P. Davis. A model for hypokinesia: Effects of muscle atrophy in the rat. **J. Appl. Physiol.** 48:479-486, 1980.

25. Nicogossian, A.E. and J.F. Parker, Jr. **Space Physiology and Medicine.** NASA, SP-447, 1982, 324 p.

26. Nixon, J.V., R.G. Murray, C. Bryant, et al. Early cardiovascular adaptation to simulated zero gravity. **J. Appl. Physiol.** 46:541-548, 1979.

27. Popovic, V. Antiorthostatic hypokinesia and circulation in the rat. **Physiologist** 24(suppl):S15-S16, 1981.

28. Sfakianos, P.N., A.R. Hargens and W.H. Akeson. Microvascular flow adjustments with postural changes in humans. **Physiologist** 28(suppl):S175-S176, 1985.

29. Shellock, F.G., H.J.C. Swan, and S.A. Rubin. Early central venous pressure changes in the rat during two different levels of head-down suspension. **Aviat. Space Environ. Med.** 56:791-795, 1985

30. Tucker, B.J., A.R. Hargens, O.W. Peterson and R.C. Blantz. Alterations in glomerular and tubular dynamics during simulated weightlessness. **Physiologist** 25(suppl):S67-S68, 1982.

31. Ushakov, A.S., T.A. Smirnova, G.C. Pitts, et al. Body composition of rats flown aboard Cosmos-1129. **Physiologist** 23(suppl):S41-S44, 1980.

32. **USSR Space Sciences Digest, 6.** Edited by L.R. Hooke, M. Radtke, R. Teeter and J.E. Rowe. NASA Contractor Report 3922 (07), 1986, 124 p.

33. **Zero-g Simulation for Ground-Based Studies in Human Physiology, with Emphasis on the Cardiovascular and Body Fluid Systems.** Proceedings of a workshop held in Toulouse, France. European Space Agency, 1982, pp. 39-40.

Table 1. Select maximal changes associated with simulated weightlessness (-5°) for eight hours

Parameter	Baseline Values	Percent Change (%)	Statistically Significant	Time Period (Hr)
Calf circumference (cm)	36.9 ± 0.05	-3.2	yes	4
Lower leg water displacement (ml)	3,359 ± 1.04	-6.6	yes	4
Muscle interstitial pressure (mmHg)	4.6 ± 0.6	-160.8	yes	8
Subcutaneous interstitial pressure (mmHg)	0.6 ± 0.5	-450.0	yes	8
Interstitial fluid colloid osmotic pressure (mmHg)	8.5 ± 1.1	-21.2	no	8
Capillary blood colloid osmotic pressure (mmHg)	26.0 ± 0.6	+3.8	no	8
Soleus muscle water percentage (%)	76.2 ± 1.1	-3.4	no	8
Fluid intake (ml/min)	4.1 ± 0.9	-29.3	no	8
Urine output (ml/min)	1.9 ± 0.3	+110.3	yes	4
Plasma aldosterone (ng/dl)	9.6 ± 2.7	-57.3	no	4
Plasma renin (ng/ml/hr)	4.6 ± 1.1	-43.5	no	4
Plasma AVP (μU/ml)	1.0 ± 0.2	-40.0	no	4
Na^+ excretion (μeq/min)	170 ± 28	+41.2	no	4
K^+ excretion (μeq/min)	81 ± 6	+34.6	yes	4

Data from reference 11; means and SE are listed; 6-8 male were subjects measured.

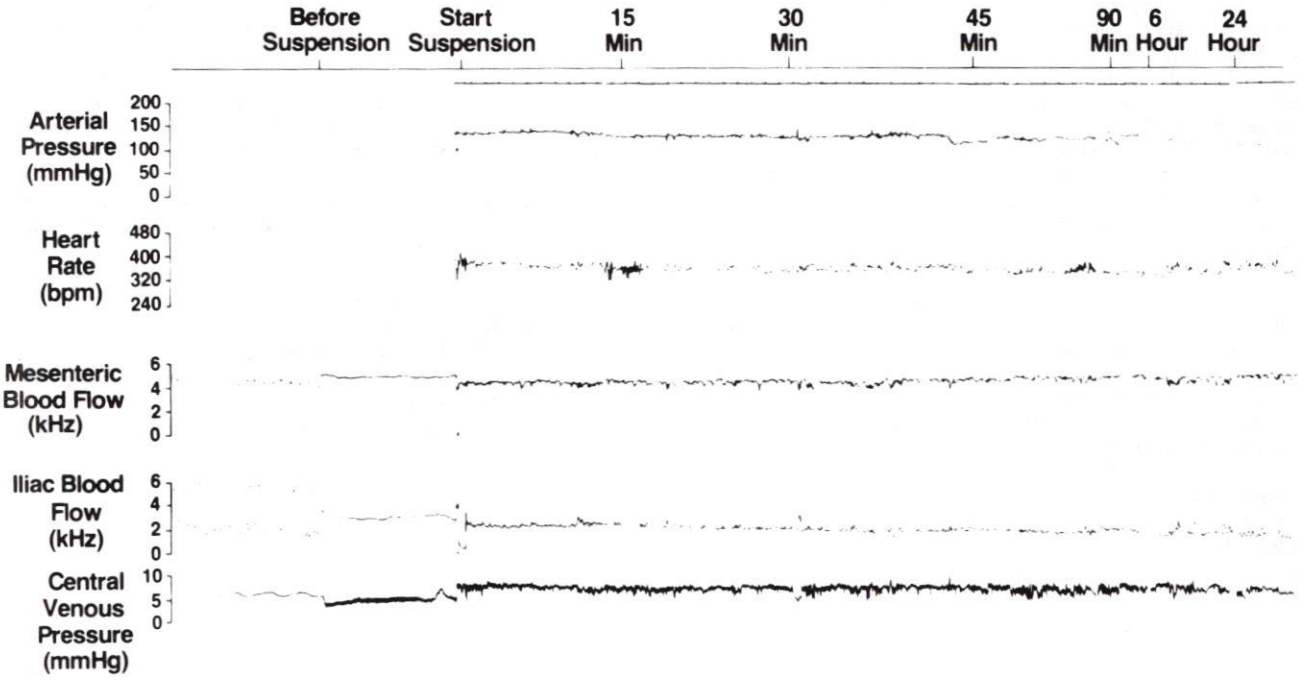


Figure 1: The influence of -30° head-down suspension (HDT) on select cardiovascular parameters. Results from six mature male HDT rats showed significant increases in CVP for 90 minutes after which it returned to baseline or lower values by 24 hours. Heart rate was significantly decreased at 24, 72, and 120 hours. Iliac and mesenteric blood flows were also significantly decreased after 90 minutes (iliac) or 180 minutes (mesenteric). Both flows remained reduced thereafter. Mean arterial pressure was not significantly changed by the process.

METABOLIC ADAPTATION IN HYPOKINESIA IN HUMANS

H.Saiki, J.Nakajima,* M.Nakaya,* Y. Sugita,* M.Sudoh,* K.Shioda,* and Y.Saiki**

Dept. of Physiology II, St. Marianna Univ. School of Med., Kawasaki, 213 Japan
*Space Med. Lab., The Jikei Univ. School of Med., Tokyo 105 Japan
**The Saiki Institute, Tokyo 143 Japan

INTRODUCTION

To conduct an analytical study of biological functions under hypogravics from the viewpoint of metabolic adaptation, we performed prolonged experiments of several days on human subjects under modeled hypogravics.

In this paper, changes of circadian rhythms of urinary excretion of minerals and hormones during the initial process of adaptation and readaptation from a normal environmental condition were studied by mathematical analysis of the data, with special consideration of diurnal and nocturnal differences of such biological functions. To estimate the adaptation process of nocturnal characteristics, the chronological distribution patterns of each sleep stage were also studied.

EXPERIMENTAL METHODS

Using three healthy male adults, as human subjects, a 6 days' thermal neutral water immersion (W.I.) experiment was performed with the subjects in a head-out, supine position. During the pre-and post-exposure periods, the subjects were led a normal constant scheduled ambulatory life. Concerning the sleep period, the time of turning out lights for sleep was fixed and the sleep patterns were measured and analysed by APSS [1] method. Biochemical functions (each 2 hours urinary excretion of K+, Na+,17-OHCS and catecholamine) and other functions were determined.[2] The data were analysed mathematically by one-way periodic regressions. [3]

As a sleep characteristic, the fluctuation in the distribution of each of the sleep stages, before, during and after water immersion period, was calculated.

The relationship between chrono-physiological rhythm and adaptation to a hypogravic environment was discussed from next 3 points:

1) The course of the fluctuation of diurnal and nocturnal urine excretion values of several substances.

2) Each day circadian rhythm of the same parameter.

3) The pattern of each sleep stage.

RESULTS

On the fluctuation of daily, diurnal and nocturnal urine excretion volume before, during and after W.I. modeling exposure, the incline of the graph of diurnal fluctuation line (d.f.l.) during the water immersion period (W.I.P.) became steeper than that of nocturnal fluctuation line (n.f.l.) from the first day, and they approached each other. The point of time when the balance of diurnal and nocturnal excretion levels was attained, is regarded as an approach point (a.p.). In this case, the a.p.is located at W.I.P.-5. The circadian rhythm of the day was too irregular to express as an equation. After the a.p. was attained, both lines (d.f.l. and n.f.l.) kept the same steady level until the end of the W.I.P. During the post W.I.P., the daily value promptly returned to the control level but the balance of diurnal and nocturnal values did not return to the control condition yet.

Fig. 1 and 2 show the case of Na+. The lower part of Fig. 1 describes chronological series of daily circadian rhythm of this parameter. Fig. 2 shows the circadian rhythm equations of every day and piled circadian rhythm courve of them. The lower graph of polygonal line shows the fluctuation of term -A-that expresses the amplitude of each daily circadian curve, before, during and after W.I. period. The broken line shows the irregular parts.In this case, W.I.P. -3 was the a.p. as shown in lower polygonal graph. At the post W.I.P. -3 after a transient and strong decrease corresponding to the comparative irregularity of the rhythm, the same deviation of the balance of diurnal and nocturnal values was also observed.

Fig. 3 and 4 show the case of 17-OHCS of which the a.p. is W.I.P. -4. There were no irregularities in the circadian rhythms without the comparataive increase of nocturnal excretion. At W.I.P. -6, the adaptation was perfect in respect to circadian rhythm, diurnal-nocturnal balance and daily excretion.

Fig. 5 and 6 show the case of adrenalin, of which the a.p. is at W.I.P. -2. The same tendency was observed as that of 17-OHCS. This circadian rhythm curve (Fig.6), also reveals the same tendency. In the case of noradrenalin as shown in Fig. 7, the fluctuation of the balance in diurnal and nocturnal values had the entirely same courses, but as shown in Fig. 8, the a.p. was at W.I.P. -3, and no regularity in rhythm was observed. The rhythm of W.I.P. -4,5 showed a comparatively irregular form. There is some possibility that this phenomenon is an expression of the special role of noradrenalin to sleep. Jouvet at al.[4][5] reported the special relation between REM sleep and noradrenalin.

As shown in Fig.9, the REM distribution of one night had the lowest level during W.I.P. 1-2-3 days,and in the REM distribution curve during early, middle and late parts of night sleep,as shown in Fig.10, we could see an entirely different distribution at W.I.P. -3 and a

comparatively different distribution at W.I.P.-4,-5, corresponding to the above mentioned irregularity of the circadian rhythms of noradrenalin excretion level.

Fig. 11 and 12 indicate the case of K+, of which the a.p. is located at W.I. P. -4. A comparative irregularity was found as shown in curve 4 (Fig. 12).

$Y=1.55-0.011u_1+0.22v_1+0.16u_2+0.09v_2+0.04u_3$
$-0.14v_3+0.08u_4+0.06v_4$

At W.I.P. -6, the level of diurnal and nocturnal excretion separated again as shown in Fig.11, and both lines increased in parallel, also during the post W.I. P., up to post-3.

DISCUSSION

From the above mentioned viewpoints, 2 types of adaptation courses were noticed in these 5 metabolic parameters, during 7 days W.I. modeling hypokinetics conditioning. In the first type, a new steady level was attained after a increase or decrease in the level of the parameters. In this experiment, urine volume and sodium excretion rate belong to this type, as it has been explained respectively above in the experimental results. Namely, the diurnal fluctuation line of urinary excretion of the substances that were used as parameters increased and attained the maximum plateau and leveled off. On the other hand, the nocturnal fluctuation line increased more slowly compared with the daily diurnal excretion line. The circadian rhythm at this a.p. showed no regularity. At the end of W.I.P. the regularity of the rhythm was regained, although the relation betweeen the values of the two lines did not recover to that of the control, showing the adaptation phase at the new level.

In the second type, the initial steady level at pre W.I. conditioning was attained again at the end of the W.I. period after the deviated course during the conditioning. In this experiment, 17-OHCS, cathocholamines belong to this type, as it has been explained respectively above in experimental results. Namely, in terms of the relation between the courses of dirunal and nocturnal fluctuations, an a.p. was also observed during the W.I. period. But at the day of a.p., such variety of the rhythm, as observed at the case of the upper first group, was not appeared except the case of noradrenaline, and even in this case, the regularity of the circadian rhythm was regained after 2 days' irregular period. The distribution curve of the sleep stage-REM during early, middle and late parts of night sleep showed an entirely different distribution from the control curve at W.I.P.-3 and a comparatively different curve at W.I.P.-4,5, too. Such phenomena correspond to the variety of the regularity of the circadian rhythm of noradrenalin, too.

There is also another type of the course, during the W.I. hypokinetics conditioning. In this case, no steady state, that is understood as a kind of adaptation to such a new environmental factor, was found during the experimental course. K+ is a parameter that belong to this case. Namely, the diurnal fluctuation line during initial 4 days did not change the level. After that, they continued a steady increase and especially, the nocturnal line increased from the beginning, and after a.p., the line continued to increase with the diurnal line untill the end of the experiment. They have no sighs to have a new steady level.

SUMMARY

1. On renal-metabolic functions of human subjects, who were exposed to water immersion, the process of adaptation is characterized by the diurnal-nocturnal balance and circadian rhythm. The characteristics differ in each parameter. On the 6 parameters in this experiment, it was noticed that two groups attained the steady state during the conditioning period,and that another group was difficult to attain the steady state during conditioning.

2. Urine volume and urinary excretion rate of Na+ are the first group. They attained the new steady level of the parameter during the conditioning.

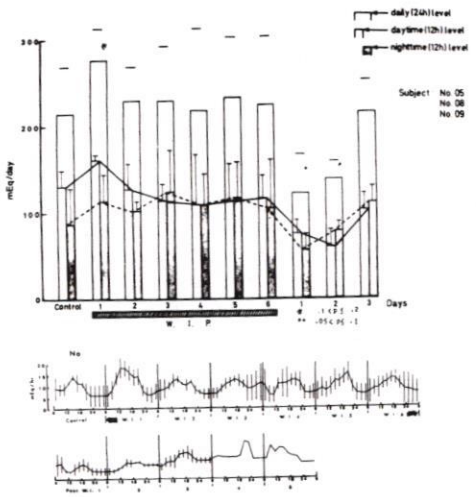


Fig.1. Daily urinary excretion of sodium.

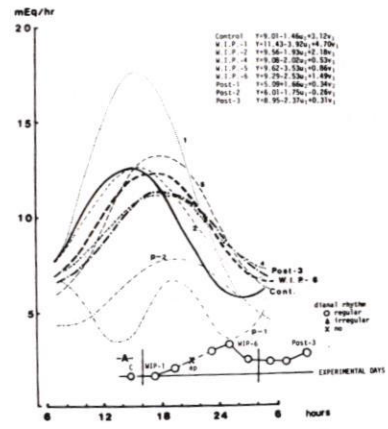


Fig.2. Circadian rhythms of daily urinary excretion of sodium, pre,during and post water immersion exposure.

The various equilibrium reactions of crayfish, including leg movement and uropod steering (9) are primarily controlled by these four pairs of descending interneurons. Each of these interneurons connects with a particular set of uropod motoneurons. Interneuron C_1, which responds maximally to body tilting in the same-side-down and head-up directions, makes excitatory connections with closer motoneurons on the same side and opener motoneurons on the opposite side.

Connections between these interneurons and motoneurons are organized as on the input side, in parallel mono- and polysynaptic pathways. Our recent study indicates that a newly found class of interneurons, local nonspiking interneurons, might be involved in this polysynaptic pathway.

Gating of an equilibrium reaction

Careful observation of the equilibrium reactions reveals a great deal of variation in their probability of occurrence, especially for the abdominal appendages. The uropod steering reactions in response to the body roll are primarily controlled by the statocyst sensory system. When the crayfish is tilted in the roll plane without touching to a substratum, the uropod on the upper side will open and the uropod on the lower side will close to produce a righting torque in swimming. The extent of this reaction, i.e., the opening and closing angle of uropod is strictly proportional to the tilt angle (9). However, this reaction is facilitated by the abdominal posture movement either in the extending or bending direction (7). When there is no abdominal movement, no steering of the uropod will occur. The equilibrium reactions are thus affected by the animal's behavioral context at the moment. Simultaneous recording from the interneuron C_1 and the uropod motoneurons showed that the tilt-increased activity of C_1 caused the steering reaction of uropod motoneurons only when the abdominal posture system was activated. A blockage or "gating" of the statocyst information takes place between the interneurons and the uropod motoneurons inside the terminal abdominal ganglion (7).

We have analysed the neural mechanism underlying this postural facilitation of the steering act using intracellular recording and staining techniques. The synaptic transmission between the statocyst interneurons and the motoneurons was found to be subthreshold to the generation of spikes in the uropod motoneurons. Intracellular observation of the activity of uropod motoneurons during the fictive abdominal posture movement revealed that they received sustained, continuous excitation from the abdominal system. During the abdominal movement, input from the statocyst interneurons to the uropod motoneurons would be thus positively biased and made suprathreshold with the long lasting depolarization (6).

Local nonspiking interneurons

The sustained depolarization of uropod motoneurons during the abdominal movement was found to be mediated by local nonspiking interneurons. These interneurons do not generate spikes, but effectively control the spike activity of uropod motoneurons by changes in their membrane potential (1,2).

The majority of local nonspiking interneurons that were presynaptic to uropod motoneurons were found to be polarized during the abdominal movement in appropriate directions depending on their functional connectivity to the motoneurons. The local nonspiking interneurons that had noninverting (excitatory) connections to the motoneurons were depolarized whereas those with inverting (inhibitory) connections were hyperpolarized. Current injection into the interneuron could mimic the excitatory effect on uropod motoneurons during the abdominal movement. Cancellation of the membrane potential change in the interneuron during the abdominal movement could also cancel the excitation of uropod motoneurons. We conclude that the local nonspiking interneurons are functioning in producing the positive biases in the motoneurons to bring out their spiking to the otherwise subthreshold input from statocyst interneurons (Fig.2;6).

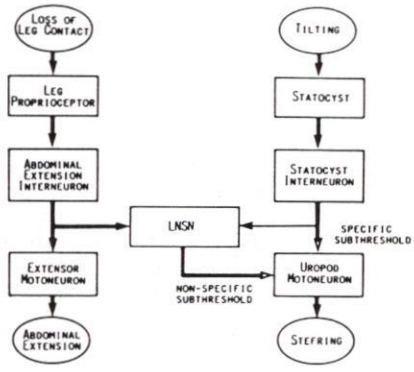


Fig.2. Modulatory role of local nonspiking interneurons (LNSN) in the equilibrium control system of crayfish (1).

Conclusion Although the principal circuitry controlling the equilibrium reactions is relatively simple in comparison with that of other behavioral acts, it is complex enough to allow the modulation or modification of the reactions internally by the behavioral context of the animal. The neuronal substrate of this modulation, i.e., gating in this study, includes a newly found local nonspiking interneurons that are suitable to the long term control of the motoneuron activity. This study may serve to provide an insight into the mechanism of the response variability in the equilibrium control system of animals under natural conditions as well as the physiological basis of the so-called motivational process.

References

1. Hisada, M., Takahata, M. and Nagayama, T. Zool. Sci. 1:681-700, 1984.
2. Nagayama, T., Takahata, M. and Hisada, M. J. Comp. Physiol. 154:499-510, 1984.
3. Ozeki, M., Takahata, M. and Hisada, M. J. Comp. Physiol. 123:1-10, 1978.
4. Takahata, M. and Hisada, M. J. Comp. Physiol. 130:201-207, 1979.
5. Takahata, M. and Hisada, M. J. Comp. Physic 149:301-306, 1982.
6. Takahata, M. and Hisada, M. J. Neurophys 56:718-733, 1986.
7. Takahata, M., Yoshino, M. and Hisada, M Comp. Physiol. 157:547-554, 1985.
8. Yoshino, M., Kondoh, Y. and Hisada, M Tis. Res. 230:37-48, 1983.
9. Yoshino, M., Takahata, M. and Hisada, Comp. Physiol. 139:243-250, 1980.

RECEPTOR MECHANISM AND NEURONAL CIRCUIT SUBSERVING GRAVITATIONAL RESPONSES IN CRAYFISH

Mituhiko Hisada, Masakazu Takahata,
Toshiki Nagayama and Masami Yoshino

Zoological Institute, Faculty of Science, Hokkaido University, Sapporo 060, Japan

Abstract Neural mechanisms underlying the equilibrium reflexes of crayfish are briefly reviewed in this paper with special reference to the gating of reflex circuit by local nonspiking interneurons. Positional change of the animal body is detected by a pair of statocysts that are specialized equilibrium sense organs in crayfish. Basically, each statocyst transmits information about the magnitude and direction of body tilt within a certain range, working in a complementary way to each other. The statocyst information is transmitted in the brain to four pairs of interneurons that descend the ventral nerve cord down to the terminal abdominal ganglion where they make synaptic connections with motoneurons to control the steering response of uropods. The tilt direction is represented by the combination of interneurons activated while the magnitude is coded in their spike discharge frequency. This descending statocyst pathway is "gated" by the activity of abdominal system through a novel class of interneuron, i.e., local nonspiking interneurons, so that the response occurs only while the animal is performing the abdominal posture movement.

Introduction

As in many other animals, crustaceans require equilibrium reactions to restore and maintain their body posture against disturbances brought about by external forces or by an animal's own locomotor activity. Sensory organs involved in detecting the change in body posture include the statocysts, leg proprioceptors and eyes. Righting torque is produced by body appendages --- antennae, antennules, legs, swimmerets and uropods. Their concerted action produces corrective righting reactions, and this requires a highly coordinated functions of both neuronal and muscular systems of the animal. Intersegmental and bilateral coordination is essential to perfect the equilibrium responses. Yet modification of the movement of individual appendage is often necessary to meet the requirement of fine adjustment of the righting torque during the equilibrium responses. Such appearance or disappearance (gating) of the movement of an appendage(s) can be observed.

A description of the function of the main gravitational sense organ, statocyst, and the neuronal system subserving the coordination, in particular of the gating mechanism of the appendage movement in common American red crayfish, Procambarus clarkii, will be given in the following sections.

Statocyst

A pair of statocysts are located at the basal segments of antennules of crayfish. The crayfish statocyst is a deep cuticular depression connected to the outside through an opening covered with a thicket of non-sensory hairs. About one hundred hairs are aligned in a crescent on the floor of the statocyst. A statolith, a congregation of fine sand grains, lies on top of these hairs. A change in shearing force exerted by the statolith onto these hairs causes a change in their deflection angle. The sensory neurons attached to the hairs respond with increase or decrease of the frequency of the spike discharge depending on the direction of the hair deflection: for instance, inward deflection of the hair causes a frequency increase in tonic-type sensory neurons (3,4). The arrangement of hairs in a crescent form in each statocyst thus results in an increase of the spikes in one population of sensory neurons and in a decrease in the other ones which are situated just opposite to the former and functionally polarized in an opposite direction. The anatomical finding that sensory neurons from different regions of the statocyst crescent directly project to different parts of the brain (8) indicates that the direction of position change is coded by the topographic pattern of stimulation and the magnitude is coded by the amount of excitation of sensory neurons. The brain projection of the sensory neurons basically represents this topographic pattern. Interneurons having their dendritic arborization in this region may receive the positional information by connecting to a specific area of this primary projection.

Statocyst interneurons

Coordinated control of the movement of appendages can only be realized by transmission of the statocyst information to the motor systems. The central pathway has been studied in the crayfish (5). The transmission is undertaken by four pairs of directionally sensitive statocyst interneurons which descend the ventral nerve cord to the last abdominal ganglion. Each of them responds maximally to body tilting in particular directions. These four interneurons in each hemicord are named C_1, C_2, I_1 and I_2 respectively depending on their major source of gravitational information, i.e., contralateral or ipsilateral statocyst (Fig.1). The connection between the statocyst interneuron and the statocyst afferent is both mono- and polysynaptic (5). The polysynaptic pathway seems to be responsible for transmitting positional information from the statocyst.

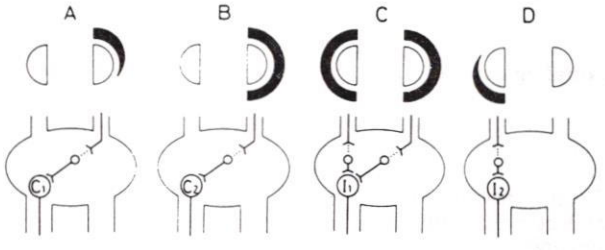


Fig.1. Functional connection of statocyst interneurons C_1 (**A**), C_2 (**B**), I_1 (**C**) and I_2 (**D**) with statocyst afferents in the brain. Each interneuron is connected to the statocyst hairs located in the shaded portion of the crescent (5).

chronic weightlessness, antigravity muscles as a group might shorten when relieved of the burden of postural support thus increasing the passive stretch on their syngravity antagonists. This could result in atrophy of the former and hypertrophy of the latter. Conversely, the centrifuged animal might be forced into a more "squat" posture resulting in stretch with hypertrophy of extensors and shortening with atrophy of flexors. In any case this model increases the possibilities for explaining mass changes in muscles. Looking at total musculature rather than individual muscles, whether the net change is atrophy or hypertrophy will depend upon the number and extent of each kind of mass change present.

In order to clarify the responses of muscles to weightlessness and centrifugation, simultaneous measurements are needed on exposed animals of both antigravity and syngravity muscles (the latter having been virtually ignored). Furthermore, because it is reported that hypertrophy is often transient (8,11,20,22), a chronological series of measurements (probably necessitating a transverse experimental plan) is needed to characterize both transient changes and the eventual steady state condition. Such studies are likely to yield a more complex web of interactions but one which may nevertheless be easier to understand in terms of physiological principles.

REFERENCES

1. Feller, D.D., H.S. Ginoza, and E.R. Morey. Physiologist 24 Suppl.:S9-S10, 1981.

2. Feng, T.P., H.W. Jung, and W.Y. Wu. In: The Effect of Use and Disuse on Neuromuscular Functions. Edited by E. Gutmann and P. Hník. Elsevier Pub. Co.: New York, 1963, p. 431-441.

3. Goldspink, D.F. J. Physiol. 264:267-282, 1977.

4. Hamosh, M., M. Lesch, J. Baron, and S. Kaufman. Science 157:935-937, 1967.

5. Herbison, G.J. and J.M. Talbot. Physiologist 28:520-527, 1985.

6. Hubbard, R.W., C.D. Ianuzzo, W.T. Matthew, and J.D. Linduska. Growth 39:85-93, 1975.

7. Ilyina-Kakueva, E.I., V.V. Portugalov, and N.P. Krivenkova. Aviat. Space Environ. Med. 47:700-703, 1976.

8. Kurakami, K. Nagoya Med. J. 12:165-184, 1966.

9. Laurent, G.J. and M.P. Sparrow. Growth 41:249-262, 1977.

10. Laurent, G.J., M.P. Sparrow, and D.J. Millward. Biochem. J. 176:407-417, 1978.

11. Macková, E. and P. Hník. Physiol. Bohemoslov. 21:9-17, 1972.

12. Musacchia, X.J., D.R. Deavers, G.A. Meininger, and T.P. Davis. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48:479-486, 1980.

13. Pace, N., A.H. Smith, and D.F. Rahlmann. Physiologist 28:S17-S20, 1985.

14. Pitts, G.C. and J. Oyama. Life Sci. Space Res. 17:225-229, 1979.

15. Pitts, G.C., L.S. Bull, and J. Oyama. Am. J. Physiol. 223:1044-1048, 1972.

16. Pitts, G.C., L.S. Bull and J. Oyama. Am. J. Physiol. 228:714-717, 1975.

17. Pitts, G.C., A.S. Ushakov, N. Pace, A.H. Smith, D.F. Rahlmann, and T.A. Smirnova. Am. J. Physiol. 244 (Regulatory Integrative Comp. Physiol. 13):R332-R337, 1983.

18. Portugalov, V.V. NASA Technical Translation-NASA TT F-17257, 1976.

19. Ralston, H.J., B. Feinstein, and V.T. Inman. Fed. Proc. 11:127, 1952.

20. Schiaffino, S. Experientia 30:1163-1164, 1974.

21. Steffen, J.M. and X.J. Musacchia. Am. J. Physiol. 247 (Regulatory Integrative Comp. Physiol. 16):R728-R732, 1984.

22. Stewart, D.M. Am. J. Physiol. 214:1139-1146, 1968.

23. Tischler, M.E., S.R. Jaspers, E.J. Henricksen and S. Jacob. Physiologist 28, Suppl.:S13-S16, 1985.

THE RESPONSE OF SKELETAL MUSCLE MASS TO CHANGES IN ACCELERATION

Grover C. Pitts

Department of Physiology, School of Medicine
University of Virginia, Charlottesville, VA
22908, USA

ABSTRACT

The older literature supported the prediction that chronic centrifugation would cause hypertrophy of antigravity skeletal muscle but instead it is found to cause atrophy of both antigravity muscles and total musculature. It also supported the prediction that chronic weightlessness would cause atrophy but instead both hypertrophy and atrophy are found. Trying to explain these apparently contradictory results we have evaluated data in the literature on the influence of a variety of factors upon muscle mass. Two factors which might help provide an explanation are passive stretch or shortening which cause hypertrophy or atrophy respectively, and the distinction between antigravity and syngravity muscles in their responses. At each skeletal joint circumstances (including centrifugation or weightlessness) which cause antigravity hypertrophy are likely to cause syngravity atrophy and vice versa. The change in net mass of total musculature will depend upon the cumulative amount of hypertrophy and atrophy present.

A considerable body of literature, as well as a feeling of what is physiologically sensible, prompts the prediction that skeletal muscle will hypertrophy when overloaded by chronic centrifugation and will atrophy when the load is virtually eliminated by weightlessness. Consequently, the findings that centrifugation causes atrophy in total musculature (13,14,15) and that weightlessness may produce net hypertrophy of total musculature (17) and of an antigravity muscle (18) as well as the expected atrophy (7,18) constitutes a dilemma. Unfortunately, a recent report of a working group study of muscle responses as they pertain to NASA's mission (5) does not address these anomalous findings. Our evaluation of the role of stretch and the different responses obtained from synergists and antagonists, as reported in the literature, suggest a rationale for explaining the anomalous findings.

METHODS

Several definitions are required. "Muscle" without further qualification will refer to skeletal variety. Muscles which function with help of gravity, as opposed to antigravity will be identified as "syngravity". Hypertrophy and atrophy will refer to increases and decreases respectively in muscle mass with no implications on the biochemical or micro-morphological levels. Growth of muscle has been largely controlled by experimental design in the papers referred to here and its role as a primary factor will not be considered.

RESULTS AND DISCUSSION

First we shall examine findings on the effects upon muscle mass of stretch and of absence of stretch, and next findings on the differential effects upon antigravity and syngravity muscles. Then we shall consider the bearing of these findings upon the dilemmas of weightlessness and of centrifugation and upon the planning of future experimentation.

A number of species (rat, rabbit, guinea pig, chicken) have been studied using several techniques for in vivo muscle stretch: a cast holding muscle in the extended position (3,8,19), surgical shortening of the tendon (20), weighted chicken wing causing it to droop and stretch the flexor (9,10) and denervation of the chicken wing muscle causing it to droop by its own weight (2). In each case stretch resulted in hypertrophy.

While physical exercise plays an important role in determining muscle size, there is reason to believe that part of this effect may be achieved through stretch. Thus, tenotomy of the extensor synergists at the rat heel-joint increases both the work done by, and the stretch of, the remaining intact soleus or plantaris resulting in hypertrophy (4,6,11). Denervation of a hemidiaphragm in the rat results in its hypertrophy which has been attributed to it being stretched by the contractile activity on the intact side (22).

The expectation that in the absence of stretch atrophy will occur, is borne out. Thus, muscles held in a neutral or a shortened position by a cast will atrophy (3,8,19). Hindlimbs suspended above the floor to relieve them of weightbearing and thereby simulate weightlessness show antigravity atrophy (1,12,21). This can be attributed, in part, to their shortening due to inherent tonus.

It is likely that losses in mass such as those described will be due in part to the stress generated by the experimental procedures. There are several bits of evidence suggesting that stress is not the sole (and perhaps only a minor) factor. For example: adrenalectomy had little influence on the muscle atrophy observed in rats with rear limbs suspended (23), chronically centrifuged rats showed normal growth curves (15), after termination of weightlessness (18) and centrifugation (15) rats showed normal recovery in muscle mass, and the loss in body mass at the beginning of centrifugation appears to be regulated (16).

Both hypertrophy and atrophy can occur simultaneously at the same joint, for example, by a cast (3,8,19) or by denervation of the chicken wing (2), each causing stretching with hypertrophy of one muscle and shortening with atrophy of an antagonist. The normal posture and activity at such a joint are probably responsible for the position of each muscle on the hypertrophy-atrophy continuum. Changes at this joint, such as altered chronic acceleration, will probably cause a change of each muscle mass to a new steady state. Thus we might speculate that in animals exposed to

Though in varying degrees, blood pressure underwent a sharp drop immediately after the centrifuge stopped. Then, it moved for recovery, but not completely. It settled itself on a value lower than control level. It seems that the drop in blood pressure is directly in proportion to the intensity of gravity applied. After load application, blood pressure quickly returned to the control level. Respiration rate was subjected to a fairly large variance between 3, 4 and 5G, but differed little from the control values. After a 6G load application, respiration rate gradually continued to quicken for the next 10 minutes, but was kept stabilized thereafter throughout load application. After halting the load application, respiration rate returned to the control level.

Upon application of gravity in the -Gz direction, it appears that the -Gz load application had greater impact than the -Gx and the +Gz load application. Specifically, heart rate dropped by 10% under 3, 4, 5 and 6G. Likewise, blood pressure dropped by about 20% in all gravitational intensities. On the other hand, respiration rate differed little between 3, 4, and 5G. But immediately after a 6G load application, the respiration rate started to decline gradually. It dropped by as much as 40% up to 30 minutes after load application. Since it suffered such a drastic drop during load application, it could not immediately return to the control level.

Fig. 3. shows values in terms of the ratio of deviation from control values in a phase preceding the application of gravity.

Heart rate varies little with the application of gravity in the -Gx and +Gz directions except that it shows a trend to increase slightly. After the -Gz load application, heart rate shows a decline both in 3 and 6G intensities.

Transthoracic impedance Zo, measured concurrently with impedance pneumogram, increased. In view of this fact, a decrease in interthoracic blood volume can be inferred, and reaction in good accord with human head-up tilt was observed together with an increase in heart rate.

A drop in blood pressure was observed in subjects of every group. It appears that blood pressure tends to drop with an increase in the intensity of gravity applied. After the -Gz load application, a rise in blood pressure of the part of the body above the neck, a drop in heart rate and blood pressure and a drop in aortic arch were observed.

On the other hand, respiration rate tended to increase unless 6G gravity was applied in the -Gz direction. Specifically, after the -Gz load application respiration rate increased with an increase in the gravitational intensity applied. After the +Gz and -Gz load application, respiration rate remained relatively stable within a range of 3 to 5G intensities. However, when 6G gravity was applied, heart rate increased by 25% in the case of the +Gz, but decreased by 25% in the case of the -Gz.

A decrease in respiration rate under the -6Gz is attributable to the fact that, due to the application of excessive gravity, lungs are oppressed to cause blood congestion, thereby making breathing difficult, as evidenced by bleeding through the trachea.

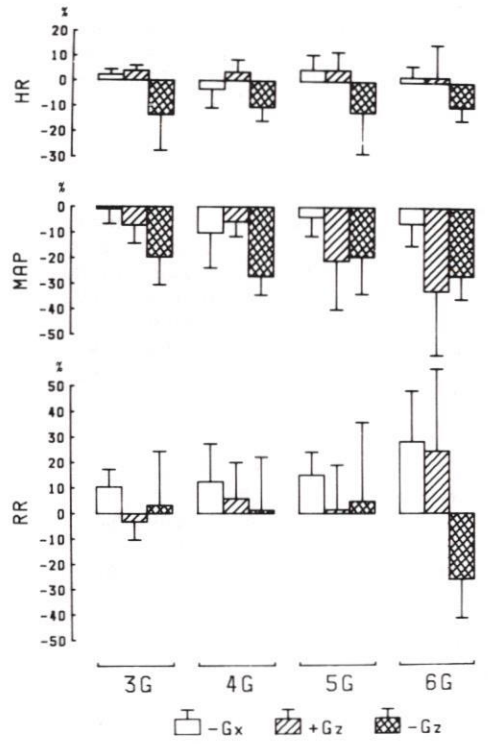


Fig. 3. Change rate of heart rate, mean arterial pressure and respiration rate of rats, exposed to 3, 4, 5 and 6G gravities in -Gx, +Gz and -Gz directions for 30 minutes.

Summary

We have reported some findings on cardiopulmonary responses of rats to centrifugal accelerations. And the results obtained were summarized as follows :

1) While heart rate did not change during the -Gx and +Gz load application, it decreased during the -Gz load application.

2) Mean arterial pressure decreased during every group of the load application.

3) Although transthoracic impedance Zo decreased during the -Gx and -Gz load application, it increased during the +Gz load application. This suggests that interthoracic blood volume in the lower body is increased by +Gz load application.

4) Respiration rate increased during the -Gx load application, and it showed a increasing tendency corresponding to the intensity of the accelerations.

In view of these findings, we may reasonably conclude that application of 5G or less gravity has no lethal effect on rats and that prolonged experiments for several weeks on end can be conducted safely if they are implemented with a gravity of 5G or less.

References

1) Arita,H., Kohgo,N., Saiki,H., Sudoh,M., Kohno,M. and Ikawa,S. : Hemodynamic responses to head-up tilt during 7-day satulation dive at 31 ATA. J. Physiol. Soc. Japan, 47, 608, 1985.

2) Bengele,H.H. : Water intake and urine output of rats during chronic centrifugation. Am. J Physiol. 216, 659-665, 1969.

3) Kelly,C.F., Smith,A.H. and Winget,C.M. : animal centrifuge for prolonged operation. Appl. Physiol. 15, 753-757, 1960.

4) Pitts,G.C. and Oyama,J. : Rat growth dur chronic centrifugation. Life Science and Research. 17, 225-229, 1979.

CARDIOPULMONARY RESPONSE OF RATS TO CENTRIFUGAL ACCELERATIONS.

Masamichi Sudoh*, Kumiko Shioda*, Miharu Kohno*, Satio Ikawa*, Kenji Kawakami** and Hisashi Saiki***

*Space Medicine Laboratory, The Jikei University School of Medicine
**Department of Radiology, The Jikei University School of Medicine
***St. Marianna University School of Medicine

Introduction

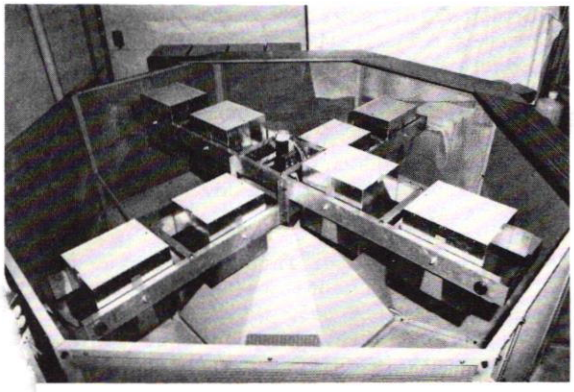
Lately, flight in outer space over an extended period of time has become possible. Consequently, exposure of human bodies to gravity of different intensities is becoming a reality. In this regard, extensive research has been conducted on the effects of high gravity on human bodies for a short duration and on human tolerance of such an environment.

Commonly, a centrifuge is used to simulate a high gravity environment. We designed and manufactured a centrifuge capable of operating continuously at 8G for an extended period of time. This study reports on the performance of our centrifuge and the resulting effects on cardiopulmonary response in terms of heart rate, blood pressure and respiration rate. Cardiopulmonary response varies with the intensity of gravity. The intensity of gravity range from 3G through 6G.

Performance of Centrifuge

The centrifuge is fitted with an arm with a radius of 1.3m and cages mounted respectively 45cm and 1m from its center (Fig.1.). It can accelerate within a range of 0 to 8G and operate continuously for several months on end.

It is also equipped with a 0.4kW gearmotor and a general purpose inverter for controlling rotation.



. 1. 1.3m radius centrifuge for animal.

In order to improve dynamic balance, a pair of arms, 2.6m in diameter, were crossed. Static balance can be maintained by setting a weight on each end of the arm.

Experimental Methods

In this experiment, we used female rats of Wister strain, each weighing about 200g, and anesthetized with 3mg of pentobarbital sodium per 100g of the body weight. We applied gravity in intensities of 3, 4, 5 and 6G in three directions of back to adbomen (-Gx), head to tail (+Gz) and tail to head (-Gz).

Fig. 2. shows an example of the experimental recordings. Of these, respiration rate was determined based on the frequency of the peak per minute of the pneumogram. Blood pressure was measured by a catheter inserted through the left carotid into the aortic arch.

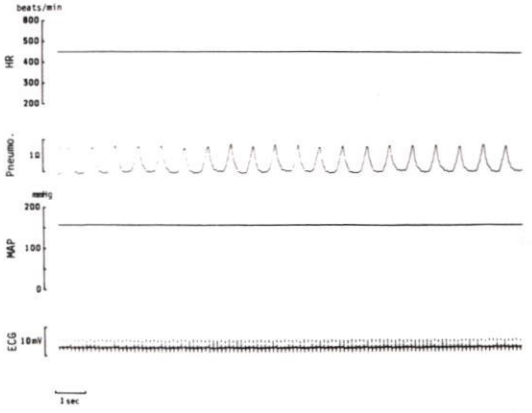


Fig. 2. An example of a record when 3G gravity is applied in the -Gx direction. From top to bottom, the picture shows mean heart rate, impedance pneumogram, mean arterial pressure and ECG.

Results and Discussion

The control showed stable conditions in respect to heart rate, blood pressure and respiration rate, with small standard deviation. Upon application of gravity in the -Gx direction, there occurred a slight increase in heart rate. It remained virtually unchanged with only negligible deviations. We noted a drop in blood pressure in the latter half of 4G load application and only slight variance on the blood pressure. But, there was no major fluctuation in blood pressure. It returned to the control level immediately after the centrifuge stopped.

Respiration rate increased upon application of load and continued to increase during load application. The respiration rate quickly returned to the control level after load application was halted except after 6G load application. It appears that the magnitude of increase is in proportion to the gravitational intensity.

Upon application of gravity in the +Gz direction, heart rate remained virtually unchanged as in the case of the -Gx. Variance in heart rate by individual increased with an increase of the intensity of gravity.

Blood pressure underwent minor fluctuations under 3 and 4G, but dropped upon 5 and 6G.

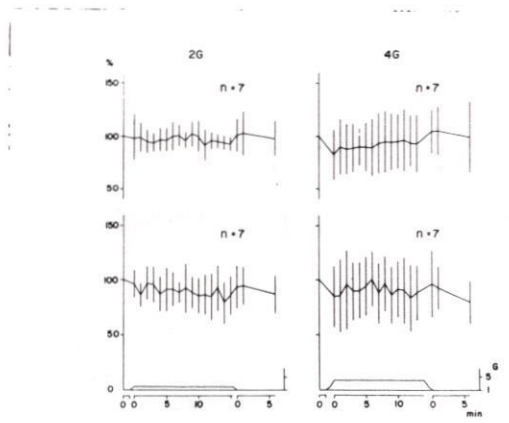


Fig. 3. Normalized stroke volume in hyper G exposure. Upper trace shows that of the control group. Lower traces the decerebellated.

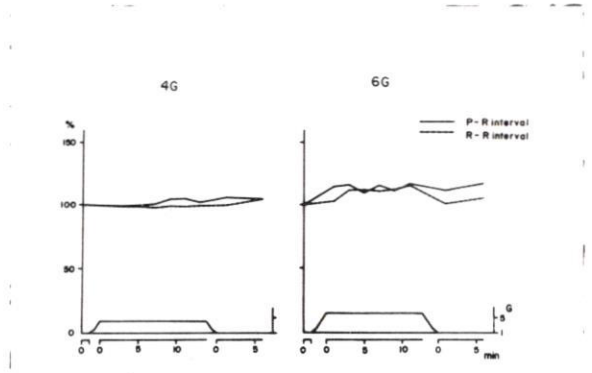


Figure 4. Examples of P-R and R-R intervals. Solid lines show P-R interval. Dashed lines, R-R intervals.

standard deviation in 4G was larger than that in 2G. According to Kubicek's method, SV is calculated as the product of maximum amplitude of the first derivative of impedance plethysmogram and the ejection time. In 4G and 6G exposure, this derivatives were severely distorted in many cases. Therefore, it was difficult to estimate correctly the standard deviation for SV. In the decerebellated group, SV showed a decreasing tendency. Difference in SV between control and decerebellated groups was not significant. However, at 6 minutes after cessation in 4G exposure, SV of the decerebellated group was below the initial level in almost all cases. CO was calculated by the product of HR and SV. The pattern of change in CO in any G exposure was similar to that of SV. Therefore, compensation between HR and SV was not observed.

P-R and R-R intervals in the decerebellated group are illustrated in Fig. 4. The control group showed similar change, so we referred to only the result from the decerebellated group. In the 4G condition, R-R interval was constant except at 6 minutes after cessation of exposure. While P-R interval became large at 7 minutes in steady phase of 4G exposure. In the 6G condition, P-R interval elongated at 1 minute in steady phase. P-R interval elongated also. After cessation, R-R interval returned to almost initial level, while P-R interval did not. Such changes in P-R interval were observed almost all cases at 4G or 6G exposure. But at 2G exposure, such changes were not observed. We also measured the duration of the QRS complex. The duration of QRS was constant in both control and decerebellated groups in all G exposure. It can be concluded from the preceding results that hyper G exposure induced the first degree AV block. In some cases, HR abruptly fell. However, still 1:1 atrioventricular conduction was preserved until to the level of 120 bpm.

In summary, the control and the decerebellated hamsters were exposed to hypergravity condition in -Gz direction, and following results were obtained.

(1) HR in the control group decreased in 4G or 6G exposure, and those in the decerebellated group increased slightly in 2G, but showed decreasing tendency in 4G or 6G.

(2) In the rising phase of G exposure, HR showed a transient increase in the control group but not in the decerebellated group.

(3) In both groups, the first degree AV block was observed in 4G or 6G exposure.

CHANGES OF CARDIAC SYSTEMS OF DECEREBELLATED HAMSTERS IN HYPERGRAVITY CONDITIONS

S. UEKI, T. KAWASHIMA, H. SATAKE, M. NAKASHIMA*, K. MATSUNAMI

Dept. of Neurophysiology, Inst. of Equilibrium Res. and *Dept. of Pharmacology, Gifu Univ., Sch. of Med. Gifu 500

Cardiovascular regulation in response to hypergravity conditions has been studied on the fluid shift theory; that is, cardiovascular change in hypergravity is explained mainly due to the decrease of venus return. Vasomotor centers in the brain stem was also taken account. It was also considered that cardiovascular system received informations from baroreceptor or chemical receptor that responded to gas concentration in blood. Then, how about the neural mechanism receiving informations of gravity ? In this paper, we considered the cerebellar function in the control of the cardiovascular system under hypergravity conditions.

We used Sylian golden hamsters, 15 control 13 decerebellated. The cerebellum was aspired off 1 or 2 days before the experiments. The hamsters were anesthetized with sodium Amobarbital injected intraperitonealy. Initial dose was 125 mg/kg. Its effect continued over 1 hour. They were exposed to hypergravity by a centrifugal accelerator over 10 minutes. The applied G was in -Gz direction (from tail to head), with the magnitude of 2G, 4G or 6G. We recorded ECG and impedance plethysmogram. The parameters measured for cardiac function were heart rate (HR), stroke volume (SV), cardiac output (CO), P-R interval and R-R interval. SV was estimated by Kubicek's method. We measured HR, SV and CO at 1 minute before G exposure, every minute during G exposure, at the cessation of G exposure, and 1 minute and 6 minutes after the cessation. We also measured HR at every G during rising and falling phase of G exposure to observe transient response during these periods.

In the control group, HR showed no change in 2G. But two points could be referred to for 4G experiments. The first point was the presence of a transient change during rising phase of G exposure. However, it was not clear during falling phase. The second point was a slight decrease in HR during the steady phase. HR did not return to the initial level after cessation. It is also pointed out that the estimated values had large standard deviation. This is because two groups with different characteristics in the change of HR were

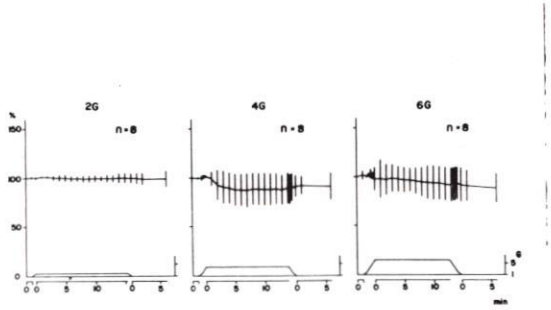


Figure 1. Normalized heart rate in G exposure in the control group.

counted together; one group showed only a slight change, while the other showed reduction of more than 30% of the initial level, probably due to atrioventricular (AV) block. In 6 G exposure, HR showed similar changes to those in 4G exposure.

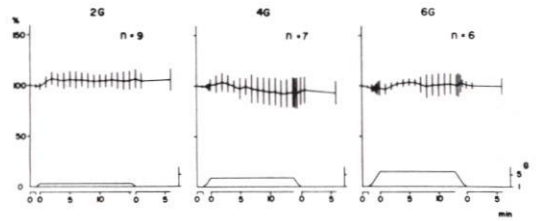


Figure 2. Normalized heart rate in G exposure in the decerebellated group.

In the decerebellated group, HR increased slowly during the first 2 minutes. After that, it kept a constant value of 105% of the initial level. And even after the cessation of G exposure, it did not return to the initial level. In 4G and 6G exposure, we could not observe the transient change during rising phase. During steady phase, the animal responded in two different ways as observed in the control animals during 4G application. Standard deviation was smaller in 6G exposure. However, the estimated values were only for the animals which showed little change of HR. For other animals, HR decreased so severely in the early phase of G exposure (below 100 bpm) that we could not continue the experiment for fear of fatal damage.

Figure 3 represents SV. In the control group, SV showed a slight decrease during 2G and 4G exposure. It returned almost the initial level after cessation. The

proportional to metabolic rate [4]. Increased metabolic rate is increased with an increasing acceleration field [9,15] also may be a factor in liver and kidney hypertrophy. However, heart and brain also fall in this category, but do not exhibit an acceleration hypertrophy. The reduction in size of the g-i tract is difficult to rationalize. Size of the g-i tract is generally related to feed intake, which increases proportionately with an increasing acceleration field [17].

In two of the experimental groups (Zulu and Alpha) the left leg was dissected and bone and muscle masses determined and evaluated as gms per kg FFCM. Leg bone and leg muscle sizes, and the bone/muscle mass ratios were standardized as functions of to the equivalent control observations. Bone mass and bone/muscle ratio increased and muscle mass decreased proportionally to the increasing acceleration field:

$$\text{Std. Leg Bone Mass} = 0.93 + 0.1\ G \quad (r = 0.977;\ p<0.001)$$

$$\text{Std. Leg Muscle Mass} = 1.10 - 0.1\ G \quad (r = -0.977;\ p<0.001)$$

$$\text{Std. Bone/Muscle Mass} = 0.76 + 0.26\ G \quad (r = 0.961;\ p<0.001)$$

The decrease in leg muscle mass may appear paradoxical in view of the increased postural requirements during centrifugation. However, when changes in extensor and flexor muscles are compared [2], a marked increase in the antigravity extensors and decrease in the flexors is apparent. Consequently the functional capacity of the leg muscle will be enhanced in spite of its decrease in mass. The increase in leg bone mass in chronically accelerated fowl is consistent with the increased bone mineral mass (whole body) in chronically accelerated small mammals [10]. However, other reports on skeletal mass in chronically accelerated rats indicate a small (-3%/G) but statistically significant decrease [13].

DISCUSSION:

It is evident that the influence of the gravitational loading of animals, induced by chronic acceleration, is not anatomically symmetrical. Some organs are selectively increased in size whereas others are decreased, and presumably these changes are functionally related. It is perhaps important that the changes induced in some organs by gravitational loading are dissimilar from those associated with loading resulting from increased body size [4]. With increasing body size the relative sizes of visceral organs are decreased and the relative bone and muscle masses are increased. Mass loading (by "weighting" animals at earth gravity) also selectively increases bone size [19].

REFERENCES:

1. Briney, S. R., and C. C. Wunder, 1962. Comparative study of effects of gravity on the growth of hamsters and mice. Proc. Iowa Acad. Sci. 67:495-500.
2. Burton, R. R., E. L. Besch, S. J. Sluka and A. H. Smith, 1967. Differential effect of chronic acceleration upon skeletal muscles. J. Appl. Physiol. 23:80-84.
3. Evans, J. W., A. H. Smith and J. M. Boda, 1969. Fat metabolism and chronic acceleration. Am. J. Physiol. 216:1468-71.
4. Holliday, M. A., D. Potter, A. Jarrah and S. Bearg, 1967. The relation of metabolic rate to body weight and organ size: A review. Pediat. Res. 1:185-95.
5. Nordstrom, J. O., 1966. Avian Liver Function Studies. Doctoral Thesis (Physiology). Univ. Calif. Davis.
6. Oyama, J., and W. T. Platt, 1965. Effects of prolonged centrifugation on growth and organ development of rats. Am. J. Physiol. 209:611-15.
7. Oyama, J., L. Solgaard, J. Corrales and C. B. Munson, 1985. Growth and development of mice and rats conceived and reared at different G-intensities during chronic centrifugation. The Physiologist 28(6 suppl):S83-84.
8. Pace, N., D. F. Rahlmann, A. M. Kodama and A. H. Smith, 1978. Body composition changes in monkeys during long-term exposure to high acceleration fields. COSPAR Life Sci. and Space Res. XVI:71-76.
9. Pace, N., and A. H. Smith, 1983. Scaling of metabolic rate on body mass in small mammals at 2 G. The Physiologist 26(6 suppl):S125-26.
10. Pace, N., A. H. Smith and D. F. Rahlmann, 1985. Skeletal mass change as a function of gravitational loading. The Physiologist 28(6 suppl):S17-20.
11. Palsson, H., 1955. Conformation and Body Composition. In: Progress in Physiology of Domestic Animals. Ed., J. Hammond. Butterworths [London].
12. Pitts, G. C., 1951. Gross composition of fat-free mammalian body. Fed. Proc. 10:105.
13. Pitts, G. C., 1982. Effects of chronic acceleration on body composition. The Physiologist 25(6 suppl):S13-16.
14. Pitts, G. C., and L. S. Bull, 1977. Exercise, dietary obesity and growth in the rat. Am. J. Physiol. 232:R38-R34.
15. Smith, A. H., 1978. The roles of body mass and gravity in determining the energy requirements of homoiotherms. COSPAR Life Sci. and Space Res. XVI:83-88.
16. Smith, A. H., 1982. Enhancement of chronic acceleration tolerance by selection. The Physiologist 26(6 suppl):S85-86.
17. Smith, A. H., R. R. Burton and C. F. Kelly, 1971. The influence of gravity on the maintenance requirement of chickens. J. Nutr. 101:13-24.
18. Smith, A. H., O. Sanchez P., and R. R. Burton, 1975. Gravitational effects on body composition in birds. COSPAR Life Sci. and Space Res. XIII:21-27.
19. Tulloh, N. M., and B. Romberg, 1963. An effect of gravity on bone development in lambs. Nature 200:438-39.

CHRONIC ACCELERATION AND ORGAN SIZE IN DOMESTIC FOWL

A. H. Smith
Department of Animal Physiology
University of California
Davis, California 95616 USA

In several experiments with chronically accelerated mature fowl, masses of selected visceral organs, bones and muscles were determined. Evaluation and comparisons of such observations are complicated by other acceleration induced changes in body composition.

A common finding after protracted exposure of animals to increased gravitational fields (chronic acceleration) is a decreased body mass, largely the result of a decrease in body fat. The degree of loss of body fat is proportional to field strength and to body size [16]. The only exception so far reported is with monkeys, 10 kg Macaques exhibiting neither a loss of body fat nor body mass after several months at 2.5 G [8]. Asymmetric change in body composition pose difficulties in providing a somatic reference for the evaluation of changes in organ sizes. Nutritionists at Cambridge [11] have used the brain as a suitable reference organ, since it develops early and is not affected by subsequent somatic change. In other studies, the fat free body mass (FFBM) has been found to provide a useful reference for changes in body composition [12,14].

PROCEDURES:

Experimental animals consisted of three groups of male fowl from an acceleration-selected line [16], designated: Tango (S_8), Zulu (S_{14}) and Alpha (S_{15}). All were centrifuged for at least 250 days, when the analyses were performed. The heads, shanks and skin were removed to prepare a carcass, approximating the edible portion, comprising 74± 1.1% of the empty body mass. Individual organs were removed, weighed and then the musculoskeletal component and the total viscera were comminuted and samples taken for determination of fat, fat-free dry matter and water contents. Relative organ sizes were calculated as gms per kg fat-free carcass mass (FFCM). Although scaling factors apply generally to the relationships between organ size and body size, the small range in body size of these experimental animals (Table 1) was such that a scale correction was not warranted.

TABLE 1.Comparison of Fat-Free Carcass Masses Among Groups

	Mean (kg) FFCM ± SD (n) subjects per group				
Group	Control	1.5 G	2 G	2.25 G	2.5 G
T (S_8)	(6)1.36 ±0.36	(6)1.35 ±0.04	(5)1.31 ±0.04		
Z (S_{14})	(13)1.38 ±0.07	(5)1.21 ±0.17	(7)1.15 ±0.46		(9)1.33 ±0.11
A (S_{15})	(4)1.42 ±0.22		(5)1.27 ±0.17	(5)1.34 ±0.12	

RESULTS:

No consistent or statistically significant covariance of relative organ size with the gravitational field was observed for heart, lung or spleen. Relative kidney and liver sizes increased, and relative g-i tract size decreased with increasing gravitational field strength. However, differences also were apparent in relative organ sizes among control groups, e.g., liver, Fig. 1. Some of this variation may be technical, since the experiments were conducted at different times

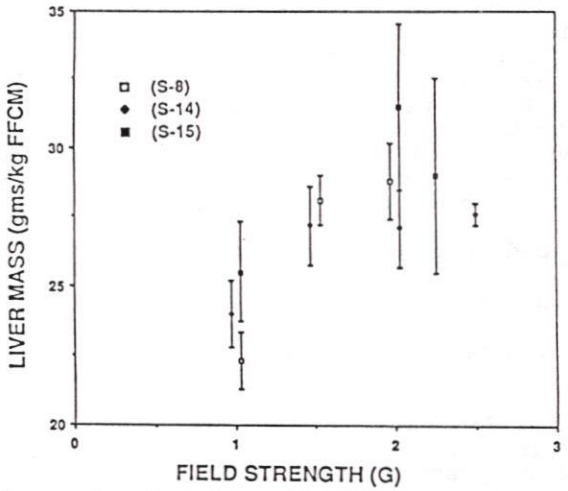


Figure 1. Relative Liver Size.
Liver sizes (gm liver per kg FFCM) are indicated as group means ± SE.

and with different people, allowing for a possible variation in dissection between, but not within groups. Some of this variation also may be biological, since the animals were from successive generations of a line selected for acceleration tolerance which may have produced anatomic change. For example, liver responds to increasing metabolic requirements -- selecting fowl for increased egg production produces an increase in relative liver size proportional to the increase in egg production [5]. Consequently, observations from these chronically accelerated animals were standardized by presenting them as ratios to the equivalent control observations:

$$\text{Std. kidney mass} = 0.83 + 0.23\ G \quad (r = 0.817;\ p<0.01)$$
$$\text{Std. liver mass} = 0.92 + 0.13\ G \quad (r = 0.650;\ p<0.05)$$
$$\text{Std. g-i mass} = 1.18 - 0.16\ G \quad (r = -0.732;\ p<0.05)$$

Increases in liver and kidney sizes also have been found in centrifuging mice and hamsters [1], rats [6] and mouse and rat fetuses and mothers [7]. Gravitational hypertrophy of liver and kidney (and lack of change for heart, lung and spleen) appear to be general phenomena. The liver hypertrophy is associated with gravitational changes in fat metabolism -- a continuing formation of free fatty acids, but with a marked reduction in the deposition of depot fat [3]. This increases hepatic fat metabolism promoting liver hypertrophy. Also, kidney and liver are among the principal organs determining metabolic rate and their sizes tend to be

However, after -Gz acceleration ceased, the decreased SV returned quickly to the control level, and sometimes rebounded over 100%.

In every -Gz load, CO of hamsters decreased significantly during exposure ($p<0.01$). It fell down to 85% in 4G, 80% in 6G, 70% in 8G, and 63% in 10G. As the magnitude of applied acceleration became larger, CO reduced more remarkably. After cessation of -Gz exposure, however, it returned soon to the control level even when -10Gz was applied. It can be concluded that changes of CO is similar to those of SV when hamster was applied to -Gz acceleration.

3) +Gz group

Hamsters were applied to only smaller +Gz exposure (2G and 4G). HR reduced slightly in +2Gz, but it was not significant. SV decreased transiently only for the early phase of G load, followed by an increase to reach a steady level, but it was still less than the control level. CO changed in a similar manner to SV. The reduction of CO was significant ($p<0.01$). After +2Gz exposure ceased, both SV and CO returned to over 100% level.

On the other hand, hamsters under +4Gz application could be divided into two groups by the condition of cardiac responses. One group suffered the vital damage and did not recover even after cessation. We named these the unrecovered group. The other group was the recovered group, whose biological parameters returned to the control level after cessation. The latter group showed a significant decrease in HR and this reduced level was sustained after cessation ($p<0.01$). Obviously, SV and CO showed biphasic responses, namely, transient and sustained reductions ($p<0.01$) during exposure. After exposure, an overshooting reaction was observed. It is suggested that the adaptive state after a transient decrease means the adaptation of cardiac system. It is supposed that these changes (transient decrease and the return to the steady state) expressed a homeostatic response. The unrecovered group showed only a gradual decrease, without producing such homeostatic response. HR and SV decreased in a sawtooth wave pattern. These changes would imply that a hamster made an effort to compensate for decreasing state under +4Gz. Body weight, sex, amount of anaesthetics or any other physical signs could not offer any remarks to separate the unrecovered and the recovered group. Almost all animals in the unrecovered group exhibited negative P wave on ECG followed by sino-atrial block and atrio-ventricular dissociation during +4Gz exposure.

4) Comparison among -Gx, -Gz and +Gz group

Fig.2 shows the comparison in changes among -Gx, -Gz and +Gz groups. Applied acceleration was 4G in every case. Open bar indicates -Gx group, shadowed one, -Gz, and closed bar represents +Gz group. From top to bottom, each graphs shows heart rate, stroke volume and cardiac output respectively. +Gz group represents the value obtained from only the recovered group. Asterisks indicate the statistical significance between each group.

HR did not show the remarkable significant difference among the three groups. In +Gz group, however, the decrease of HR was more remarkable than in other two groups. Moreover, the reduction in HR was smaller than that in SV or CO.

On the other hand, the comparison in SV showed a statistical significance. Especially, during exposure, +Gz group is different from both -Gx and -Gz group ($p<0.01$). The least reduction is observed in -Gx group.

CO, shown in the lower part, had a similar pattern to SV. CO decreased in all three groups. But the reduction in -Gx group is the least and that in +Gz is the most. Furthermore, the result of +Gz group revealed a significant difference from that of both -Gx and -Gz group ($p<0.01$). The difference was not observed after cessation of hyper-G, but only during exposure.

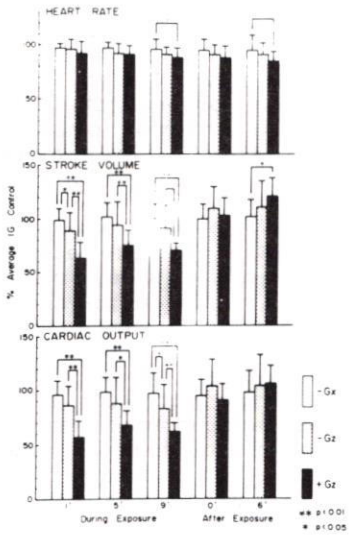


Fig. 2 Comparison in HR, SV and CO among -Gx, -Gz and +Gz groups

CONCLUSION

Cardiac responses of the anaesthetized hamster exposed hyper-G along three directions (-Gx, -Gz and +Gz directions) was investigated. HR, SV and CO were all decreased during the exposure in every direction. The amounts of reduction in these parameters were different among three directions. When hamsters were exposed to +4Gz acceleration, ten hamsters survived and six died. It is supposed that the gravity along Z axis, that is -Gz or +Gz direction, is less adapted environment to a hamster. So, -Gz and +Gz acceleration may cause more shift of body fluid than -Gx which is normal and adapted gravity direction. It is supposed that the reduction of stroke volume is produced by the body fluid shift. Moreover, the hydrodynamical footward fluid shift resulting from +Gz, particularly in 4G, may cause heavy damage to an animal, such as myocardial and cerebral ischemia. From the above results, it is considered that the tolerance of hamsters for hyper-G is smaller in the order of -Gx, -Gz and +Gz.

DIRECTIONAL DIFFERENCE IN EFFECTS OF LONG-TERM HYPER-GRAVITY UPON THE CARDIAC SYSTEM OF THE HAMSTERS

Hirotaka Satake, Yoshio Mizuno[1], Satoru Watanabe[2] and Ken'ichi Matsunami

Dept. of Neurophysiol., Inst. of Equilibrium Res., Gifu Univ., Sch. of Med., Gifu, 500 Japan
[1] Dept. of Phys. Educ., Daido Inst. of Tech., Nagoya, 457 Japan
[2] Dept. of Aerospace Physiol., Res. Inst. of Environ. Med., Nagoya Univ., Nagoya, 464 Japan

When human and animals are in the hyper-gravity environment, it's expected that changes of gravity affect the cardiac reactions. It's also assumed that effects of hyper-gravity depend on the directions of the body axes. In this study, the cardiac responses of anaesthetized hamsters under hyper-gravity for over 10 minutes were investigated. When animals were exposed to -Gz acceleration, the reduction of heart rate (HR), stroke volume (SV) and cardiac output (CO) were observed. In -Gz exposure, these parameter decreased. Meanwhile, animals exposed to the acceleration in the opposite direction (+Gz) showed a significant reduction with smaller weaken acceleration. Moreover, 6 out of 16 hamsters exposed to +4Gz was suffered. From the above results, it was concluded that a quadruped animal, such as a hamster, has the highest tolerance to the -Gx. It was also considered that the footward fluid shift resulting from +Gz exposure caused fatal risk to hamsters. Accordingly, it was supposed that animals are more vulnerable to +Gz than to other two directions (-Gx and -Gz).

METHODS

We used 56 Syrian golden hamsters (Mesocricetus auratus) weighing 100 to 190 grams. They were divided into 3 groups according to the direction of hyper-gravity. One is -Gx group, which is exposed to hyper-gravity from back to abdomen. Another is -Gz group; the direction of hyper-gravity is from foot to head of the animal. And the other is +Gz group, with the gravity of head to foot direction. These animals were slightly anaesthetized with pentobarbital (Nembutal), injected intraperitonealy (50 mg/kg body weight). Nembutal was added 20 mg/kg every hour to keep the animal in the stable anaesthetized condition. The centrifugal acceleration was generated by a spatial disorientator for animal. This apparatus has 1.5 m radius. The gondola, which hangs on the one end of horizontal arm, is allowed to swing out passively during the rotation of arm. This rotator was controlled by a micro-computer. Biological signals were fed into an 8 channel telemeter monitoring with polygraph and then stored on a data recorder. To observe the cardiac reactions to the centrifugal acceleration, it is important to examine a precise time course of the responses. Fig.1 shows the profiles and directions of centrifugal acceleration applied to an animal in this experiment. The magnitude of acceleration was 2, 4, 6, 8 or 10G. These acceleration were applied to an animal (over 10 min) in random series. In both ascending and descending phase, the changing rate of acceleration was 0.025 G/sec from 1 to 2G, and thereafter 0.05 G/sec. Electrocardiogram (I and II leads), and impedance plethysmogram on the chest were recorded through the telemeter. The stroke volume was estimated from impedance plethysmogram by Kubicek's method (1970). Statistical analysis was performed using the t-test.

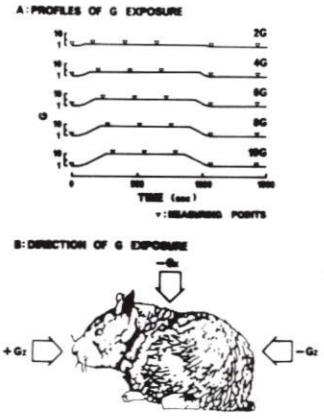


Fig. 1 Profiles and direction of exposure

RESULTS

1) -Gz group

When the hamster was exposed to -Gx acceleration, HR decreased slightly in both 4 and 6G. However, it decreased remarkably in 8 and 10G, with statistical significance ($p<0.05$ in 8G, $p<0.01$ in 10G). SV hardly changed in -4Gx. However, it decreased significantly in 6G exposure ($p<0.05$ in both 6 and 8G, $p<0.01$ in 10G). In -6Gx, stroke volume decreased to 87 %, in -8Gx to 81 %, and in -10Gx to 76%.

Although CO maintained the control level in -4Gx, it decreased remarkably during 6G ($p<0.05$), 8G ($p<0.05$) and 10G exposure ($p<0.01$). Particularly in -10Gx, CO did not readily return to the control level within 6 min after the cessation of acceleration.

The decreases of HR, SV and CO were more with increase in -Gx acceleration.

2) -Gz group

Hamsters in -Gz group showed a smaller decrease in HR during the exposure and this decrease sustained after the cessation of exposure ($p<0.01$). HR maintained 85% even at 10G exposure, in which the maximum decrease occurred.

SV decreased during -Gz exposure, to 90% in 4G, 85% in 6G, 75% in 8G, and 72% in 10G. Although the decrease was not significant in -4Gz, the decrease of SV was significant in over 6G ($p<0.01$).

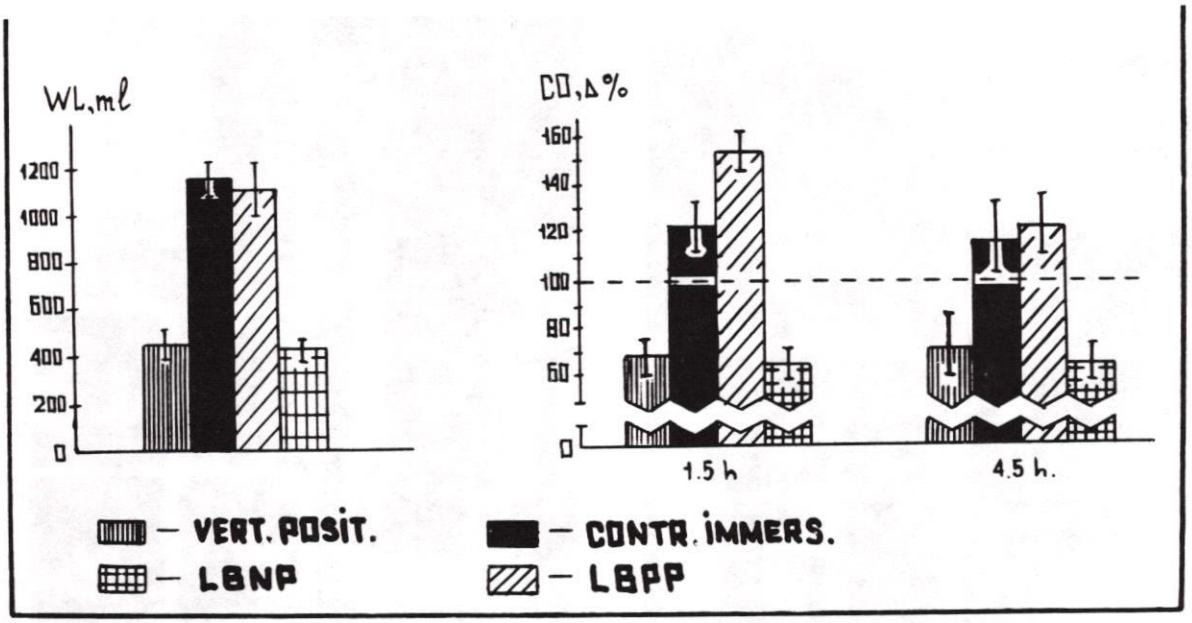


Figure 5. Water loss (WL, ml) and cardiac output change (CO, %) in some experimental conditions of 4.5 hour duration.

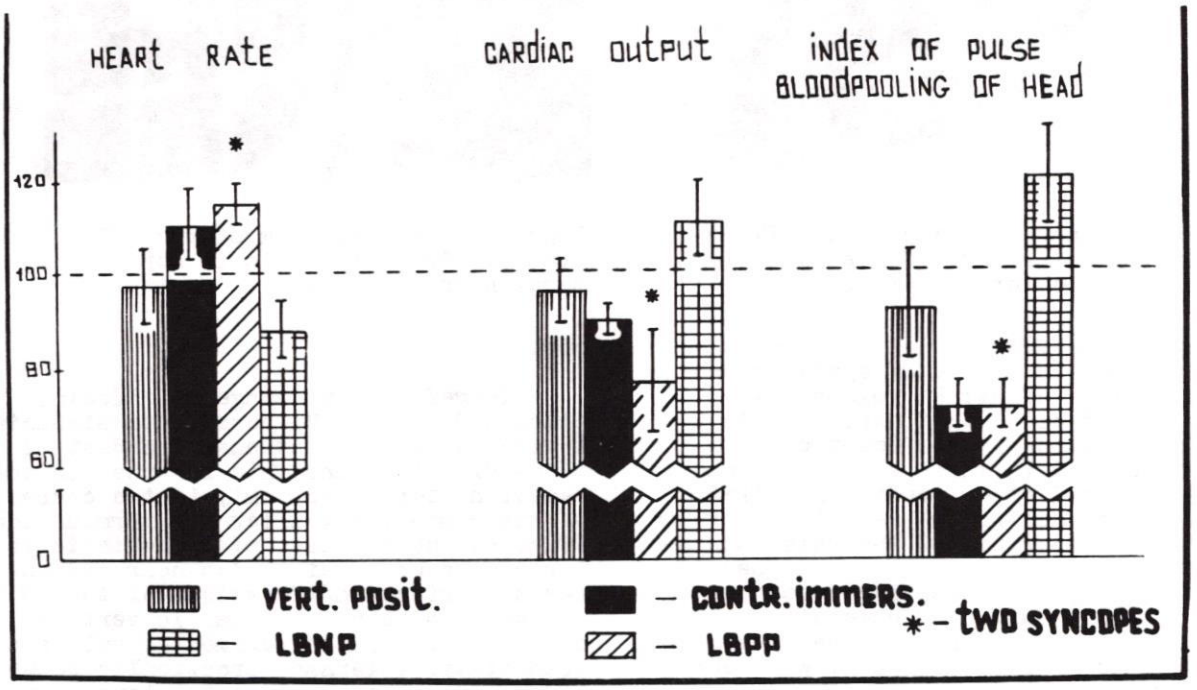


Figure 6. Reactions of tilt test after some experimental conditions (in % to preexperiment data).

and applied problems of space physiology.

References

1. Tsyolkovsky K.E. In: Complete Selection of Works, v.2. Soviet Academy of Sciences Publishing House, Moscow, 1954, p.134-135, 257.

2. Pestov I.D., Genin A.M. In: Vth Annual Symposium of Commission on Gravitational Biology of International Union of Physiological Sciences. Moscow, July 26-29, 1983. Abstracts of Papers. Moscow: Nauka, 1983, p.58.

3. Genin A.M., Pestov I.D. In: Man in Space. Proceedings of the International Man-in-Space Symposium. Yerevan, USSR, October 1-6, 1971. Moscow: Nauka, 1974, p.76-90.

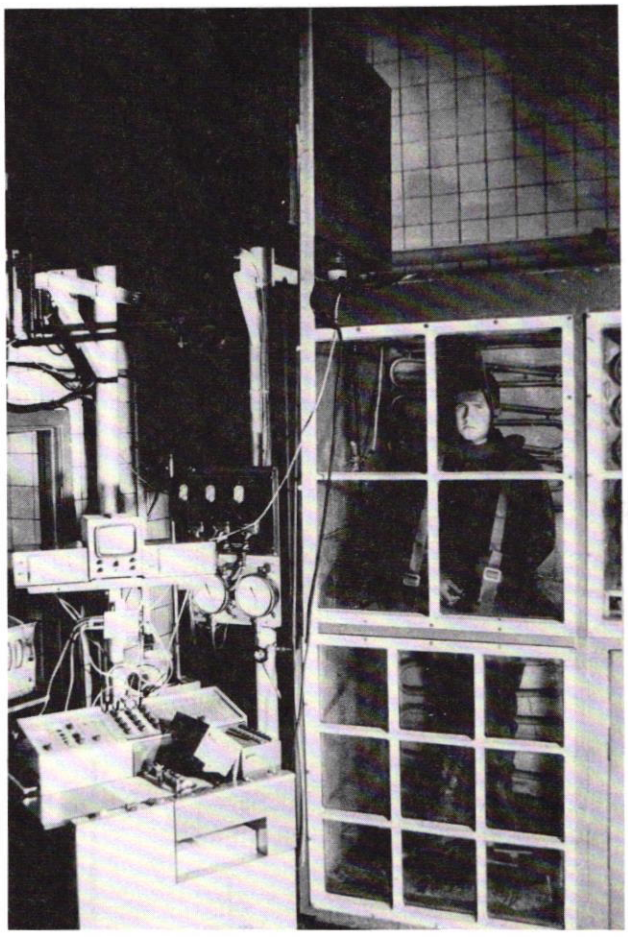


Figure 3. General view at the CWIM assembly without water. (The subject is in vertical posture condition).

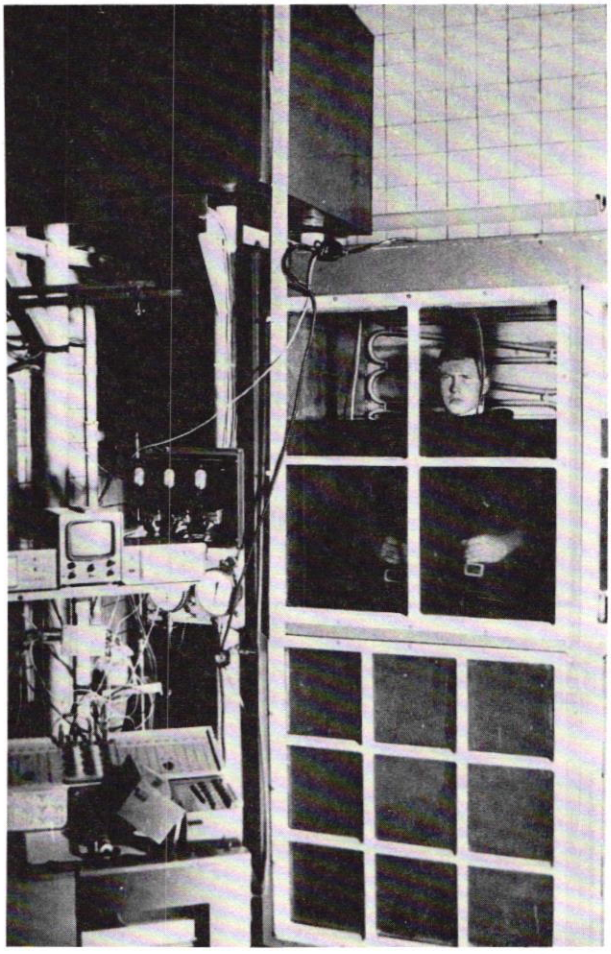


Figure 4. General view of the CWIM assembly. (The subject is in control immersion condition).

adaptation process, which manifested more distinctly in the CV system reactions. Values of stroke volume (SV), (Fig. 5) indicate, that exposures to 2 experimental conditions (control WI and LBPP) resulted in their elevation, and exposures to 2 other conditions (LBNP and vertical control) - resulted in their decrease. Comparison of the data obtained after 1.5 and 4.5 hours of exposures demonstrates, that adaptive reactions aimed at restoration of homeostasis develop more rapidly in response to a more marked initial changes (as it was seen with LBPP).

This relationship was correct for the subjective reactions. Data analysis indicate, that during LBPP subjective sensations of cranial blood pool were mostly noticeable during 1-2 hours of exposure, and by the end of 4.5 hour period they were less noticeable. During control WI sensations of cranial blood pool were of lesser magnitude, but longer in duration.

The dynamics of the described reactions resembles the behaviour of the automatically controlled systems, which tend to not only more rapidly react upon stronger impulses, but often to "over-control".

Therefore, the range of effects, simulated with CWIM, permits to simulate a wide range of reactions dependent of blood distribution. This is true for the reactions formed not only in the course of experiment, but after its termination. (Fig. 6) shows values of orthostatic tolerance recorded after 4.5 hour exposures to various modifications of the CWIM and vertical control data. In vertical control group postexperimental values of orthostatic tolerance practically do not differ from pre-experimental level, but exposures to WI resulted either in significant decrease of orthostatic tolerance (WI coupled with LBPP resulted in 2 orthostatic collapses out of 6 cases) or in a moderate manifestation of tolerance decrease (control WI), or in tolerance increase comparing to the pre-experimental values (case with LBNP).

Hence, CWIM permits for a short-time simulation of qualitatively different states of gravity tolerance. It extends the possibilities to study cause/effect relationship between controlled changes in a blood distribution pattern and resulting reactions, and also contributes to successful resolving both theoretical

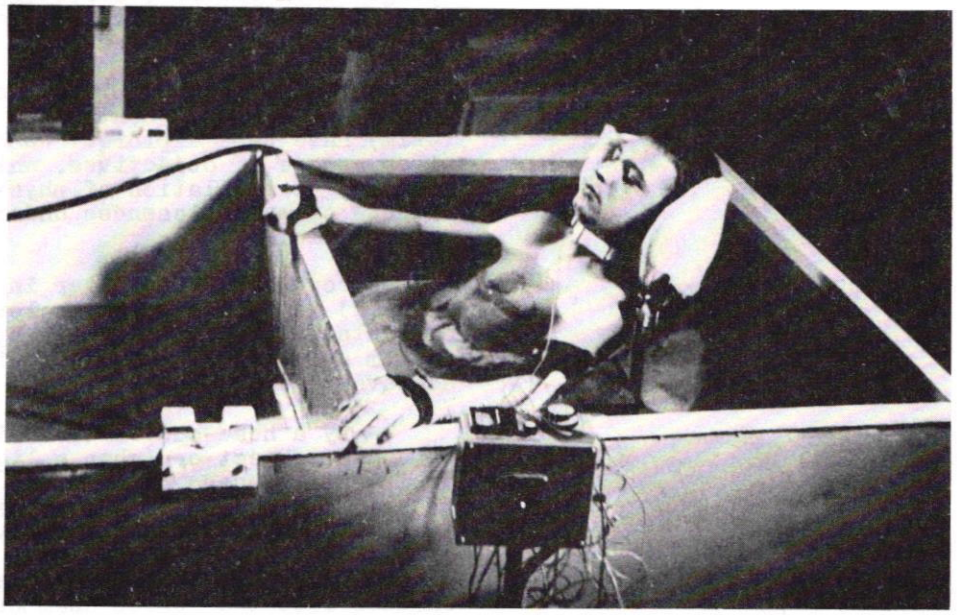


Figure 1. General view of the immersion bath with reducing of water pressure upon lover body.

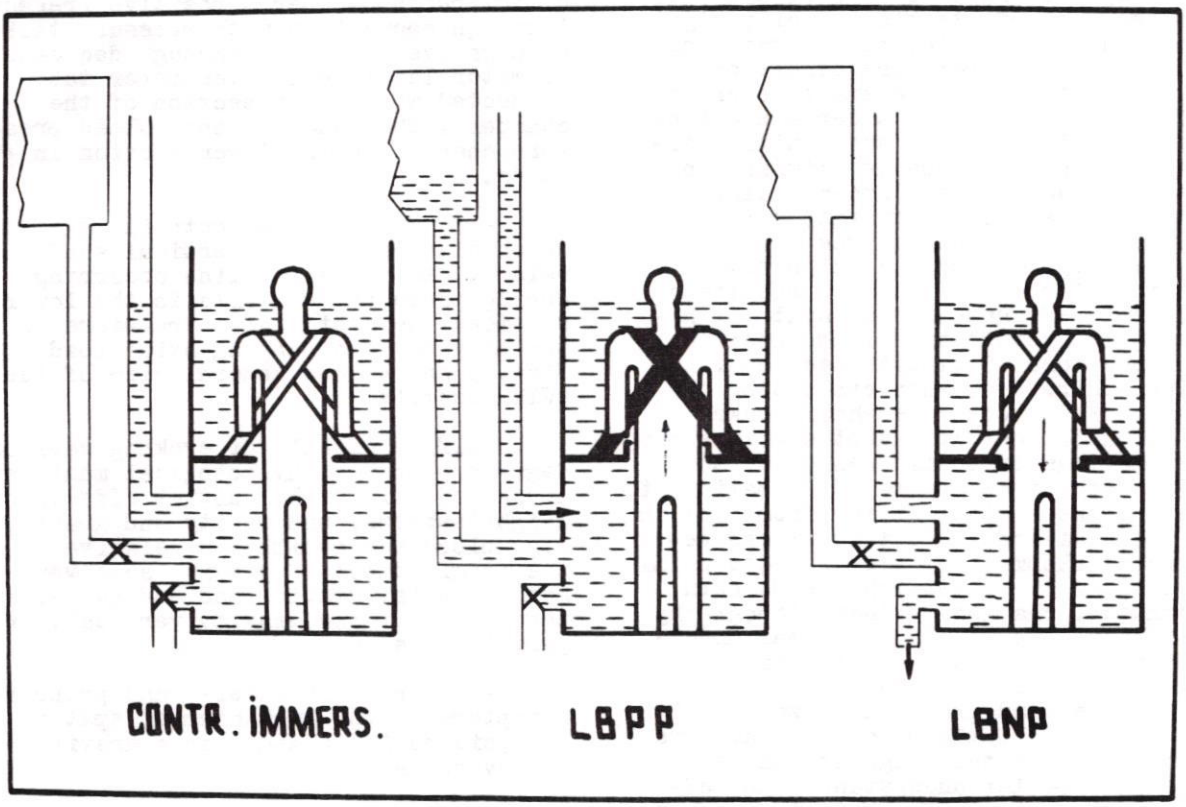


Figure 2. Controlled water immersion model of weightlessness. Variants of use.

wide range of dependent from blood distribution pattern physiologic reactions of water-electrolyte and cardiovascular (CV) systems. Total fluid losses during 4.5 hour WI coupled with - 30 mm Hg LBNP were low and quite comparable with vertical posture conditions (Fig. 5). LBPP (+30 mm Hg) and control immersion evoked increase in water loss by a factor of 2.5. Although, due to a technical reasons we could not assess the rate of water losses, indirect data indicate, that during 1 to 1.5 hour of LBPP this rate was highter than control WI and afterwards - lower. As a result, total values of water losses for 4.5 hours levelled. Such a dynamics might be connected to some of peculiarities of the

CONTROLLED WATER IMMERSION AS A MODEL OF WEIGHTLESSNESS

I.D. Pestov, A.V.Pokrovsky

Institute of Biomedical Problems, Moscow, USSR

Water immersion (WI) technique as a model of weightlessness was originally theoretically substantiated by K.E.Tsyolkovsky, and over a quarter of a century has been actively employed in space medicine to study sensory, motor and vegetative reactions typical for zero gravity. As any other model, WI technique is not a complete analog of a prototype, but simulates some of its biologically significant characteristics, thus permitting to obtain under laboratory conditions important information relevant to gravitational biology. WI to a certain extent can adequately simulate such initial effects of weightlessness as elimination of weight load upon skeleto-muscular apparatus and removal of gravity effect upon blood distribution. The technique can partially reproduce a subjective sensation of being weightless resulting from suspended, unsupported state of human subject, but nevertheless specific gravioreceptors of otolyth keep on functioning. Therefore, when evaluating the adequacy of WI model one should take into account, that it cannot simulate the whole spectrum of bodily responses to zero gravity, that a rate of formation of these responses might differ from that in a real spaceflight, and that it can result in development of side effects which are atypical to spaceflight, e.d. skin marceration, changes in thermotopography etc. (Pestov, Genin, 1983). Clear understanding of potentials and limitations of the model can widen the scopes of its substantiated and proved utilization. By modifying some of the model's parameters one can increase the range of simulated conditions, better understand cause/effect relationships and substantiate practical recommendations. Thus, modification of WI technique (Genin, Pestov, 1974) as a model of weightlessness by introducing means of arbitrarily reducing a compensatory counter-pressure of immersion medium upon lower body (Fig. 1), permitted to obtain both pronounced changes in water-electrolyte metabolism and complete absence of such changes. The same was observed for orthostatic tolerance in man. Hence, the dependence of these changes from factors, affecting transmural pressure and blood redistribution, was clearly demonstrated.

To further developing this idea the potentialities of a controlled WI model (CWIM) have been explored. We hoped to widen ascope of objectives, which might achieved by simulation of physiological effects of weightlessness under laboratory conditions.

A controlled parameter in this model (Fig. 2) is also a variable level of hydrostatic pressure exerted by immersion medium upon lower body. This effect is achieved:

- by a head-out vertical immersion of human subject or (when a light diving equipment is used) by complete immersion in a liquid medium (water or salt solution with density equal to body density);

- by separation of an immersion chamber into two sealed chambers: upper and lower - to house upper and lower parts of body. Sealing in this case is supplied at the level of illiac crest;

- by creating in the lower section of immersion chamber a positive pressure (through connectors with pressure tank) or negative pressure (through decrease of water level in a water-meter tube connected with lower section of the chamber). The range of controlled pressure changes in the lower section in $\pm$50 mm Hg;

- by utilizing a restraint system, which eliminates body vertical shifts relative to a sealing line occurring during pressure overfalls in the lower section; the system also transfers to the body an accompanying axial load. Figs. 3 and 4 show general view of the CWIM assembly.

CWIM is capable of evoking various degrees of psychophysiological manifestations resulting from initial effects of weightlessness, subgravity and gravity, e.g. blood redistribution relative to the longitudinal body axis, some variants of axial static load and subjective perception of the gravity vertical. CWIM permits to study:

- the role of inter- and proprioreceptors in the mechanism of spatial analysis during changes in a gravitational environment;

- interaction between rate of physiological reactions and quantitative characteristics of simulated effects;

- various variants of effects regulation observed during physiological reconstructions of a manifestation degree, determined by the conditions of simulation.

Experimental results demonstrate, that CWIM provides for a simulation of a

3. On the case of the second group,urinary excretion such hormones as 17-OHCS, adrenalin and noradrenalin attain adaptation at the control level, within 6 days' W. I.P. exposure. In the case of 17-OHCS and adrenalin, the extreme irregularity of circaidan rhythms was not observed at the approach point of diurnal-nocturnal level balance during the process to adaptation, and the stabilized new level was attained at the level of control. In the case of noradrenalin, some changes, which seem to correspond with the changes in quality of the sleep patterns, were observed during the adaptation process. and these changes were recoginized also by analysis of the circadian rhythms

Dr. Hildebrandt set synchronization as an important factor in the nonspecific trophotropic adaptive responses in his schematic representation of adaptive sequences. We may also emphasize the significance of diurnal rhythms in monitoring the development of adaptation for hypodynamics conditioning and in the study of the adaptation mechanisms.

4. On the case of the last group, as the case of K+, the attainment of adaptive steady state wa difficult during conditioning. Even on this case, some signs for stabilization were observed during the pre-stabilized phase on the feature of dirunal-nocturnal line and the circadian rhythmicity.

5. It seems that one of prospectable techniques for studying the machanism, of adaptation during prolonged hypogravics is to study the diurnal-nocturnal balance and circadian rhythm of some parameters during the pre-stabilized phase.

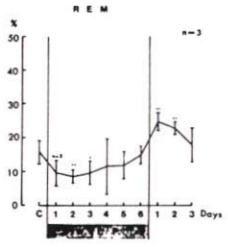


Fig.9. Fluctuation of the distribution of the REM-stages, pre, during and post water immersion exposure.

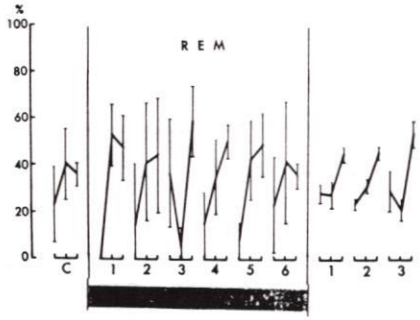


Fig.10. Distribution of the REM-stages for early, middle and late parts of night sleep.

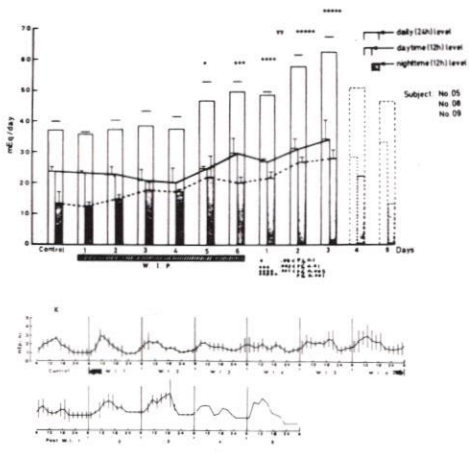


Fig.11. Daily urinaly excretion of potassium.

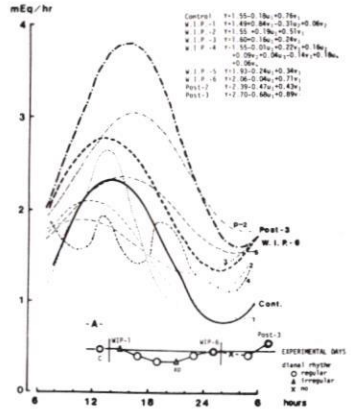


Fig.12. Circadian rhythms of daily urinary excretion of potassium, pre, during and post water immersion exposure.

REFERENCES

1) Rechtschaffen, A. and A. Kales (Eds), R. J. Berger, W. C. Dement, A. Jacobson, L.C. Johnson, M. Jouvet, L. T. Monroe, I. Oswald, H. P. Roffwarg, B. Roth and R. D. Walter, 1968. A mannal of Standardized terminology, techniques and scoring system for sleep stages human subjects. Public Health Service, U.S. Government Printing Office, Washington, D.C.

2) Doe, R. P., J. A. Vennes and E. Flink. 1960, Diurnal variation of 17-hydroxy-conrticosteroids, sodium, potassium, magnesium in case of treated adrenal insufficiency and Cushing's syndrome. J. Cl. Endocri. 20:253-265

3) Bliss, C.I., 1970. Statistics in Biology, 2*219-287, McGraw-Hill Book Company, new York.

4) Jouvet, M., 1969. Biogenic amines and the states of sleep. Science 163:32-41.

5) Pujol, J.P., J. Mouret, M. Jouvet and J. Glowinbski. 1968. Increased turnover of cerebral norepinephrine during rebound of paradoxical sleep in the rat. Science 159:122-114

6) Saiki, H., M. Nakaya, Y. Sugita and M. Kamachi. 1976 Metabolic and hormonal mechanisims of mineral metabolic adaptation to induced hypokinetics in rats. Aviat. Space Environ. Med., 47(8):846-852.

7) Hildebrandt, G., 1966. The time factors in adaptation. In. Biometeorology Vol.2, part 1, Eds. by S. W. Tromp and W. H. Weihe, Pergamon Press, Oxford:258-275.

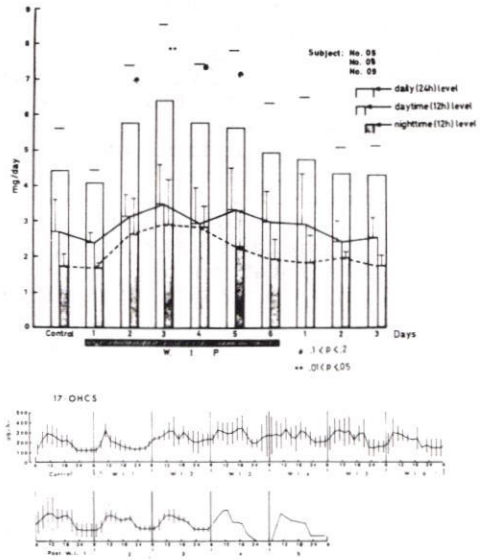


Fig.3. Daily urinary excretion of 17-OHCS.

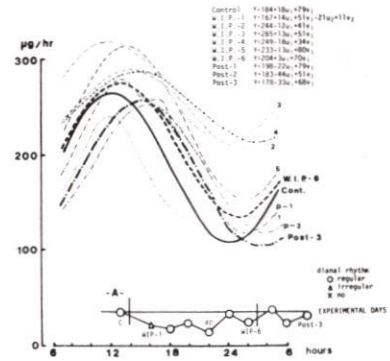


Fig.4. Circadian rhythms of daily urinary excretion of 17-OHCS, pre, during and post water immersion exposure.

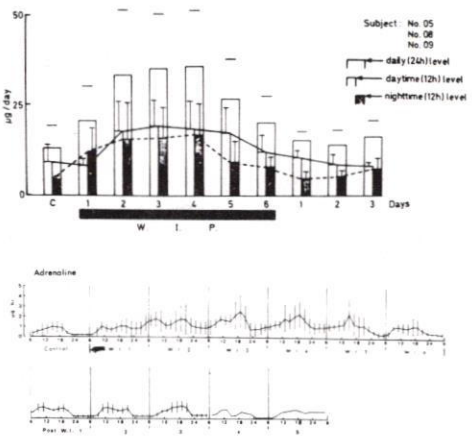


Fig.5. Daily urinary excretion of adrenalin.

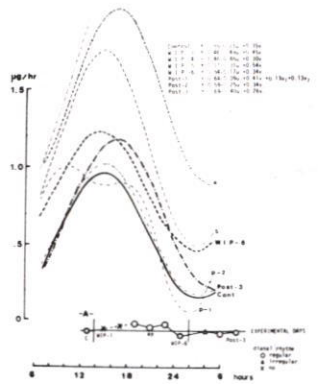


Fig.6. Circadian rhythms of dail urinary excretion of adrenalin, pre, during and post water immersion exposure.

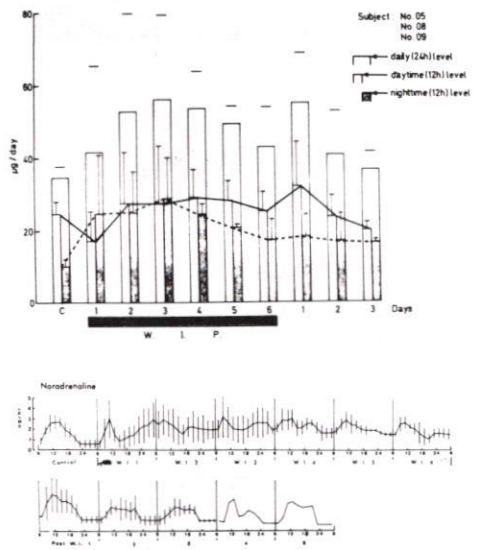


Fig.7. Daily urinary excretion of noradrenalin.

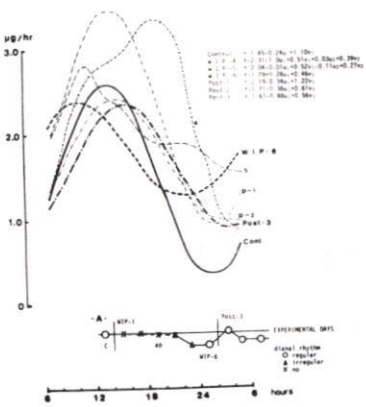


Fig.8. Circadian rhythms of daily urinary excretion of noradrenalin, pre, during and post water immersion period.

PHYSIOLOGICAL ROLES OF CALCIUM IN LIGHT-INDUCED GRAVITROPISM IN ZEA PRIMARY ROOTS

Atsushi Miyazaki
Tadashi Fujii

Institute of Biological Sciences
University of Tsukuba
Sakura-mura, Ibaraki 305
Japan

No asymmetric redistribution of plant hormones, indoleacetic acid (IAA) and abscisic acid (ABA), which have been thought to be prime candidates for inducing gravicurvature in roots, was observed between upper and lower halves of elongation zones during the latent period (0-60 min after stimulation) of the gravitropic reponse in Zea primary roots. The content of calcium (Ca) increased in the lower half of horizontally oriented roots which had been briefly exposed to light, while there was no marked difference in distribution between upper and lower halves of non-irradiated roots. The Ca increase in lower half was observed 15-30 min after irradiation in root caps and 30-60 min after irradiation in elongation zones. We concluded that the Ca accumulation in the lower half of elongation zones in gravi- and light-stimulated roots induced a apart (50%) of the downward curvature in the presence of ABA.

Since gravitropic curvature is thought to result from the asymmetric elongation between upper and lower sides of elongation zones, the information involving in the curvature must be transmitted during the latent period after gravistimulation from graviperception site to gravireaction site. Asymmetric redistribution of a growth inhibitor, either IAA or ABA has been believed to cause the gravicurvature in roots. However, it was reported that no asymmetry of IAA and ABA content in root tips containing elongation zones was observed in gravireacting Zea and Vicia roots. These results indicate that the roles of IAA and ABA in the gravicurvature of roots are ambiguous. Recently, Ca gradients has been suggested to play a key role in linking graviperception and gravicurvature in plant roots, although none provide evidence that the Ca gradients occur naturally in gravistimulated roots.

It can be, therefore, thought that the determination of information involving in the gravicurvature is the most important problem to dissolve the complicated and ambiguous processes of gravitropic response.

Plant material

Caryopses of Zea mays L. cv. Golden Cross Bantam 70 were soaked in running tap water for 24 h in the dark. The grains were grown vertically in a moist chamber in the dark at 26 ± 1°C. Primary roots, 2.0-2.5 cm in length, were used for the experiments. All manipulations were carried out under a dim green safe light.

Development of gravitropic curvature

Kinetics of gravitropic curvature was measured after light- and/or gravi-stimulation (Fig. 1). When the roots were exposed to white light for 30 s, curvature started about 1 h after the light irradiation, continued for the following 1.5 h, and then ceased. In this condition, maximum curvature reached at about 30 degrees. When no exposure was given to the roots, the curvature was not obseved. This result indicates that the information involving in gravitropic curvature must be transmitted within 1 h after light irradiation from the perception site of gravity to the elongation zones of the roots. In the following expepriments, therefore, the changes within 1 h after light- and/or gravi-stimulation was given attention.

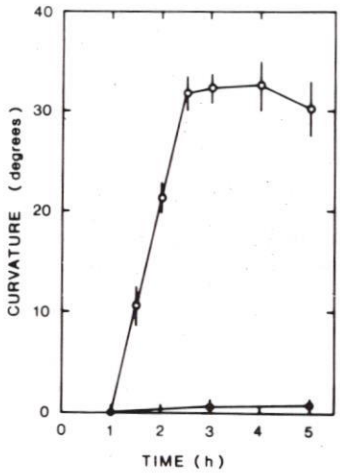


Fig.1. Gravitropic response of Zea primary roots under gravistimulation with (○) and without (●) a light exposure. (From Miyazaki et al. Plant Cell Physiol. 27: 693-700, 1986)

Distribution of IAA and ABA under gravistimulation

IAA and ABA contents in upper and lower halves in elongation zones were measured 60 min after gravistimulation in roots which had been exposed to white light (30 s) or kept in darkness. No asymmetric redistribution of both IAA and ABA was observed between upper and lower halves in elongation zones during the latent period (0-60 min after the stimulation) of gravitropic reponse. Light irradiation increased by approx. 20% the content of ABA in both upper and lower halves of elongation zones, but did not increase that of IAA. Calculated concentrations of IAA in the tissues were approx. 0.3 μM, and those of ABA approx. 0.05 μM in roots kept in darkness and approx. 0.06 μM in light-irradiated roots.

These results indicate that neither IAA

nor ABA can be the informations related to root gravitropism in general.

Redistribution of Ca under gravistimulation

When vertically-grown roots were horizontally oriented and kept either in continuous darkness or treated with a brief (30 s) exposure to white light, the content of Ca, which was quantified using particle-induced X-ray emission, in the lower halves of roots which had been exposed to light became higher than in the upper ones, while no such difference was found in horizontally oriented roots kept in darkness. The increase of Ca in the lower halves was observed 15-30 min after irradiation in cap zones, and 30-60 min after irradiation in elongation zones. When the roots were kept in the horizontal position, gravitropic curvature started about 1 h after the light exposure (see Fig. 1). These results indicate that the redistribution of Ca occurs before the gravitropic curvature.

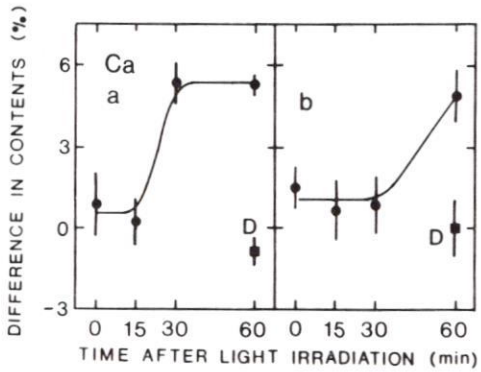


Fig.2. Redistribution of Ca in cap (a) and elongation (b) zones in upper and lower halves of gravistimulated primary roots with (●) and without (■) a light exposure. (From Miyazaki et al. Plant Cell Physiol. 27: 693-700, 1986)

Effects of $CaCl_2$ on IAA and ABA action related to root elongation

The root sections containing elongation zones continued to elongate at a constant rate for at least 4 h in 5 mM 2-(N-morpholino)ethanesulfonic acid buffer (pH 6.0).

Single application of $CaCl_2$ had no effect on the elongation of root sections at concentrations lower than 0.3 mM. Though the inhibition of root elongation increased with increasing IAA concentration higher than 0.01 μM, the extent of inhibition at each IAA concentration was not affected by the addition of $CaCl_2$ below 0.3 mM.

ABA promoted the elongation of root sections when no calcium was added to the incubation medium. However, ABA exerted its inhibitory effect on the elongation in the presence of $CaCl_2$. The extent of inhibition by addition of ABA at a concentration comparable to endogenous level was approx. 20% in the presence of 0.1 mM $CaCl_2$ at a concentration equivalent to the difference between upper and lower halves of elongation zones of gravitropically stimulated roots (Table 1).

Table 1. Effects of $CaCl_2$ on the elongation of root sections in the presence of ABA

ABA conc. (μM)	0.1 mM $CaCl_2$		Inhibition (%)
	-	+	
0.01	0.72[a]	0.56	22
0.1	0.71	0.57	20

[a]Elongation ; mm/4 h.

Kinetics of elongation in upper and lower sides of gravireacting roots

The elongation in upper and lower sides of gravireacting roots was continuously recorded with a time-lapse video recorder. The elongation in upper side linearly continued for at least 3 h after the gravitropic curvature had already ceased (see Fig.1). On the other hand, the elongation rate in lower side started to diminish 1 h after gravistimulation and lasted for 1.5 h during which the curvature took place, and then regained the initial growth rate. The calculated inhibition rate of elongation in the lower side was 45% of that in the upper side of gravistimulated roots.

These results strongly suggested that, even if no asymmetric redistribution of IAA and ABA occurs in elongation zones during the latent period of gravicurvature, the Ca accumulation (approx. 0.1 mM) in the lower half of elongation zones of gravistimulated roots can inhibit by approx. 20% the elongation in the lower side of roots by altering the sensitivity of root tissues to ABA. As the elongation rate in the lower side was reduced by 45% of that in the upper side of gravi- and light-stimulated roots, the gravicurvature (approx. 50%) may result from the inhibition of the elongation in the lower side through ABA-Ca interactions.

CARDIOVASCULAR RESPONSES TO CENTRAL HYPOVOLAEMIA IN MAN: PHYSIOLOGY AND PATHOPHYSIOLOGY.

T. Bennett

Department of Physiology and Pharmacology
Medical School Queen's Medical Centre
Nottingham NG7 2UH

The reflex responses to changes in posture or to haemorrhage have been the topic of many studies since the earliest investigations of cardiovascular physiology in man. However, it was not until Greenfield and his colleagues (3,13,23) devised the technique of applying subatmospheric pressure to distal parts of the body (LBNP) of a supine subject (to simulate the shift of blood that occurs on standing) that the way was clear for detailed analyses of the cardiovascular responses to central hypovolaemia in man. The technique of LBNP, together with that of manipulating carotid sinus transmural pressure using a similar principle, i.e. neck suction (17) or neck pressure (28) have been the basis of many of the studies that currently influence our concepts about normal "orthostatic" reflexes. In summary, cardiopulmonary receptors appear to have important influences on efferent vasomotor outflow to skeletal muscle (25,30,41), with relatively little effect on the splanchnic vascular bed and no influence on the sinoatrial node (25,30,41). The latter two effectors are influenced, mainly, by changes in activity of the carotid sinus baroreceptor afferents (1,25,28,41), but it should always be remembered there is no technique available for selective manipulation of aortic arch baroreceptors in man, and the latter may influence responses elicited from the carotid sinus (28). Furthermore, it should not be forgotten that there are many other types of receptor (e.g. ventricular receptors (18), visceral receptors and skeletal muscle receptors) that may be involved in the cardiovascular responses to standing, tilting or LBNP. It is very likely that different patterns of afferent involvement occur with exposure to these manoeuvres, and it may be that such differences account for the dissimilar patterns of hormonal change as well as the variations in cardiovascular responses to orthostatic manoeuvres and central hypovolaemia (e.g. 11-13,16,20-22,24,27,31-33). However, comparison of the studies published highlights marked variations in the responses to what appears to be the same manoeuvre. There is obviously a need here for a systematic comparison of the hormonal and cardiovascular responses to standing, tilting and LBNP in the same subjects.

Notwithstanding these various qualifications, evidence supporting current beliefs about afferent/efferent relations in human cardiovascular reflex responses to central hypovolaemia comes from the following findings:-

1) Exposure to low levels of LBNP that cause reductions in central venous pressure, but no changes in systemic arterial systolic, diastolic or mean blood pressure, or systemic arterial dP/dt, causes significant forearm vasoconstriction with little increase in splanchnic vascular resistance and no tachycardia (25, 41).

2) Exposure to high levels of LBNP, sufficient to reduce central venous and systemic arterial blood pressures, causes forearm and splanchnic vasoconstriction and tachycardia (17, 28).

3) Neck suction causes no change in central venous pressure (and hence, presumably, no change in venous return from the head) no change in forearm vascular resistance, but a significant systemic arterial hypotension and bradycardia (1,28). (A puzzling feature of this experiment is that there was no significant change in splanchnic vascular resistance with neck suction (1), although this finding is consistent with the results of a previous study (10) in which carotid sinus suction caused hypotension due to a fall in cardiac output with no change in total peripheral resistance. The anomalies in this area have been referred to elsewhere (28)).

4) Exposure to neck suction (40 mmHg) and LBNP (40 mmHg) concurrently (1) had no significant effect on the forearm vasoconstriction seen with LBNP alone, but prevented the tachycardia and most of the splanchnic vasoconstriction. (There are two aspects of these results that require further explanation. One is how it came about that the effects of the two manoeuvres on carotid sinus transmural pressure were exactly matched (i.e. to cancel effects on heart rate), and the other is that the hypotensive effect of LBNP plus neck suction was no greater than that of neck suction alone (1), in spite of the evidence that splanchnic vaso-constriction constitutes a major defence against "postural" hypotension (34)).

Contrary to some of the findings above there is evidence that the forearm vascular bed may be influenced by changes in signalling of carotid sinus afferent fibres (28). Most recently, Victor and Mark (40) found a significant forearm vasoconstriction in response to neck pressure, but in that same study various arguments were put forward in support of the proposition that "nonhypotensive LBNP per se does not produce a major perturbation in the carotid baroreflex." Thus, although some contentious points remain to be resolved, all investigators in the field seem to be agreed that the forearm vasoconstriction seen during exposure to low levels of LBNP is due, solely, to unloading of cardiopulmonary baroreceptors. However, for this to be a tenable hypothesis something unexplained must be happening since:-

1) if exposure to low levels of LBNP does not decrease cardiac output, then systemic arterial pressure should go up, due to the vasoconstriction in skeletal muscle. The absence of a pressor response to low levels of LBNP could be due to concurrent vasodilatation in another vascular bed (besides the splanchnic - see above), but this effect would have to be precisely matched to cancel the vasoconstriction in skeletal muscle, and it is not at all clear how it could be brought about without invoking the mediation of systemic arterial baroreceptors (see below).

2) if exposure to low levels of LBNP does reduce stroke volume, then this change must be offset exactly by the increase in skeletal muscle

vascular resistance in order to prevent the occurrence of any change in those features of systemic arterial pressure to which carotid sinus baroreceptors are sensitive. This seems most unlikely since the afferent system considered to be responsible for the reflex adjustment of forearm vascular resistance is not exposed to what appears to be the controlled variable (i.e. some feature (s) of carotid sinus transmural pressure). On balance, it seems more likely that the cardiovascular reflex responses to low levels of LBNP may be due to subtle, interactive effects between cardiopulmonary, aortic arch and carotid baroreflexes. The anomalies mentioned above may be due to our inability to monitor the relevant variable (specifically, carotid sinus and/or aortic arch afferent discharge rate). The fact that simultaneous exposure to neck pressure and LBNP augments forearm vasoconstrictor responses but not tachycardic responses (40) does not argue against this proposition, particularly since exposure to low levels of LBNP not infrequently causes a transient bradycardia (unpublished observations). The latter finding is consistent with studies in animals, but has not been reported routinely in man (30).

In spite of our ignorance of normal mechanisms, many (e.g. 4,7,8) have applied the technique of LBNP to the assessment of cardiovascular regulation in various patho-physiological conditions. In retrospect, some useful information came out of those studies, but various findings require further investigation. For example, exposure of patients with orthostatic hypotension to low levels of LBNP may cause a normal pattern of forearm vasoconstriction (7,8). However, these same patients when exposed to higher levels of LBNP may show forearm vasodilatation (8). While this could be due to relative preservation of neural vasodilator pathways (2,4,6), it is not known to what extent B_2-adrenoceptor-mediated vasodilator effects of adrenal medullary adrenaline (22) or the vasodilator effects of circulating dopamine (26) might be involved.

One approach in future studies would be to make simultaneous measurements in several regional vascular beds during exposure of patients to different levels of LBNP, since the forearm may not be representative of regional perfusion elsewhere. This proposition is supported by the recent finding that simultaneous monitoring of foot, calf, hand and forearm blood flows during a thermoregulatory challenge in patients with diabetic autonomic neuropathy detects subtle abnormalities in the control of foot and calf perfusion in the absence of dysfunction in the forearm (35).

Another problem in the investigation of cardiovascular responses to central hypovolaemia in patients with orthostatic hypotension is that they frequently have systolic arterial hypertension when supine, and the latter factor could influence cardiovascular reflexes (8). However, it has been observed that patients with primary hypertension may show augmented forearm vasoconstrictor responses to low levels of LBNP (9,29), whereas this phenomenon is not found in patients with orthostatic hypotension (7,8).

Perhaps an even more important consideration in the assessment of abnormal responses to LBNP is the "physiological" state of the subject. This may be particularly significant in regard to patients with diabetes mellitus, since changes in plasma glucose and insulin could impinge on cardiovascular regulation (14,15), although it is not clear to what extent changes in circulating, endogenous insulin levels influence cardiovascular variables in normal subjects (5). Complications such as these can be avoided, or studied, by deliberate manipulation of plasma variables during exposure to central hypovolaemia. For example, during a hyperinsulinaemic, euglycaemic clamp it is possible to detect impaired vasoconstrictor responses to LBNP in normal subjects in the absence of systemic arterial hypotension (36). However, a similar experiment in patients with diabetic autonomic neuropathy causes marked augmentation of the hypotension seen during LBNP, but without a consistent effect on forearm vascular resistance (37).

Finally, recent observations indicate that modest levels of exercise can cause resetting and increased sensitivity of the baroreflex responses to LBNP (9), or to pharmacologically-induced increases in systemic arterial pressure (26), thus providing objective evidence for the intuitive feeling that subjects should be "rested" before being investigated. It is of particular interest that exercise-induced changes in cardiovascular control mechanisms may be due to a centrally-mediated, opioidergic suppression of sympathetic efferent outflow, consequent upon activation of skeletal muscle afferent fibres (19,39).

In summary, it is likely that our understanding of the subtleties of the cardiovascular responses to central hypovolaemia in normal man is incomplete. However, it is quite possible that we will gain useful information about the normal condition by studying the disordered processes in various pathophysiological states.

REFERENCES

1. ABBOUD, F.M., D.L. ECKBERG, V.J. JOHANNSEN, AND A.L. MARK. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. J.Physiol.Lond. 286: 173-184, 1979.

2. ABBOUD, F.M., AND J.W. ECKSTEIN. Active reflex vaso-dilatation in man. Fedn.Proc. 25: 1611-1617.

3. ARDILL, B.L., R.G. BANNISTER, P.H. FENTEM, AND A.D.M. GREENFIELD. Circulatory responses of supine subjects to exposure of parts of the body below the xiphisternum to subatmospheric pressure. J.Physiol.Lond. 193: 57-72, 1967.

4. BANNISTER, R., L. ARDILL, AND P.H. FENTEM. Defective autonomic control of blood vessels in idiopathic orthostatic hypotension. Brain 90: 725-746, 1967.

5. BENNETT, T., I.W. FELLOWS, AND I.A. MACDONALD. Lack of effect of intravenously infused glucose on cardiovascular variables or plasma catecholamines in man. J.Physiol.Lond. 364: 72P, 1985.

6. BENNETT, T., D.J. HOSKING, AND J.R. HAMPTON. Cardiovascular reflex responses to apnoeic face immersion and mental stress in diabetic subjects. Cardiovasc.Res. 10: 192-199, 1976.

7. BENNETT, T., D.J. HOSKING, AND J.R. HAMPTON. Cardiovascular responses to lower body negative pressure in normal subjects and in patients with diabetes mellitus. Cardiovasc.Res. 13: 31-38.

8. BENNETT, T., D.J. HOSKING, AND J.R. HAMPTON. Cardiovascular responses to graded reductions of central blood volume in normal subjects and in patients with diabetes mellitus. Clin.Sci.Lond. 58: 193-200, 1980.
9. BENNETT, T., R.G. WILCOX, AND I.A. MACDONALD. Post-exercise reduction of blood pressure in hypertensive men is not due to acute impairment of baroreflex function. Clin.Sci.Lond. 67: 97-103, 1984.
10. BEVEGARD, B.S., AND J.T. SHEPHERD. Circulatory effects of stimulating the carotid arterial stretch receptors in man at rest and during exercise. J.Clin.Invest. 45: 132-142, 1966.
11. BORST, C., J.F.M. VAN BREDERODE, W. WIELING, G.A. VAN MONTFRANS, AND A.J. DUNNING. Mechanisms of initial blood pressure response to postural change. Clin.Sci.Lond. 67: 321-327, 1984.
12. BORST, C., W. WIELING, J.F.M. VAN BREDERODE, A. HOND, L.G. DE RIJK, AND A.J. DUNNING. Mechanisms of initial heart rate response to postural change. Am.J.Physiol. 243 (Heart Circ. Physiol.12): H676-H681, 1982.
13. BROWN, E., J.S. GOEI, A.D.M. GREENFIELD, AND G.C. PLASSARAS. Circulatory responses to simulated gravitational shifts of blood in man induced by exposure of the body below the iliac crests to sub-atmospheric pressure. J.Physiol.Lond. 183: 607-627, 1966.
14. CHRISTENSEN, N.J.. Acute effects of insulin on cardiovascular function and noradrenaline uptake and release. Diabetologia 25: 377-381, 1983.
15. DA COSTA, D.F., C. McINTOSH, R. BANNISTER, N.J. CHRISTENSEN, AND C.J. MATHIAS. Unmasking of the cardiovascular effects of carbohydrate in subjects with sympathetic denervation. J.Hypertension 3 (suppl.3): S447-S448, 1985.
16. DAVIES, R., M.L. FORSLING, AND J.D.H. SLATER. The interrelationship between the release of renin and vasopressin as defined by orthostasis and propranolol. J.Clin.Invest. 60: 1438-1441, 1977.
17. ERNSTING, J., AND D.J. PARRY. Some observations on the effects of stimulating the stretch receptors in the carotid artery in man (Abstract). J.Physiol.Lond. 137: 45P-46P, 1957.
18. FERGUSON, D.W., M.D. THAMES, AND A.L. MARK. Effects of propranolol on reflex vascular responses to orthostatic stress in humans. Circulation 67: 802-807.
19. FLORAS, J.S., P.E. AYLWARD, C. SINKEY, AND A.L. MARK. Post-exercise decreases in blood pressure are accompanied by decreases in muscle sympathetic nerve activity. Clin.Res. (Abstract) 34: 708A, 1986.
20. GOLDSMITH, S.R., A.W. COWLEY, G.S. FRANCIS, AND J.N. COHN. Effect of increased intracardiac and arterial pressure on plasma vasopressin in humans. Am.J.Physiol. 246 (Heart Circ. Physiol.15): H647-H651, 1984.
21. GOLDSMITH, S.R., A.W. COWLEY, G.S. FRANCIS, AND J.N. COHN. Reflex control of osmotically stimulated vasopressin in normal humans. Am.J.Physiol. 248 (Regulatory Integrative Comp. Physiol. 17): R660-R663, 1985.
22. GRASSI, G., C. GAVAZZI, A.M. CESURA, G.B. PICOTTI, AND G. MANCIA. Changes in plasma catecholamines in response to reflex modulation of sympathetic tone by cardiopulmonary receptors. Clin.Sci.Lond. 68: 503-510, 1985.
23. GREENFIELD, A.D.M., E. BROWN, J.S. GOEI, AND G.C. PLASSARAS. Circulatory responses to abrupt release of blood accumulated in the legs (Abstract). Physiologist 6: 191, 1963.
24. HARRISON, M.H., G. GEELEN, L.C. KEIL, C.A. WADE, L.C. HILL, S.E. KRAVIK, AND J.E. GREENLEAF. Effect of hydration on plasma vasopressin, renin, and aldosterone responses to head-up tilt. Aviat. Space Env. Med. 57: 420-425, 1986.
25. JOHNSON, J.M., L.B. ROWELL, M. NIEDERBERGER, AND M.M. EISMAN. Human splanchnic and forearm vasoconstrictor responses to reductions in right atrial and aortic pressures. Circ.Res. 34: 515-524, 1974.
26. KUCHEL, O., N.T. BUU, P. HAMET, P. LAROSCHELLE, J. GUTKOWSKA, E.L. SCHIFFRIN, M. BOURQUE, AND J. GENEST. Orthostatic hypotension. Am.J.Med.Sci. 289: 3-10, 1985.
27. LEIMBACH, W.N., P.G. SCHMID, AND A.L. MARK. Baroreflex control of plasma arginine vasopressin in humans. Am.J.Physiol. 247 (Heart Circ. Physiol. 16): H638-H644, 1984.
28. MANCIA, G., AND A.L. MARK. Arterial baroreflexes in humans. In: Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow, edited by J.T. Shepherd and F.M. Abboud. Bethesda, MD: Am.Physiol.Soc., 1983, sect.2, vol.III, pt.2, chapt.20, p.755-793.
29. MARK, A.L., AND R.E. KERBER. Augmentation of baroreflex control of forearm vascular resistance in borderline hypertension. Hypertension 4: 39-46, 1982.
30. MARK, A.L. AND G. MANCIA. Cardiopulmonary baroreflexes in humans. In: Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow, edited by J.T. Shepherd and F.M. Abboud. Bethesda, MD: Am.Physiol.Soc., 1983, sect.2, vol.III, pt.2, chapt.21, p 795-813.
31. MOHANTY, P.K., J.R. SOWERS, F.W.J. BECK, M.F. GODSCHALK, J. SCHMITT, M. NEWTON, C. MCNAMARA, J.G. VERBALIS, AND M. MCCLANAHAN. Catecholamine, renin, aldosterone and arginine vasopressin responses to lower body negative pressure and tilt in normal humans: effects of bromocriptine. J.Cardiovasc.Pharmacol. 7: 1040-1047, 1985.
32. RASMUSSEN, S., B. HESSE, F. BONDE-PETERSEN, M.D. NIELSEN, N.J. CHRISTENSEN, J. GIESE, AND J. WARBERG. Haemodynamic and humoral effects of lower body negative pressure in normal, sodium-replete man during angiotensin-converting enzyme inhibition with captopril. Scand.J.Lab.Clin. Invest. 46: 81-88, 1986.
33. ROBERTSON, D., G.A. JOHNSON, R.M. ROBERTSON, A.S. NIES, D.G. SHAND, AND J.A. OATES. Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. Circulation 59: 637-643.
34. ROWELL, L.B., J.-M.R. DETRY, J.R. BLACKMON, AND C. LYSS. Importance of the splanchnic vascular bed in human blood pressure regulation. J.Appl.Physiol. 32: 213-220, 1972.
35. SCOTT, A.R., T. BENNETT, AND I.A. MACDONALD. Diabetes mellitus and thermoregulation. Can.J.Physiol.Pharmacol. (in press).
36. SCOTT, A.R., T. BENNETT, AND I.A. MACDONALD. Insulin-induced impairment of vasoconstriction in normal subjects during a hyperinsulinaemic euglycaemic clamp. J.Auton.Nerv.Syst. (Abstract) (in press).
37. SCOTT, A.R., I.A. MACDONALD, AND T. BENNETT. Insulin and hypotension in diabetics with autonomic neuropathy. J.Auton.Nerv.Syst. (Abstract) (in press).
38. SOMERS, V.K., J. CONWAY, M. LEWINTER, AND P. SLEIGHT. The role of baroreflex sensitivity in post-exercise hypotension. J.Hypertension 3, suppl.3: S129-S130, 1985.

39. SHYU, B.C. Endorphin mechanisms and physical exercise. M.D. Thesis, University of Goteborg, 1986.
40. VICTOR, R.G., AND A.L. MARK. Interaction of cardiopulmonary and carotid baroreflex control of vascular resistance in humans. J.Clin.Invest. 76: 1592-1598, 1985.
41. ZOLLER, R.P., A.L. MARK, F.M. ABBOUD, P.G. SCHMID, AND D.D. HEISTAD. The role of low pressure baroreceptors in reflex vasoconstrictor responses in man. J.Clin.Invest. 51: 2967-2972, 1972.

THE EFFECTS OF EXERCISE TRAINING ON FACTORS AFFECTING ORTHOSTATIC TOLERANCE

Peter B. Raven, Michael L. Smith
Donna L. Hudson, and Howard M. Graitzer

Department of Physiology
Texas College of Osteopathic Medicine
Fort Worth, Texas 76107

Earlier investigations have suggested that the well-trained aerobically fit individual is more susceptible to gravitational stress than his sedentary counterpart. The primary reason presented to explain the loss of blood pressure control in the dynamically exercise trained population during an orthostatic challenge was based on the finding of a strong positive correlation between maximal aerobic capacity ($\dot{V}O_{2max}$) and lower limb compliance. However, our earlier work failed to identify a fitness related difference in lower limb compliance. Subsequently, we demonstrated that tolerance to LBNP was significantly altered if the somato-pressor reflex was activated. In all our previous work comparing high fit ($\bar{x}$ $\dot{V}O_{2max}$ > 63 ml O_2/Kg/min) and low fit ($\bar{x}$ $\dot{V}O_{2max}$ < 42 ml O_2/Kg/min) we consistently observed an attenuated baroreflex response to both hypotensive and hypertensive challenges. Comparison of low fit (LF) and (HF) subjects at rest consistently identified marked plasma volume expansion and significantly lower resting heart rates of the HF subjects compared to the LF subjects. In addition, it has been well recognized that weight trained (WT) subjects are more tolerant to centrifugation than either HF or LF subjects. Subsequently, we hypothesized that these fitness related differences in blood pressure control were a manifestation of an exercise training induced alteration in the autonomic nervous systems control of blood pressure. In order to examine this hypothesis, we evaluated the physiological responses during lower body negative pressure to -40 torr on three distinct groups of subjects with full cardiac efferent autonomic blockade using metoprolol tartrate and atropine sulphate. The three groups of subjects were designated as untrained (UT), dynamically exercise trained (ET), and weight trained (WT). Changes from 0 -40 torr in heart rate (HR), systolic blood pressure (SBP) and forearm vascular resistance (R) were compared across groups during the control (CON) and blocked (DBL) conditions. In addition, a calculated index of baroreflex responsiveness (HR/SBP) was obtained from 0 to -40 torr of means of five subjects in each group are summarized below:

		UT	WT	ET
	HR/ SBP	2.5+0.6	1.5+0.3	0.64+0.2
Con R	(units)	+ 7.4+1.1	8.1+1.5	3.6 +1.2*
SBP	(mmHg)	- 21.0+3	-20.0+4	-27.0+2*
DBL R	(units	+12.1+1.4	+14.0+1.1	+9.6+2.0**

*Both UT and WT > ET, P<0.05; **WT > ET P<0.05

It was concluded from these data that endurance trained significantly attenuated baroreflex responsiveness to a hypotensive challenge however, heavy resistance weight training has little effect on the baroreflex. (Supported in part by U.S. Air Force Contract #F33615-85-C14511)

INTRODUCTION

For more than a decade the affect of endurance exercise training in producing an altered blood pressure control system has been investigated (1-5). In all our previous work (5,6) in which we evaluated differences between high fit (maximal aerobic capacity = $\dot{V}O_{2max}$ > 60 ml O_2/kg/min) and low fit ($\dot{V}O_{2max}$ < 45 ml O_2/kg/min) individuals, we consistently observed an attenuation of the integrated baroreflex responsiveness of HF subjects. Despite the recent findings of longitudinal studies refuting the link between endurance exercise training and orthostatic tolerance (7,8), the question as to whether this attenuated responsiveness is a component of the endurance trained subjects reported orthostatic intolerance remains unanswered. Differences between highly endurance trained (ET) and untrained (UT) subjects at rest indicate that the HT will have greater resting blood volumes (9), and lower resting heart rates (10) consistent with a more dominant parasympathetic nervous system. Furthermore comparisons of weight trained (WT) subjects with HT and UT subjects during centrifugation indicated that the WT subjects were more tolerant to centrifugation (8,11). This increase in tolerance of the WT may be related to their training mode and a resultant alteration in the autonomic nervous system's control of blood pressure (12). Subsequently, we hypothesized that "these fitness related differences in blood pressure control were a manifestation of an exercise training induced alteration in the autonomic nervous system's control of blood pressure during orthostasis." This hypothesis forms the basis of a series of investigations presented here.

MATERIALS AND METHODS

Before embarking on the major questions we had one major technical concern related to the cardiovascular response to LBNP. This concern was related to the presence or absence of a significant somato-pressor effect (13) which may or may not confound the cardiovascular response to lower body negative pressure. In this preliminary investigation we evaluated eight male subjects (see Table 1 for subject description) with progressive lower body negative pressure (LBNP) to -50 torr during three levels of EMG activity of the lower limbs, these being relaxed (<10 μV); 5% MVC (80 μV) and 10% MVC (175 μV).

Table 1

Anthropometic and Physiologic Description of Subjects (N=8)

Age (years)	28.1 ± 1.4
Weight (Kg)	71.8 ± 2.9
Height (cm)	177.1 ± 3.2
$\dot{V}O_{2max}$ (ml O_2/Kg/min)	51.1 ± 2.7
Leg volume (liters)*	7.94 ± 0.32

* Volume for one leg
Values represent mean ± S.E.M.

Six of the 8 subjects had pre-synocopal reactions during the relaxed state while no pre-syncopal responses occurred during the elevated muscle tensions, see Table 2.

Table 2

LBNP Tolerance at Three Levels of Muscle Tension

Test EMG Level (μV)	Cumulative Stress Tolerated (torr.min)	Pre-synopal Incidents
< 10	590	6
80	618*	0
175	618*	0

Data based on N = 8
* All 8 subjects completed the Protocol

In addition, the experiment was repeated with the same levels of EMG activity being held in the arm musculature while the lower limbs were relaxed. Both levels of EMG activity (regardless of which limbs, arms or legs) attenuated the stroke volume and the cardiac output response to LBNP and subsequently augmented the heart rate response, see figures 1 and 2.

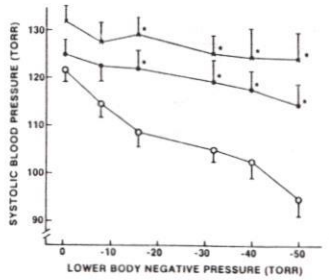


Fig. 1 Response of systolic blood pressure during LBNP at lower limb EMG activities of <10 μV(●-●); 80 μV(O---O), 175 μV(x---x). *Response significantly different (p<0.05) from the relaxed condition (EMG<10 μV).

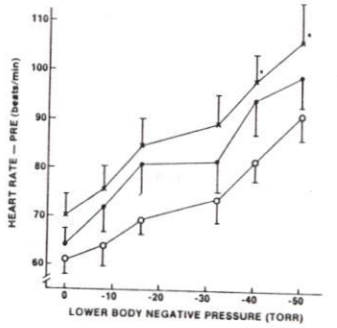


Fig. 2 Response of heart rate during LBNP at lower limb EMG activities of <10 μV(O-O); 80 μV(●---●), 175 μV(x---x). *Response significantly different (p<0.05) from the relaxed condition (EMG<10 μV)

We concluded that a low level of muscle tension would induce a somato-pressor reflex accompanied by slight mechanical compression of the vascular tree resulting in a maintenance of blood pressure and an enhanced tolerance to LBNP. Therefore, we recommend that evaluation of cardiovascular reflexes be investigated when the somato-pressor reflex is quiescent (14).

While, much of the difference in orthostatic tolerance to centrifugation by weight trained subjects appears related to an increased muscle mass and greater intramuscular forces being generated during an M1 or L1 maneuver (8,11). The increased capacity to develop muscular tension would result in a greater somato-pressor reflex and a greater mechanical constriction, thereby maintaining blood pressure more effectively during the G stress. However, WT subjects may have different blood pressure regulation by reason of their training regime. For example, a recent investigation by MacDougall et al. (15) documented intra-arterial pressures in excess of 420 mmHg during weight lifting. In high performance weight lifters such peaks in blood pressure generated for the periods of time they devote to weight training may cause the high pressure baroreceptor to reset. Furthermore, we already know that the cardiovascular system of the WT subjects is afterload conditioned (16,17) while ET subjects is pre-load conditioned (16,17), and that Keul et al (12) reports that WT subjects have an

augmented sympathoadrenal drive. Because these documented changes provide a base upon which one can propose a difference in blood pressure regulation, we first asked the question what is the difference in response to an orthostatic stress, such as LBNP between the ET subjects, the UT subjects and the WT subjects?

In this investigation, we utilized three groups of subjects; (N=8) classified as Endurance Trained (ET) Weight Trained (WT) and Untrained (UT), see table 3 for subject description.

TABLE 3
Descriptive data for the three subject groups
(N=8)

	ET	WT	UT
Age (yr)	27.9 ± 1.4	23.0 ± 1.1	27.4 ± 1.2
Weight (kg)	67.5 ± 1.5	82.9 ± 1.9	78.9 ± 4.4
Height (cm)	176.5 ± 2.0	180.2 ± 2.2	177.7 ± 1.0
Lean Mass (kg)	61.1 ± 2.0	72.0 ± 1.9	62.7 ± 2.9
Leg Volume (ml)*	7603 ± 389	9583 ± 664	10423 ± 289

Values represent mean ± S.E.M. ET = Endurance trained; WT = Weight trained; UT = Untrained. *Volume for one leg.

Further physiological description of the subject groups is summarized in table 4 below.

TABLE 4

Baseline physiological data for the three subject groups

	ET	WT	UT
$\dot{V}O_{2max}$ ($ml O_2$/kg/min)	62.0 ± 2.0 **	43.5 ± 2.6	38.8 ± 2.1
Grip Strength (kg)	44.9 ± 1.9 *	74.8 ± 3.4 *	41.8 ± 2.9
Resting Heart Rate (bpm)	52.1 ± 1.3 *	60.0 ± 3.0	68.4 ± 3.6
Resting Cardiac Index $\frac{(l/min)}{(m_2)}$	3.23 ± 0.13 *	2.88 ± 0.20	2.62 ± 0.10
Resting Stroke Index $\frac{(ml/beat)}{(m_2)}$	54.7 ± 0.2 **	45.7 ± 0.2 **	35.8 ± 0.2

Values represent mean + S.E.M. ET = Endurance trained; WT = Weight trained; UT= Untrained. *Significantly different from UT group ($p < 0.05$); **Significantly different from both of the other two groups ($p < 0.05$)

The expected qualitative physiological responses to LBNP were observed in all three groups. LgV increased significantly from rest with a concomitant decrease in SI and QI which was significant. As a result of different resting values for several variables between the three groups the data is presented as percent changes from rest, see figures 3 A & B.

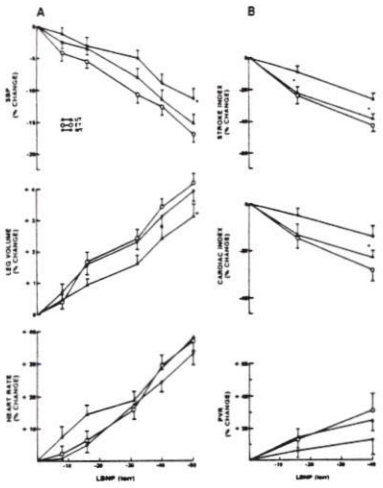


Fig. 3 The change in hemodynamic variables plotted as percent difference from pre-LBNP values (mean ± S.E.M.) for the ET (O-O), WT (●-●) and UT (Δ-Δ) subjects. *Represents significant difference ($p<0.05$). Reprinted with permission of the authors and the American College of Sports Medicine. Ref. M.S.S.E. 18:545-550, 1986.

Five ET, one UT and one WT subject failed to complete the protocol at -50 torr due to pre-syncopal reactions (nausea, severe dizziness, rapid-onset bradycardia and sweating), consequently, data describing the cardiovascular response during -50 torr LBNP was not obtained for these subjects. However, the calculated baroreflex index from 0 to -50 torr LBNP (ΔHR/Δ SBP) was significantly lower for the ET subjects (0.99) in comparison to both UT (1.38) and WT (1.51) subjects. There was no significant difference between WT and UT groups.

In this comparison using LBNP to -50 torr the WT subjects appeared to maintain blood pressure better than the ET and UT by reason of their greater stroke index and cardiac index while the peripheral vascular resistance (PVR) was not different, suggesting an enhanced cardiac contractile response even though the amount of blood pooled in the legs was the same. Once again the ET subjects were less effective in maintaining BP than the UT and WT subjects and this phenomenon was apparently due to an attenuated integrated baroreflex responsiveness.

In an effort to assess whether the differences observed during LBNP induced hypotension were present during hypertension we evaluated the same group of subjects (i.e., ET, WT and UT) using progressively increasing doses of phenylephrine hydrochloride. Infusion rates of 12, 24, 48, 60, 90 and 120 μg/min were introduced via a venous cannula into a hand vein of each subject. Each infusion rate was maintained until stable hemodynamic variables were obtained and measurements made. There were no physiologically significant differences in blood pressure response to the graded infusions of phenylephrine, see figure 4.

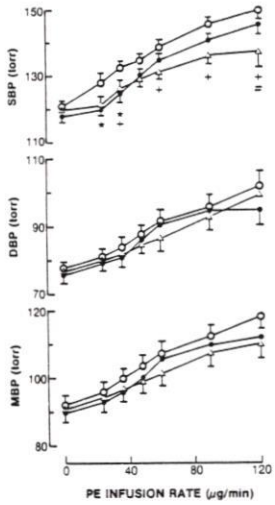


Fig. 4 The blood pressure response of ET (O-O), WT (Δ-Δ) and UT (●-●) subjects to progressive incremental infusion rates of phenylephrine. Differences in SBP response ET v WT (+) were not reflected in MBP or DBP, nor were the differences between UT and ET (*) or UT and WT (#).

However, the ET subjects had a significantly lower resting heart rate (HR) than the UT and WT subjects. This difference in HR disappeared across infusion rates and reflected a greater decrease in HR for the UT subjects, see figure 5.

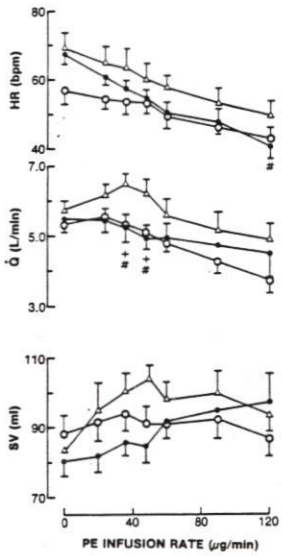


Fig. 5 The heart rate (HR), cardiac output ($\dot{Q}$) and stroke volume (SV) response of the ET (O-O), WT (Δ-Δ) and UT (O-O) subjects during incremental infusions of phenylephrine (PE).

Further analysis of the findings indicated that there were no differences across groups in vasoconstrictive capacity when compared at equal doses per unit of plasma volume. A finding suggestive that no group differences existed with respect to alpha-receptor sensitivity. However, it was clear that the baroreflex of the ET was significantly attenuated during the hypertensive challenge, see figure 6.

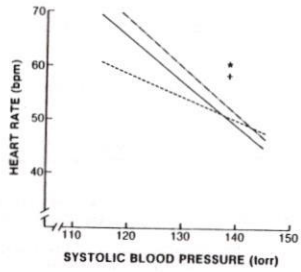


Fig. 6 Linear regression analysis of the HR and SBP data obtained from the ET (---), UT (-'-) and UT (-) subjects during incremental infusions of phenylephrine. The slope of the line for ET subjects was significantly less than either UT or WT subjects. While the slopes of the lines for UT and WT subjects was not different ($p>0.05$).

Subsequently, we focused our attention on the often reported decreased resting HR of the ET subjects which appears related to a greater vagal tone (10). Prelimanary investigations (reported in the abstract) indicated that comparisons between WT to UT and to ET was not different to the comparison of ET and UT subjects during LBNP. Therefore, we will present only the comparison between the ET and UT subjects (N=4) in the experiments using the pharmacologic blockade of metoprolol, atropine, and combinations of both.

In these investigations, we singly blocked B_1 and vagal efferent actions with metoprolol tartrate and atropine sulphate respectively, and carried out progressive LBNP to -40 torr following achievement of full blockade. Subsequently, we produced a double blockade of both B_1 and vagal efferent activity and once again used progressive LBNP to -40 torr. Full blockade was verified on each individual using heart rate response to valsalva maneuver and stepwise isoproteronol challenge to 50 μg prior to and following LBNP.

In control conditions, we once again demonstrated a loss of control of BP of the ET at -40 torr and -50 torr of LBNP compared to UT subjects, see figure 7.

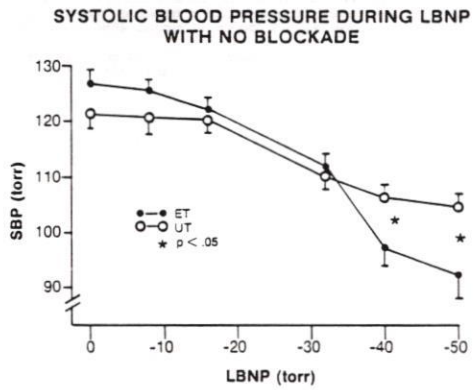


Fig. 7 SBP response of ET (●) and UT (O) subjects during the control (no pharmacologic blockade) condition of progressive LBNP to -50 torr.

During Metoprolol block we noted a significant depression of the HR response to LBNP (in both gorups) with the UT becoming more like the ET group. However, this had only a minor effect on the vasoconstrictive response of both groups to LBNP, see figure 8.

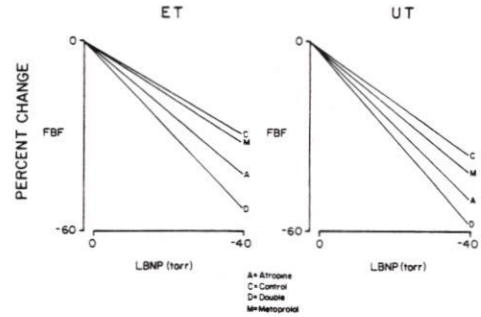


Fig. 8 The response of forearm blood flow (FBF) of the ET and UT subjects to LBNP to -40 torr during control (C), B_1 blockade with metoprolol (M), vagal blockade with atropine (A), and Double blockade with Metoprolol and atropine combined (D)

Hence, the SBP response of the subjects during metoprolol was more like that of ET and in fact at -40 torr some 3 subjects had pre-syncoal responses. During atropine block to -40 torr LBNP, SBP of the ET subjects was maintained similar to the UT subjects and appeared related to an improvement in sympathetic responses with respect to HR and FVR, see figures 8 and 9.

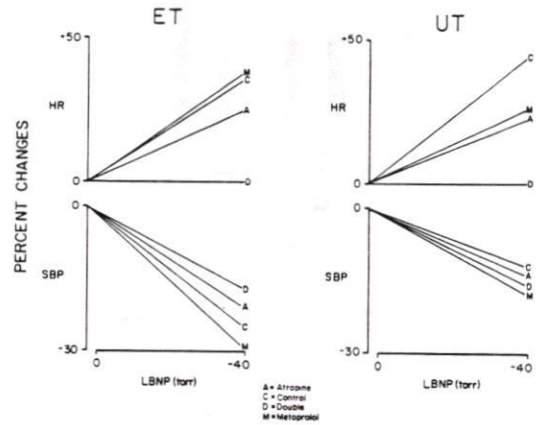


Fig. 9 The response of HR and SBP of the ET and UT subjects to LBNP to -40 torr during control (C), B_1 blockade with meloprolol (M), vagal blockade with atropine (A), and Double blockade with Metoprolol and atropine combined (D).

Calculated reflex response $\Delta HR/\Delta SBP$ from 0 to -40 torr LBNP shows that each block condition appears to bring the total reflex to an equal sensitivity. See Table 5.

Table 5

Summary of $\Delta HR/\Delta SBP$ during LBNP to -40 torr and during pharmacologic blockade

	Control	Metoprolol	Atropine
ET	0.86	0.95	0.84
UT	2.21	1.20	1.10

ET = Endurance Trained
UT = Untrained

However, metoprolol appeared to affect similar changes in FVR in the two groups, yet produced a greater change in the UT with respect to HR, which would suggest that the UT group operates with a significantly greater cardiac sympathetic response than ET subjects during control. Whereas, the atropine block affects a greater vasoconstrictor response to LBNP in ET group than in the UT group as well as equalizing the HR response. Hence, it appears that the vagal arm of the cardiovascular control system serves to buffer the responsiveness of the blood pressure control mechanisms.

Subsequently in our double blockade studies we clearly demonstrated maintenance of SBP by vasoconstriction alone, see figure 10, and further demonstrated a greater vasoconstrictive capacity in ET subjects than in UT, see figure 11.

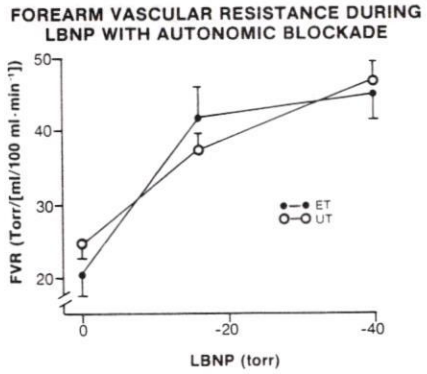


Fig. 10 The response of calculated forearm vascular resistance (FVR) of the UT and ET subjects to LBNP to -40 torr during double blockade with metoprolol and atropine.

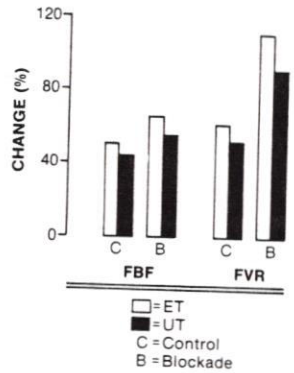


Fig. 11 The changes in FBF and FVR of the ET (□) and UT (■) during -40 torr LBNP expressed as a percentage from pre LBNP values.

Furthermore, it was noted that when atropine was used to block vagal function either singly or during double blockade maintenance of blood pressure was improved and no incidence of syncopy was observed.

We concluded that endurance training affects blood pressure regulation during orthostasis via vagal modulation of the effector responses. Whether this modulation is a result of afferent difference from cardiopulmonary receptors or during central integration cannot be ascertained at this time! However, this modulation of the integration of effector responses appears to be present during both hypotensive and hypertensive stress and results in an altered baroreflex function curve which is schematically depicted in figure 12 below.

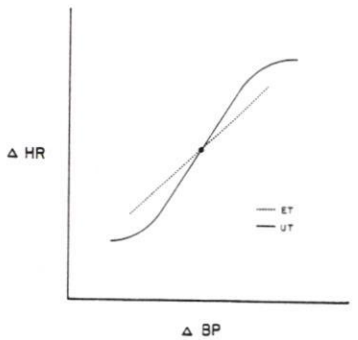


Fig. 12 A schematic depiction of our concept of the ET subjects altered linear portion of the integrated baroreflex function curve in comparison to the normally observed curve of the UT subjects.

References

1. Stegemann, J. A Busert and D. Brock. Influence of fitness on the blood pressure control system in man. Aerospace Med. 45:45-48, 1974.

2. Goldwater, D.J., M. Delada, A. Polise, K. Keil and J.A. Leutscher. Effect of athletic conditioning on orthostatic tolerance after prolonged bed rest (Abs.) Circ. (Suppl) 65:287, 1980.

3. Klein, K.E., H.M. Wegmann and P. Kuklinski. Athletic endurance training advantage for space flight? The significance of physical fitness selection and training of space lab crews. Aviat. Space Environ. Med. 48:215-222, 1977.

4. Mangseth, G.R. and E.M. Bernauer, Cardiovascular response to tilt in endurance trained subjects exhibiting syncopal reactions (Abs.) Med. Sci. Sports Exer. 12:140, 1982.

5. Raven, P.B., D. Rohm-Young and C.G. Blomqvist. Physical fitness and the cardiovascular response to lower body negative pressure. J. Appl. Physiol. 56:138-144, 1984.

6. Raven, P.B. and M.L. Smith. Physical fitness and its effects on factors affecting orthostatic tolerance. Physiologist (Suppl) 27:59-60, 1984.

7. Convertino, V.A., L.D. Montgomery, and J.E. Greenleaf. Cardiovascular responses during orthostasis: Effect of an increase in VO_{2max}. Aviat. Space Environ. Med. 55:702-708, 1984.

8. Epperson, W.L., R.R. Burton and E.M. Bernauer. The effectiveness of specific weight training regimes on simulated aerial combat maneuvering G tolerance. Aviat. Space Environ. Med. 56:534-539, 1985.

9. Holmgren, A., F. Mossfeldt, J. Sjostrand and G. Strom. Effect of training on work capacity, total hemoglobin, blood volume, heart volume and pulse rate in recumbent and upright positions. Acta. Physiol. Scand. 50:72-83, 1960.

10. Scheuer, J. and C.M. Tipton. Cardiovascular adaptations to physical training. Ann Rev. Physiol. 39:221-251, 1977.

11. Tesch, P.A., H. Hjort and K.I. Balldin. Effects of strength training on G. tolerance. Aviat. Space Environ. Med. 54:691-695, 1983.

12. Keul, J., H.H. Dickuth, H. Lehmann and J. Staiger. The athlete's heart - haemodynamics and structure. Intl. J. Sports Med. 3:33-43, 1982.

13. Mitchell, J.H., B. Schibye, F.C. Payne III and B. Saltin. Response of arterial blood pressure to static exercise in relation to muscle mass, force development, and electromyographic activity. Circ. Res. 48 (Suppl I): 70-76, 1981.

14. Smith, M.L., D.L. Hudson and P.B. Raven. Effect of muscle tension on the cardiovascular responses to lower body negative pressure in man. Med. Sci. Sports and Exer. (Submitted) 1986.

15. MacDougall, J.D., D. Tuxen, D.G. Sale, J.R. Moroz and J.R. Sutton. Arterial blood pressure response to heavy resistance exercise. J. Appl. Physiol. 58:785-790. 1985.

16. Longhurst, J.C., A.R. Kelly, W.J. Gonyea and J.H. Mitchell. Cardiovascular responses to static exercise in distance runners and weight lifters. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 49:676-683, 1980.

17. Morgonroth, J., B.J. Maron, W.L. Henry and E.R. Lapp. Comparative left ventricular dimensions in trained athletes. Ann. Intern. Med. 82:521-524, 1975.

IUPS Commission on Gravitational Physiology

Cumulative Author Index, 1979–1987

1979 *Physiologist* 22(6): Supplement (New Orleans)
1980 *Physiologist* 23(6): Supplement (Budapest)
1981 *Physiologist* 24(6): Supplement (Innsbruck)
1982 *Physiologist* 25(6): Supplement (San Diego)
1983 *Physiologist* 26(6): Supplement (Moscow)
1984 *Physiologist* 27(6): Supplement (Lausanne)
1985 *Physiologist* 28(6): Supplement (Niagara Falls)
1987 *Physiologist* 30(1): Supplement (Tokyo)

Abbott, U. K., (24)73; (27)139
Abe, M., (22)39: (23)149; (24) 105; (27)101
Abraham, S., (23)55
Adachi, R. R., (23)83
Afonin, B. V., (30)42
Ahlers, I., (23)131
Ahlersová, E., (23)131
Alberts, J. R., (28)81, 165
Alexandre, C., (30)45
Alexeyev, E. I., (23)51
Almon, R. R., (26)92; (28)69
Ambrus, B., (27)143
Ameln, H. von, (23)115
Andrews, R. B., (28)195
Annat, G., (26)100; (27)49, 61, 63
Apanasenko, Z., (28)81
Apostolakis, M., (23)111
Arnaud, S. B., (28)9, 227
Arno, R. D., (28)177
Asnalova, I. F., (25)49; (26)108
Asyamolova, N. M., (26)12

Babaev, B. M., (27)111
Babayev, B. M., (30)82
Bae, S. H., (22)33
Baer, R, (30)64
Baggerud, C., (27)127
Bain, J. L. W., (28)207
Baisch, F., (27)57, 103; (30)47
Bakulin, A. B., (30)45
Balldin, U. I., (23)147; (26)14; (28)71; (30)23, 64
Bandurski, R. S., (27)123; (28)111
Baranov, V. M., (28)40
Baranski, S., (23)38; (26)41
Barlow, G. H., (28)183
Barlow, P. W., (27)117
Barmin, V. A., (26)83, 108; (27)111; (28)51
Baron, R., (23)87
Baroskova, Z., (26)145
Barrere, M., (22)25; (23)151
Bartonicková, A., (26)131
Bascands, J. L., (26)9; (27)49, 61, 63
Baumgarten, R. J. von, (25)33
Baumgartner, J., (27)143
Baylink, D. J., (22)23, 73, 75; (24)97; (26)110
Beck, L., (27)57; (30)47
Behrens, P., (27)25
Belakovsky, M. S., (25)45; (26)112
Belkaniya, G. S., (26)76
Bell, N. H., (26)110
Belluschi, A., (24)93
Beloozerova, I. B., (30)82
Beloozerova, I. I., (27)111
Belyaev, S. M., (26)176
Benjamin, B. A., (27)51
Bennett, T., (30)143
Berenyi, E., (23)97; (24)11
Bes, A., (22)25; (23)151; (24)19; (25)69, 71; (26)9, 100
Besch, E. L., (28)59
Bie, P., (30)74
Bikle, D. D., (25)143; (28)123, 127
Billman, G. E., (25)75
Biro, R. L., (25)107
Bishop, V. S., (22)65
Bjorkman, T., (28)99
Bjurstedt, H., (22)3; (23)4; (24)24; (26)2; (27)1; (30)70
Black, S., (28)211
Black, S. D., (28)93
Blantz, R. C., (25)67
Blazicek, P., (23)121
Block, I., (26)129
Blomqvist, C. G., (26)81; (28)145
Blotter, P. T., (25)111
Bobyn, J. D., (24)97
Boca, A., (23)155
Boda, K., (26)145; (27)143
Bodo, G., (30)85
Bognár, L., (23)105; (26)70
Bomalaski, M. D., (25)145
Bonde-Petersen, F., (22)37; (23)7; (24)87, 89, 91; (25)73; (26)64, 72; (27)65, 67
Bordeianu, A., (23)155; (28)163
Borison, H. L., (27)81; (28)25
Borison, R., (27)91
Borredon, P., (27)43
Bousquet, J., (23)151
Braak, L., (22)25; (23)151
Briegleb, W., (22)29; (23)137; (24)109; (26)129
Brock, P. J., (22)41
Brown, A. H., (22)15; (23)135; (25)5; (26)149
Bru, A., (24)19
Buckendahl, P., (28)187
Buckey, J. C., (28)145
Bunch, T. E., (26)115
Burger, R. E., (22)59
Burns, J. W., (24)41
Burton, R. R., (23)113; (24)41; (28)59
Busch, I., (24)115
Bystrov, V. V., (26)66

Calder, W. A., (26)173
Callahan, P., (28)187
Campbell, M., (27)77; (28)217
Campbell-Grossman, C., (28)173
Cananau, S., (23)93, 155
Cann, C. E., (23)83; (28)227
Cantin, M., (28)30
Caren, L. D., (26)135
Carey, J. R., (26)123
Carlson, E., (22)55
Carter, D. R., (22)75
Castleman, K. R., (23)76
Chae, E. U., (22)33; (30)58
Chapman, D. K., (23)135; (25)5
Chappard, D., (30)45
Chee, O., (28)187, 219
Chelnaya, N. A., (26)137; (27)107
Cheng, L., (28)209
Chestukin, V. V., (30)36
Chitimia, S., (28)163
Christensen, N. J., (23)7; (25)73; (27)65; (30)74
Chui, L. A., (23)76
Chung, H.-M., (27)139
Clément, G., (26)86
Cline, M. G., (28)97
Cloke, P. L., (23)129
Code, C. F., (24)33
Cogoli, A., (22)29; (23)63; (24)109; (28)47
Cone, C. M., (28)123
Connolly, J. P., (24)111
Convertino, V. A., (25)159; (27)51
Cook, P., (28)129, 191, 193
Corbett, R., (28)211
Cordt, I., (22)29
Corrales, J., (28)83
Correia, M. J., (27)87
Corson, C., (23)129
Cowles, J. R., (25)129
Crittenden, D. J., (28)153
Crownover, J. C., (22)69
Cuellar, M. D., (28)107
Culman, J., (22)121

Daligcon, B. C., (25)87
Dalton, B., (28)187
Damaratskaya, E. S., (26)131
Darbelley, N., (27)121
Datelinka, I., (23)131
Dauwalder, M., (28)115
Davis, S., (28)151
Davtyan, J. S., (26)102
Davydova, N. A., (30)42
Dayanandan, P., (24)113; (25)101
Deavers, D. R., (23)91; (24)21
Debiec, H., (23)34, 117
DeFouw, D. O., (24)85
Deligiannis, A., (23)111
Delmoral, C., (28)153
Denisova, L. A., (25)9; (26)137, 139; (27)107; (28)5
DeRoshia, C. W., (22)79
Dettbarn, W-D., (28)133
DeVincenzi, D. L., (28)185
Dichgans, J., (26)32
Dickey, D. T., (22)27; (25)75
Dillaman, R. M., (28)65
Dolgopolova, G. V., (26)139
Dombrowski, J., (30)102
Domingo, E., (27)45
Donovan, K., (27)85; (28)219
Doty, S. B., (25)141; (27)81; (28)125, 225
Dragomir, C. T., (23)93
Dragomirescu, E., (28)163
DuBois, D. C., (26)92; (28)69
Duke, J., (27)74, 77; (28)77, 217
Dukesherer, D. R., (28)153
Dunn, C. D. R., (24)5; (25)79; (26)133; (28)195
Dupui, P., (25)71
Durnova, G. N., (23)51
Dutcher, F. R., (22)45
Duvall, P., (24)97
Dux, E., (23)105
Dux, L., (23)105
Dyomin, N. N., (23)59

Economos, A. C., (22)71
Eden, A. R., (27)87
Edes, I., (23)103
Edgar, D. M., (27)95
Edwards, K. L., (28)101
Egnor, R., (28)209
Egorov, A. D., (24)49
Egorov, I. A., (26)127
Eiken, O., (28)28; (30)64, 70
Eldridge, M. W., (22)81; (23)141; (24)1
Ellis, S., (27)37; (28)159, 207
Eloyan, M. A., (23)67; (26)102
Eltchaninova, E. G., (26)163
Enoka, R. M., (25)157; (28)137
Enyati-Gordon, E., (25)145
Evans, J. W., (22)53
Evans, M. L., (25)109; (28)119, 121

Fagan, J. M., (26)98
Fanjaud, G., (25)71

Volume no. given in parentheses, followed by page no.

Farmer, J. M., (25)123
Farr, L. A., (28)173
Farrington, M., (28)197
Fast, T., (28)187, 197
Fehér, E., (26)45
Feldman, L. J., (25)105; (28)117
Fell, R. D., (28)139; (30)94, 102
Feller, D. D., (24)9
Fermin, C. D., (28)87
Fernandez, E., (27)25
Fielding, W. J., (27)117
Finck, A., (25)121; (27)146
Fine, A., (28)209
Fisk, T.J., (27)91
Flores, H. E., (25)137
Földes, I., (26)94
France, E. P., (25)147
Franklin, C. I., (24)113; (25)101
Fujii, T., (27)131; (30)141
Fukase, Y., (27)53, 55; (30)66, 72, 75
Fukudo, N., (30)51
Fuller, C. A., (24)111; (25)91; (26)90; (27)93, 95; (28)143, 157, 181, 199, 201, 203, 205

Gaffney, F. A., (26)81; (28)145
Gajdos, L., (23)95
Galle, R. R., (25)29
Galston, A. W., (25)131, 137
Gáti, T., (26)45
Gaul, C. A., (30)56
Gauquelin, G., (25)69, (26)100; (27)49, 61, 63; (28)30
Gazenko, O. G., (23)11, 59; (27)3; (30)1, 31, 53
Gazo, M., (26)145
Gecse, A., (23)105
Geelen, G., (27)49; (28)30
Gelencsér, F., (26)45
Genin, A. M., (23)11, 121, 139; (25)29; (28)40
Gevlich, G. I., (26)108
Gharib, C., (25)69, 71; (26)9, 100; (27)49, 61, 63; (28)30
Gibson, L. A., (28)195
Giese, J., (25)73
Gillespie, L. S., (25)111
Ginoza, H. S., (24)9
Giometti, C. S., (28)159
Girolami, J. P., (27)61
Glaister, D. H., (25)25
Glasberg, M., (25)153
Globus, R. K., (25)143; (28)127
Goldsmith, W., (28)21
Goldwater, D.J., (25)167
Gonsalves, M. R., (25)145
Gorgiladze, G. I., (26)35
Gould, C. L., (28)213
Graitzer, H. M., (30)147
Grasse, M., (26)153
Greene, E. R., (22)81; (23)141; (24)1
Greene, P. R., (22)35
Greenleaf, J. E., (22)41; (28)38
Griffiths, L. D., (28)185
Grigoriev, A. I., (24)49; (26)28; (30)1, 42
Grigorieva, L. S., (25)49; (26)108
Grills, G. S., (27)99; (28)75
Grindeland, R., (28)187, 197, 227
Groza, P., (23)93, 155; (26)30; (28)163
Gruber, H., (27)35; (28)63
Gruener, R., (28)79
Gualtierotti, T., (24)103
Guan, Z., (30)13
Guba, F., (23)95, 97, 99, 101, 103; (24)17
Guell, A., (22)25; (23)151; (24)19, 89; (25)69, 71; (26)9, 100; (27)49, 61, 63; (28)30
Guenin, A. M., (26)12
Gurfinkel, V. S., (26)86
Gutierrez, C. J., (28)153
Gutkovska, J., (28)30
Guy, H. B., (25)21
Gyarmati, J., (26)94

Hall, G. M., (25)25
Halloran, B. P., (28)123, 127
Halstead, T. W., (22)1; (24)23; (25)53
Hand, A. R., (28)215
Hargens, A. R., (25)63, 67; (27)37; (28)155, 175; (30)15, 117
Hargrove, J. L., (28)229
Harris, C. S., (25)111
Harrison, M. A., (28)103
Hartman, H. B., (22)49
Hartung, W., (24)29
Hartle, D. K., (28)231, 233
Hasenstein, K-H., (28)119
Haussler, M. R., (28)223
Hayes, A. B., (25)133
Hayes, C., (28)197
Hecht, K., (23)30; (24)7; (26)153, 155, 157, 159
Heinrich, M., (28)161
Henriken, E. J., (28)13, 129, 131, 191, 193
Henriksen, O., (23)7; (24)89; (26)64
Henry, J. P., (25)17
Hensel, W., (26)60
Hesse, B., (25)73
Hideg, J., (23)97, 105; (24)11; (26)45, 70, 104
Hilchey, J. D., (28)177
Hilse, H., (26)155
Hinghofer-Szalkay, H., (24)83
Hisada, M., (30)139
Hlavacka, F., (23)153
Hoekenga, D. E., (22)81; (23)141
Hoffman, E. A., (26)20, 165; (27)46
Hoffman, L. F., (24)85, 101; (25)93; (27)89
Hollerman, J., (28)147
Homick, J. L., (26)117
Honeycutt, C., (25)77
Hong, S. K., (30)100
Horowitz, J. M., (22)57; (23)119; (24)107; (25)89, 93; (26)169; (27)89; (28)141
Horvath, S. M., (25)81; (27)68
Horwitz, B. A., (22)57; (23)119; (25)89; (26)169
Hoshizaki, T., (25)127; (26)151; (27)137
Howell, C., (27)25
Hudson, D. L., (30)147
Hukuhara, T., (27)17; (30)109
Hymer, W. C., (28)197
Ikawa, S., (28)73; (30)60, 135
Ilyin, E. A., (23)11, 27, 30; (26)121; (27)3; (30)31, 53
Ilyinia-Kakueva, E. I., (23)51
Ilyushko, N. A., (26)139
Inazawa, M., (30)66, 72, 75
Inge, W. H., (28)231, 233
Ionescu, S., (28)163
Ito, K., (27)53, 55
Ito, M., (30)81
Itoh, K., (30)66, 72, 75
Ivanova, L. N., (26)163
Iversen, T. H., (25)1; (27)127
Iwase, S., (30)62

Jacob, S., (28)13, 129, 191, 193
Jaffe, M. J., (22)43; (25)139
Jakab, G., (23)95
Janer, L., (27)75, 77; (28)77, 217
Jarosius, A. V., (28)43
Jaspers, S. R., (25)155; (26)98; (28)13, 129
Jee, W. S. S., (23)79
Johansen, T. S., (25)117
Johansson, C., (27)37
Johnson, P. C., (24)5; (25)79; (26)24, 133; (28)34; (30)113
Jones, D. P., (28)230
Jones, J. B., (28)195; (30)113
Jones, T. A., (24)107; (25)93
Joó, F., (23)105
Jordan, D. P., (22)69
Jordan, J. P., (22)69
Joyner, M. J., (30)117
Jurand, A., (26)143
Juráni, M., (26)145; (27)141
Jurgelski, W., (28)85

Kakurin, L. I., (26)66; (30)36
Kalita, N. F., (23)45
Kalmár, S., (26)70
Kaplansky, A. S., (23)38, 51; (26)76, 112; (30)53
Kaspransky, R. R., (30)85
Kass, D. A., (23)123
Kass, J. R., (25)33
Katafuchi, T., (30)106
Katkov, V. E., (28)40; (30)36
Kato, F., (30)109
Kato, K., (28)209
Katuntsev, V. P., (28)40
Kaufman, P. B., (24)113; (25)101
Kaur-Sawheny, R., (25)137
Kawakami, E., (30)60
Kawakami, K., (30)112, 135
Kawasaki, T., (30)77
Kawashima, T., (30)133
Kazarian, L. E., (25)147
Keefe, J. R., (25)115; (28)81
Keil, L., (28)187
Keil, L. C., (22)53; (25)75; (27)51
Kem, D. A., (25)75
Kenner, T., (24)13, 83; (28)169, 171
Kessler, J. O., (22)47
Keyl, M. J., (25)75
Khalig, S., (23)145
Kim, L. T., (28)145
Kimura, N., (27)17; (30)109
Kirchen, M. E., (27)35; (28)63
Kirenskaya, A. V., (26)108
Kirsch, K., (22)11; (24)115; (30)36
Kiss, G. G., (26)70
Kiss, Z., (23)101; (24)17
Klein, H. P., (23)55
Klein, K. E., (27)103
Klimovitsky, V. Y., (23)30; (24)7
Knight, D. R., (25)81; (27)69
Knight, S. L., (27)29
Kohl, R. L., (26)117
Kohno, M., (27)101; (30)135
Kolometzewa, I., (26)157
Konda, N., (30)68
Kondratyev, Y. I., (25)45
Konstantinova, I. V., (30)53
Kordyum, E. L., (26)141
Kornilova, L. N., (26)35; (30)85
Korolkov, V. I., (23)27
Korzensky, L., (23)127
Koslovskaya, I. B., (27)111
Kostal, L., (27)143
Koter, Z., (23)34
Kotovskaya, A. R., (23)27; (25)29; (26)66
Kowalski, W., (23)117
Kozerenko, O. P., (24)49
Kozlovskaya, I. B., (24)59; (25)49; (26)83, 108; (28)51; (30)1, 82
Kozlowski, S., (23)139
Kraft, L., (28)187
Krasney, J. A., (30)100
Kreidich, Y. V., (24)59; (25)49; (26)83; (27)111; (28)51
Krikorian, A. D., (22)45; (25)125; (28)167, 179
Krizková, M., (23)153
Kropácová, K., (23)133
Kujawa, M., (23)38
Kulaev, B. S., (26)164a
Kunze, M. E., (28)183
Kvetnanský, R., (23)45, 121
Kwarecki, K., (23)34, 117

Lake, T. G., (27)117
Lambert, E. H., (24)33
Lamosová, D., (26)145; (27)143
Lange, R. D., (26)133; (28)195; (30)113
Langenberg-Panzer, S. L., (28)173
Laniado, M., (24)115
LaRochelle, F. T., (25)161; (26)117
Latimer, J. C., (28)109
Laughlin, M. H., (22)67, 77
Laurinavicus, R. S., (28)43
Lavrinenko, V. A., (26)163
Lavrova, E. A., (26)139
Lazar, I., (28)163
Leach, C. S., (22)31, 61; (25)79, 161; (26)24, 117; (28)34; (30)6
Lehoczky, L., (26)70
LeMay, R., (25)129
Leonard, J. I., (22)31, 61; (24)5; (25)61, 65
Leopold, A. C., (25)97; (28)99
Lestienne, F., (26)86
Levens, M. J., (28)127
Lewis, M. L., (28)183
Lgarashi, M., (28)87
Lichardus, B. L., (26)28
Lin, C. Y., (23)55

Linnarsson, D., (28)28; (30)10
Lipshits, M. I., (26)86
Liscia, P., (27)43
Litvinenková, V., (23)153
Liu, C., (22)73
Lobachik, V. I., (26)28
Loeppky, J. A., (22)81; (23)141; (24)1
Luft, U. C., (22)81
Lundgren, P., (28)187
Lytle, J. S., (28)153

Macho, L., (23)45, 121
Mack, J. M., (28)173
Madena-Pyrgaki, A., (23)111
Magedov, V. S., (24)7
Magnuson, J. W., (28)167
Mains, R. C., (22)55; (28)165
Makeeva, V. F., (26)127; (27)107
Malacinski, G. M., (24)79; (25)119; (26)143; (27)139; (28)91
Mamatakhunov, A. I., (26)53
Mandal, A., (27)91
Mandel, A. D., (28)213
Mangelsdorf, D. J., (28)223
Mano, T., (30)62
Månsson, A., (24)87; (25)117
Manton, J., (25)153
Marion, S. L., (28)223
Marshall, G. J., (27)35; (28)63
Martin, R. B., (28)227
Matsunami, K., (30)129, 133
Mauroux, J. L., (28)30
Mazareán, H., (23)103
McCarthy, L. E., (27)91
McConnaughey, M. M., (28)203
McCutcheon, E. P., (22)55
McMahon, T. A., (22)5, 35
McMillen, B. A., (28)203
McTaggart, W. G., (27)45
Mednieks, M., (28)209, 215
Meehan, J. P., (25)17
Mehlsen, J., (30)74
Meizerov, E. S., (26)137
Mekjavic, I. B., (30)56
Melidi, N. N., (26)163
Merkys, A. J., (28)43
Merrill, A. H., Jr., (28)229
Mészáros, M. G., (23)97
Meyers, D. G., (25)123; (28)149
Mezei, Z., (23)105
Michel, C., (22)29
Michels, D. B., (25)21
Michurina, T. V., (26)131
Migliaccio, F., (25)103
Mihailowsky, N., (26)28
Miki, K., (30)68, 100
Miller, J. D., (28)143, 203
Miller, R. L., (27)17
Misúrová, E., (23)133
Mitarai, G., (23)125
Mitchell, C. A., (25)135; (27)28; (28)107
Mittleman, K. D., (30)56
Miyazaki, A., (30)141
Mizuno, Y., (23)125; (30)129
Modell, H. T., (25)95
Momonoki, Y., (27)123
Monson, C. B., (25)89; (26)169; (27)97; (28)83, 141
Montastruc, P., (24)19; (25)69
Moore, J., (28)77
Moore, R., (27)135; (28)113
Moore-Ede, M. C., (23)123
Morey-Holton, E. R., (22)23, 73, 75; (23)79, 83; (24)9, 45, 97; (25)141, 143, 145; (26)110; (27)81; (28)9, 123, 127
Morezenti, A., (27)141
Morimoto, T., (30)98
Morita, M., (30)98
Moriya, E., (30)60
Morrison, D. R., (28)183
Morrow, J., (28)217
Moser, M., (24)83; (28)169, 171
Motter, K., (28)197
Mozsary, P. G., (24)75
Mueller, W. J., (25)111
Mulkey, T. J., (25)109
Müller, M., (22)29
Murakami, D. M., (28)143, 203, 205
Murashko, L. M., (23)67
Musacchia, X. J., (22)1; (23)91; (24)21; (25)151, 163; (26)37; (27)39, 41; (28)139, 221, 237; (30)94, 102

Nace, G. W., (24)77
Nagainis, P. A., (27)73
Nagano, J., (27)53, 55; (30)66, 72, 75
Nagayama, T., (30)139
Nakajima, J., (30)121
Nakashima, M., (30)130, 133
Nakaya, M., (22)39; (23)149; (27)101; (28)73; (30)121
Naruse, M., (22)39
Natochin, Y. V., (26)139
Natsuyama, T., (30)98
Neff, A. W., (24)79; (25)119; (26)143; (27)139; (28)91
Nemeth, S., (23)45
Neubert, J., (24)81
Nicogossian, A., (26)78, 106
Nielsen, B., (23)7
Nielsen, C., (23)7
Nielsen, M. D., (25)73
Niklowitz, W. J., (26)115
Nixon, J. V., (26)81
Nogues, C., (24)99
Norsk, P., (23)7; (24)87, 91; (27)65, 67
Nose, N. J., (30)98
Novák, L., (23)139
Novikov, V. E., (30)45
Nyrova, A. N., (30)82

O'Connor, S. A., (25)125
Oehme, P., (26)155, 157
Oganessyan, S. S., (23)67; (26)102
Oganov, V. S., (23)11, 16, 30, 67, 71; (24)7, 55; (27)79; (30)53
O'Hara, D. B., (25)167
Okai, O., (30)49
Okuno, T., (30)98
Ollinger, O., (27)25
Oloff, C. M., (25)147
Oomura, Y., (30)106
Osborne, D. J., (27)115
Oser, H., (27)13; (28)241
Ossenkopp, K.-P., (28)61
Ossenkopp, M. D., (28)61
Ottlecz, A., (23)105
Overton, J. M. (30)96, 117
Oxnard, C. E., (25)37
Oyama, J., (23)119; (24)95; (25)87; (26)135; (27)97; (28)83

Pace, N., (22)51, 55; (23)41, 115; (24)37; (25)83; (26)51, 125; (27)71; (28)17, 243
Padalino, M., (25)153; (28)135
Paillard, F., (27)43
Pankova, A. S., (23)51
Papenfuss, W., (26)18
Pappas, T., (25)135, (27)29
Parfyonov, G. P., (24)69; (26)57
Park, W. K., (30)58
Patat, F., (26)66
Patil, L., (28)197
Patterson, G. T., (28)133
Patterson, S., (28)141
Patterson-Buckendahl, P. E., (28)227
Paulíková, E., (23)131
Pequignot, J. M., (26)100; (27)63
Perachio, A. A., (27)87
Perbal, G., (25)99; (27)121
Pessenhofer, H., (24)13
Pestov, I. D., (30)125
Petersen, M. J., (28)173
Peterson, C., (25)129
Peterson, D. F., (22)65
Peterson, O. W., (25)67
Petrescu, A., (23)93
Peyrin, L., (26)100
Philpott, D. E., (28)209, 211
Pickard, B. G., (28)103
Pike, J. W., (28)223
Pilet, P. E., (24)25
Pinter, H., (28)169, 171
Pitts, G. C., (23)41; (24)95; (25)13; (26)119; (27)83; (30)137
Plakhuta-Plakutina, G. I., (23)51
Pokrovsky, A. V., (30)125
Pool, S., (26)78, 106
Popov, K. E., (26)86
Popova, I. A., (30)42, 53
Popovic, P., (25)77
Popovic, V., (24)15; (25)77
Poppei, M., (23)30; (24)7; (26)153, 155, 157, 159
Portugalov, V. V., (23)51
Potapov, A. N., (23)16, 71
Pote, K. G., (23)129
Pottier, J. M., (26)66
Pourcelot, L., (26)66
Pozsgai, A., (24)11; (26)45, 70, 104
Prasad, T. K., (28)97
Praslicka, M., (23)131, 133
Pustynnikova, A. M., (27)107; (28)5

Quandieu, P., (24)99
Quinn, C. E., (22)45

Radice, G. P., (24)79
Radmer, R., (27)25
Rahlmann, D. F., (22)51, 55; (23)41, 115; (25)83; (26)51; (27)71; (28)17
Rakhmanov, A. S., (24)59
Rambaut, P. C., (22)61; (26)78, 106
Ranklin, L. L. (28)137
Rapczák, M., (23)67; (24)11; (26)94, 96, 104; (27)79
Rasmussen, S., (25)73
Rathfelder, E. L., (27)117
Raven, P. R., (27)59; (30)147
Rayle, D. L., (25)103
Reck, J., (22)29
Reilly, T., (28)187
Reinecke, D., (28)111
Remes, P., (23)105; (26)70
Repin, A. A., (28)51
Richards, K. L., (22)81
Riley, D. A., (28)159, 207
Ritman, E. L., (26)165
Roberts, W. E., (24)75
Robinson, F., (28)147
Röcker, L., (22)11; (24)115
Roer, R. D., (28)65
Rosenberg, G. D., (23)87; (28)189
Ross, M. D., (22)63; (23)129; (25)113; (27)85; (28)57, 219; (30)90
Ross-Clunis, H., III, (28)151
Rotkovská, D., (26)131
Roux, S. J., (25)107; (28)115
Rowell, L. B., (23)7
Ruder, M., (28)187
Rudiger, C. E., (28)161
Rudneva, R. I., (26)139
Rummel, J. A., (22)31
Russell, J. E., (23)87; (28)235

Sabelman, E. E., (22)23
Sack, F. D., (25)97; (28)105
Sadamoto, T., (22)37; (23)7
Sagawa, S., (30)68
Saiki, H., (22)39; (23)149; (24)105; (27)9, 101; (28)73; (30)121, 135
Saiki, M., (23)149
Saiki, Y., (28)73; (30)121
Saito, M., (30)60
Salisbury, F. B., (25)111; (27)31; (28)95
Sander-Jensen, K., (30)74
Sandler, H., (22)19, 27, 55, 79; (25)75, 159, 167; (27)51
Sapp, W., (28)211
Sass, D., (24)7
Sassolas, A., (27)49
Satake, H., (30)129, 133
Sato, Y., (30)77
Satyanarayana, T., (28)207
Sauseng, N., (24)13
Savilov, A. A., (26)66
Savina, E. A., (23)51; (26)76; (30)53
Schatte, C. L., (22)69
Schatten, G., (28)89
Schatten, H., (28)89
Schatz, A., (23)137
Scheld, H. W., (25)129; (28)167
Schertel, E. R., (22)57
Schlegel, T., (23)30; (24)7; (26)159
Schneider, H. J., (30)6
Schulze, A., (27)123; (28)111
Schwaberger, G., (24)13
Schwartz, T. W., (30)74
Sciaraffa, D., (22)41
Scibetta, S., (28)187
Scibetta, S. M., (26)135
Sedlak, F. R., (28)207

Sergeev, I. N., (25)45; (26)112
Serova, L. V., (23)11, 22; (25)9; (26)131, 137, 139; (27)107; (28)5, 81; (30)53
Setaro, F. V., (27)69
Sfakianos, P. N., (28)175
Shabelnikov, V. G., (26)12
Shakhmatova, E. I., (26)139
Shen, X., (30)13
Shioda, K., (27)101; (28)73, (30)121, 135
Shipov, A. A., (23)27; (25)29
Shiraki, K., (30)68
Shirvinskaya, M. A., (23)16, 71
Shlyk, G. G., (23)30
Shoja, S., (23)145
Shulzhenko, E. B., (26)176
Shvets, V. N., (23)51; (26)76, 112
Sickles, S. A., (25)165
Sidó, Z., (26)70
Sievers, A., (26)60
Silver, P., (25)153
Simmons, D. J., (23)87; (24)65; (28)189, 235
Simmons, J. B., (22)69
Simon, L., (23)127
Sirota, M. G., (26)108; (27)111; (30)82
Sjogaard, G., (23)7
Skagen, K., (23)7; (24)89; (26)64
Skipka, W., (24)3
Skuratova, S. A., (23)16, 67, 71; (27)79
Sliwinski, J. E., (25)111
Slocum, G. R., (28)207
Slocum, R. D., (25)131
Slonim, A. R., (30)19
Smajda, B., (23)131
Smirnov, K. V., (30)53
Smirnova, T. A., (23)41
Smith, A. H., (22)7, 51, 59; (23)41, 113, 115; (24)37, 41, 73, 101; (25)85; (26)47, 125; (27)71, 141; (28)17, 59; (30)131
Smith, J. D., (27)135
Smith, M. L., (27)59; (28)145; (30)147
Smith, R. C., (27)139; (28)91
Smith, T. J., (28)173
Snyder, R. G., (22)83
Sobick, V., (26)129
Soffen, G. A., (26)3
Sohár, I., (23)103
Solgaard, L., (28)83
Somogyiová, E., (26)145; (27)143
Sonnenfeld, G., (28)213
Sordahl, L. A., (25)149
Souza, K. A., (25)57; (28)85, 93
Spangenberg, D., (28)151
Spector, M., (24)97; (26)110
Spengler, D. M., (22)75
Spirichev, V. B., (25)45; (26)112
Sporrong, A., (23)147
Srinivasan, R., (25)61
Stadeager, C., (30)74
Steffen, J. M., (24)21; (25)151, 163; (26)37; (27)39, 41; (28)139, 221; (30)94, 102
Stegeman, J., (24)3
Steskal, J., (27)37
Stevenson, J., (28)211
Steward, F. C., (22)45
Stinemetz, C. L., (28)121
Stone, H. L., (22)27; (25)75, 149
Stroud, C., (28)89
Stuart, D. G., (25)157; (28)137
Suc, J. M., (27)61
Sudoh, M, (22)39; (23)149; (24)105; (27)101; (28)73; (30)60, 121, 135
Sugimoto, E., (30)98
Sugita, Y., (30)121
Sukhanov, Y. V., (26)28
Suki, W. N., (26)24
Sulzman, F. M., (25)165
Sutko, J., (25)153
Suzuki, M., (26)64, 72
Suzuki, Y., (22)37; (23)7; (27)53, 55; (30)66, 72, 75
Sweeney, J. R., (27)35; (28)63
Sykes, H. A., (22)69
Sytnik, K. M., (26)141
Szabová, T., (23)133
Székely, J., (24)17
Sziklai, I., (23)99, 101; (24)17
Szilágyi, T., (23)67; (24)11; (26)94; (27)79
Szöör, A., (23)67; (24)11; (26)94, 96, 104; (27)79
Szukalski, B. W., (28)67

Tairbekov, M. G., (24)69
Takács, O., (23)67, 97, 99, 101, 103
Takahata, M., (30)139
Takano, K., (27)17; (30)109
Taketomi, Y., (22)39; (23)149
Takihashi, H., (25)139
Tarasov, I. K., (26)35
Tatsunami, S., (30)51
Tedner, B., (28)28
Telegdy, G., (23)105
Templeton, G. H., (25)153; (28)135
Teoh, K. K., (22)27
Thompson, F. J., (26)74
Thuc, T. V., (23)87
Tigranyan, R. A., (23)45, 55, 59, 121, 131, 133
Tikunov, B. A., (26)102
Tipton, C. M., (25)63; (27)37; (30)96, 117
Tischler, M., (25)155; (26)98; (28)13, 129, 131, 191, 193
Todd, P., (28)183
Tomko, D., (28)147
Torikoshi, S., (27)53, 55; (30)66, 72, 75
Török, A., (23)99
Toropila, M., (23)131
Tóth, E., (26)45, 104
Tremor, J., (28)187
Tremor, J. W., (24)77, 111
Tschopp, A., (23)63; (24)109
Tucker, B. J., (25)63, 67
Turner, R. T., (22)23, 73, 75; (24)97; (26)110; (28)67

Ueki, S., (30)133
Ugolev, A. M., (26)53

Ungureanu, D., (23)93
Urano, H., (23)125
Ushakov, A. S., (23)41; (25)45; (26)112

Vacek, A., (26)131
Valluchi, M., (22)29
Vasques, M., (28)187
Vauti, F., (28)169, 171
Venters, M. D., (22)81; (23)141
Verigo, V. V., (23)30
Vernikos-Danellis, J., (25)161
Vesper, J., (26)159
Vesterhauge, S., (24)87; (25)117
Vetrova, E. G., (23)55
Vico, L., (30)45
Victor, G., (24)19
Vignery, A., (23)87
Vil-Vilyams, I. F., (28)40
Vincent, M., (27)49
Vogel, H., (25)33
Volkmann, C., (23)55
Vorobyov, E. I., (26)1
Vrabiescu, A., (22)85
Vrancianu, R., (26)30
Vyboh, P., (26)145; (27)143

Wachtel, E., (23)30; (24)7; (26)157, 159
Wakahara, M., (26)143
Wakley, G. K., (28)67
Walgenbach, S. C., (22)59
Walker, W., (23)87
Wang, E., (28)229
Warberg, J., (24)94; (25)73; (27)67; (30)74
Ward, C. H., (27)21
Watanabe, S., (23)125; (30)129
Watenpaugh, D. E., (28)145
Watson, E., (25)103
Waurick, S., (23)108
Wei, J., (30)13
Weidner, W. J., (24)85
West, J. B., (25)21
Wetzig, J., (25)33
Whedon, C. D., (25)41
Whinnery, J. E., (22)67, 77
White, M. D., (30)56
White, R. G., (25)111
Wicke, H. J., (22)11; (24)115
Williams, B. A., (24)111; (25)91
Williams, C., (28)211
Williams, J. A., (28)213
Williams, J. L., (28)203
Williams, K., (28)183
Williams, T. J., (22)63
Winget, C. M., (22)79
Winter, F., (23)87
Wirth, D., (26)18
Wojtkowiak, M., (26)161
Wolgemuth, D. J., (27)99; (28)75
Wood, E. H., (24)33; (26)20, 165; (27)47; (30)27
Wright, P., (28)195
Wright, W., (28)135
Wróblewski, S., (23)117
Wronski, T. J., (23)79; (24)45; (25)145; (28)127

Yago, N., (30)51
Yakovleva, I. Y., (26)35
Yakovleva, V. I., (23)51
Yakushin, S. B., (30)82
Yan, G., (30)13
Yates, B. J., (26)74
Yokozawa, K., (27)53, 55; (30)66, 72, 75
Yoshina, M., (30)139
Young, D. R., (26)115
Yousef, M. K., (30)68

Zamfir, V., (26)30; (28)163
Zaripov, B. Z., (26)53
Zass, D., (23)30
Zhernakov, A. F., (26)66
Zhidokov, V. V., (26)28
Zilstorff, K., (24)87; (25)117
Zorbas, Y. G., (23)145

NASA Space Biology Program

The advent of the space age provided the first access to the "gravity-free" state and an opportunity to manipulate gravity from its norm of one down to zero. Therefore NASA has assumed the responsibility to investigate the biological significance of gravity and thereby expand biological knowledge.

Objectives

The objectives of NASA's Space Biology research program are *1*) to investigate the biological significance of gravity; *2*) to use gravity to solve relevant biological questions; and *3*) to enhance our capability to use and explore space.

Goals

The goals of the program are *1*) to enhance our knowledge of normal physiological adaptive mechanisms in both plants and animals and thereby provide new insight into both normal and pathological mechanisms; *2*) to provide for the multiple generation survival of plants and animals in space through an understanding—and ultimately control—of the affects of gravity on development, adaptation, and evolution; and *3*) to enhance plant productivity through an understanding and control of gravitational and related environmental stimuli and the manipulation of response mechanisms.

The achievement of such goals depends on answers to basic scientific questions that include the following.

1) Does gravity influence fertilization and early development and can fertilization and early development proceed normally in a near 0–G environment? If gravity does affect fertilization and early development, what are the sensitive physiological systems and how are they affected? If early development is affected by gravity, is it a result of an effect on the parent or the direct effect on the embryo itself?

2) What is the role of gravity in the formation of structural elements, such as lignin, cellulose, chitin, and bone calcium, at the molecular as well as at the more complex organizational levels?

3) What role does gravity play in calcium-mediated physiological mechanisms and in calcium metabolism?

4) What is the gravity-sensing mechanism? How does it perceive information? How is the information transmitted to evoke a response?

5) How does gravity as an environmental factor interact with other environmental factors to control the physiology, morphology, and behavior of organisms? *Or* how do gravitational and other environmental stimuli interact in their control and direction of living forms? Can the action of gravity be replaced by different stimuli?

Strategy

The strategy so far has been to manipulate gravity on earth and develop weightless simulation models to develop and test gravitational hypotheses; to identify gravity-sensitive biological systems and interacting environmental response mechanisms; to address valid gravitational biological questions on earth when possible; and to plan and design future space experiments. As spaceflight opportunities, either manned or unmanned, become more prevalent, increasing emphasis will be placed on flight experiments. Similarly, as longer flight missions become available, emphasis will be directed toward biological questions that require longer periods of microgravity for adequate experimentation.

Program Content

The program has been divided into the following three broad areas: *1*) the role of gravity in reproduction, development, maturation, and evolution; *2*) gravity receptor mechanisms (these include the identification of the organ or site of gravity reception and the biological systems and mechanisms that transmit the information to a responsive site); and *3*) the physiological effects of gravity (this includes the biological mechanisms by which living systems respond and adapt to altered gravity, particularly that of the space environment, as well as the interactive affects of gravity and other stimuli and stresses on the physiology, morphology, and behavior of organisms).

This NASA program in space biology is carried out intramurally by the NASA Research Centers and by a system of extramural grants. Qualified scientists interested in learning more about the program and the development of research proposals should contact

Dr. Thora W. Halstead, Chief,
Space Biology Program, Code EBR
Life Sciences Division,
NASA Headquarters,
Washington, DC 20546
Phone: (202) 453-1525

NASA

SPACE BIOLOGY GRANT PRO-GRAM