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Cardiac baroreflex function and dynamic cerebral autoregulation in elderly Masters athletes

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[1]*Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and Department of Internal Medicine-Cardiology, University of Texas Southwestern Medical Center, Dallas, TX; and* [2]*Radboud University Nijmegen Medical Center, Department of Geriatric Medicine, Nijmegen, The Netherlands*

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Aengevaeren VL, Claassen JA, Levine BD, Zhang R. Cardiac baroreflex function and dynamic cerebral autoregulation in elderly Masters athletes. *J Appl Physiol* 114: 195–202, 2013. First published November 5, 2012; doi:10.1152/japplphysiol.00402.2012.—Cerebral blood flow (CBF) is stably maintained through the combined effects of blood pressure (BP) regulation and cerebral autoregulation. Previous studies suggest that aerobic exercise training improves cardiac baroreflex function and beneficially affects BP regulation, but may negatively affect cerebral autoregulation. The purpose of this study was to reveal the impact of lifelong exercise on cardiac baroreflex function and dynamic cerebral autoregulation (CA) in older adults. Eleven Masters athletes (MA) (8 men, 3 women; mean age 73 ± 6 yr; aerobic training >15 yr) and 12 healthy sedentary elderly (SE) (7 men, 5 women; mean age 71 ± 6 yr) participated in this study. BP, CBF velocity (CBFV), and heart rate were measured during resting conditions and repeated sit-stand maneuvers to enhance BP variability. Baroreflex gain was assessed using transfer function analysis of spontaneous changes in systolic BP and R-R interval in the low frequency range (0.05–0.15 Hz). Dynamic CA was assessed during sit-stand–induced changes in mean BP and CBFV at 0.05 Hz (10 s sit, 10 s stand). Cardiac baroreflex gain was more than doubled in MA compared with SE (MA, 7.69 ± 7.95; SE, 3.18 ± 1.29 ms/mmHg; $P = 0.018$). However, dynamic CA was similar in the two groups (normalized gain: MA, 1.50 ± 0.56; SE, 1.56 ± 0.42% CBFV/mmHg; $P = 0.792$). These findings suggest that lifelong exercise improves cardiac baroreflex function, but does not alter dynamic CA. Thus, beneficial effects of exercise training on BP regulation can be achieved in older adults without compromising dynamic regulation of CBF.

baroreflex function; cerebral autoregulation; exercise

MAINTAINING ADEQUATE CEREBRAL perfusion during every-day activities requires a fine regulation of blood pressure (BP) and cerebral blood flow (CBF) (39). Short-term BP and CBF regulation with time scales of several seconds to minutes are mainly controlled by the baroreflex and dynamic cerebral autoregulation (dynamic CA; dCA) (51). The baroreflex controls BP by modulating heart rate (HR), cardiac inotropy, and vascular tone in response to BP changes (31). Dynamic CA refers to the capabilities of the cerebral vascular bed to adjust its resistance to maintain adequate cerebral perfusion in response to transient changes in BP (8).

Aging appears to differentially affect these regulation mechanisms: aging reduces cardiac baroreflex function (14, 18, 40), however, dCA appears to be preserved with aging (8, 9). Impairment of the baroreflex function is an adverse prognostic indicator for cardiovascular diseases, and may lead to orthostatic hypotension, resulting in brain hypoperfusion, falls, or syncope if dCA cannot compensate for the augmented fluctuations in BP (24–27, 30, 53, 54).

Physical activity is a modifiable factor that may affect the regulation of BP and CBF (12, 35). For example, endurance training improves cardiac baroreflex function and reduces BP in young and older adults (6, 11, 13, 23, 26, 32, 33, 38, 48, 49), and previous studies from our group and others have shown marked cardiovascular benefits accredited to lifelong endurance training (2, 15, 38, 46). Furthermore, a high level of physical fitness appears to be associated with increased CBF velocity (CBFV) across the lifespan from young to older adults (1). However, the effects of exercise training on the regulation of cerebral hemodynamics are not clear. In young, endurance-trained subjects, Lind-Holst et al. (29) observed that dCA was less effective. Interestingly, Tzeng et al. (50) found an inverse correlation between cardiac baroreflex function and dCA, suggesting a negative interaction between BP and CBF regulation. These studies taken together raise the question whether the benefits of exercise training for baroreflex function may be counteracted by a reduced function of dCA.

Notably, these aspects have thus far been investigated only in young adults. The purpose of this study was to assess the differential effects of lifelong exercise on cardiac baroreflex function and dCA in the elderly. Masters athletes are a unique group of elderly who have participated in lifelong exercise training and competed in sports at very high levels (2). In this study, cardiac baroreflex function and dCA were measured in Masters athletes and sedentary elderly. Based on the previous findings in younger subjects, we hypothesized that lifelong endurance training in Masters athletes is associated with an improved cardiac baroreflex function but a less effective dCA.

METHODS

Subject population. Eleven Masters athletes (8 men, 3 women; mean age 73 ± 6 yr) and 12 sedentary elderly (7 men, 5 women; mean age 71 ± 6 yr) participated in the study. All subjects were nonsmokers, not on any cardiovascular medication, and normotensive. Female subjects were postmenopausal and did not take hormone replacement therapy. All subjects were carefully screened for cardiovascular and cerebrovascular diseases, diabetes, and hypertension with a detailed medical history and physical examination including a 12-lead electrocardiogram. Inclusion criterion for Masters athletes was endurance training >15 yr and still active (e.g., running about 20–50 miles weekly or the equivalent in cycling or swimming and participating in races) at the time of this study. All Masters athletes were either regionally or nationally ranked runners and were recruited from running clubs or the records of competitive running events (2). Sedentary subjects were recruited locally with newsletters and from senior centers and were excluded if they had exercised more than 30

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min three times a week in the past 2 yr. The Institutional Review Boards (IRBs) of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas approved the study protocol. All subjects signed an informed consent approved by the IRBs that conformed to the standards set by the latest revision of the Declaration of Helsinki.

Instrumentation. CBFV was measured in the right middle cerebral artery by transcranial Doppler ultrasonography (Multi-Dop X2, Compumedics/DWL, Singen, Germany). A 2 MHz Doppler probe was placed over the temporal window and fixed at a constant angle with a probe holder (Spencer Technologies, Northborough, MA). Doppler sampling depth ranged from 42 to 55 mm, and the angle of the Doppler probe and the sampling depth for each individual subject were adjusted to optimize the signal quality according to standard procedures (5). This technique allows noninvasive and repeatable estimates of changes in CBFV on a beat-to-beat basis. Continuous finger arterial BP was monitored in the left hand by photoplethysmography (Finapres Medical Systems, Amsterdam, The Netherlands). The hand was fixed at the level of the participant's heart. This method reliably assesses dynamic changes in beat-to-beat BP that correlate well with intra-arterial recordings and can be used to quantify the dynamic pressure-flow relationship of the cerebral circulation (44, 55, 56). Intermittent arterial pressure was measured in the right arm by an electrosphygmomanometer (Tango+, Suntech Medical, Morrisville, NC). This pressure measurement was used to corroborate the BP measurements of the finger pressure recordings throughout the experiment to make sure the finger cuff was properly placed to record BP. Electrocardiographic (ECG) data were recorded using a three-lead system (Hewlett-Packard, Andover, MA). End-tidal CO_2 ($EtCO_2$) was monitored with a nasal cannula using capnography (Carpnogard, Novamatrix) (4).

Study protocol. This was a cross-sectional study consisting of two visits, one visit to assess baroreflex function and dCA, and another for a peak exercise test. The visits were separated by at least 2 wk. To assess baroreflex function and dCA, after at least 10 min of rest in the sitting position, 5 min of data were recorded during spontaneous breathing. These data were used to obtain spontaneous changes in BP, R-R interval, CBFV, and baseline steady-state hemodynamics. Next, repeated sit-stand maneuvers were performed for 5 min with a duty cycle of a 10-s sit and a 10-s stand. The purpose of these maneuvers was to induce larger oscillations in BP to robustly (with high coherence) assess baroreflex function and dCA at 0.05 Hz, in addition to the estimation based on spontaneous oscillations, which is often associated with low coherence in the very low frequency range (52). For the peak exercise test, a modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity (3). Subjects first jogged or ran at a constant speed on a leveled treadmill (grade = 0). The treadmill speed was determined on the basis of individual fitness level. The grade was subsequently increased by 2% every 2 min until peak work rate was achieved. Ventilatory gas exchange was measured using the Douglas bag method. Gas fractions were analyzed by mass spectrometry (Marquette MGA1100) and ventilatory volume was measured using a Tissot spirometer. HR was monitored continuously via ECG recordings. Maximal oxygen uptake ($\dot{V}O_{2\,max}$) was defined as the highest oxygen uptake (VO_2) measured from at least a 40 s Douglas bag immediately before the end of the test. The criteria to confirm that $\dot{V}O_{2\,max}$ was achieved included an increase in $VO_2 < 150$ ml despite increasing the work rate with 2% grade; a respiratory exchange ratio >1.1; and HR within 5 beats/min of age-predicted maximal values. In all cases, at least two of these criteria were achieved. All experiments were performed in a quiet, environmentally controlled laboratory with an ambient temperature of 22°C. Each subject was asked to refrain from caffeinated beverages or alcohol at least 12 h prior to testing.

Data analysis. All signals were stored on a computer and analyzed off-line using the Acknowledge (BIOPAC Systems Inc) and Dadisp (DSP Development, Cambridge, MA) data acquisition and analysis software. Arterial pressure, ECG data, and CBFV waveforms were transferred into beat-to-beat values using a beat detection function in Acknowledge and then linearly interpolated and resampled at 2 Hz for spectral and transfer function analyses (55). The beat-to-beat time series were first detrended with third-order polynomial fitting and then subdivided into 256-point segments with 50% overlap for spectral estimation. Transfer function gain, phase, and coherence were calculated between systolic BP (SBP) and R-R interval to assess cardiac baroreflex function, and between mean BP (MBP) and CBFV to assess dCA (55).

Baroreflex function. Transfer function gain, phase, and coherence between spontaneous oscillations in SBP and R-R interval were calculated in the low frequency (LF) (0.05–0.15 Hz) range during baseline. We focused on the transfer function analysis during spontaneous oscillations at low frequencies in the specified frequency range because it is the most commonly used method to assess cardiac baroreflex function (6, 9, 23, 38, 41, 43, 50). However, we also assessed cardiac baroreflex function during repeated sit-stand at very low frequency (VLF) (0.02–0.07 Hz) to concur with the range used for dCA (see below). We did this because the increased coherence between induced changes in SBP and R-R interval made the linear transfer function analysis feasible under these conditions (Table 2) (54), whereas spontaneous oscillations in the VLF often lead to low coherence and unreliable baroreflex estimates. Of note, although perhaps somewhat confusing, the slight differences and some overlap in the LF and VLF frequency range definitions under resting and sit-stand conditions provided complementary data for assessing baroreflex function in this study. For baroreflex estimation, transfer gain quantifies the magnitude of the relationship between changes in SBP and R-R interval; a higher gain indicates higher baroreflex sensitivity because there is more R-R interval change for a given SBP change. The phase function shows the temporal displacement of R-R interval to SBP, quantifying how SBP leads the R-R interval, with the less negative phase indicating faster changes in R-R interval in response to SBP. Coherence function quantifies the extent to which changes in R-R interval are linearly correlated with changes in SBP. Coherence approaching unity in a specific frequency range suggests a linear relationship between two signals in this frequency range, whereas coherence approximating zero may indicate a nonlinear relationship, severe extraneous noise in the signals, or simply no relationship between signals.

Cerebral autoregulation. Transfer function gain, phase, and coherence between MBP and CBFV were calculated at VLF (0.02–0.07 Hz), LF (0.07–0.2 Hz), and high frequency (HF) (0.2–0.35 Hz) during baseline and at VLF during repeated sit-stand, using the methods described previously (10, 55). Both the absolute and normalized gain are presented. Normalized gain was calculated as a percentage change in CBFV, relative to the individual mean values, divided by the absolute change in MBP (CBFV%/mmHg). This corrects for the differences in individual baseline CBFV values and, with that, the spectral power of CBFV. Briefly, transfer function gain quantifies how changes in BP are transmitted into CBFV; a lower gain suggests that oscillations in CBFV in response to changes in BP are either buffered by active changes in cerebrovascular resistance, or by increases in steady-state cerebrovascular resistance, or by a combination of these (10). The phase function shows the temporal displacement of CBFV to BP. This displacement may result from the fact that CBFV recovers faster than BP from either internal or external perturbations. Thus, a reduction in phase may reflect less effective autoregulation (52). Coherence has the same explanation as that given for baroreflex estimation.

Statistical analysis. All steady-state hemodynamic values during baseline and sit-stand maneuvers were obtained by averaging the beat-to-beat data. Data were analyzed using Sigmaplot 11.0 (Systat Software). When data were normally distributed, a *t*-test was performed. When data were not normally distributed (e.g., baroreflex gain and phase, and other spectral measures), a Mann-Whitney's rank

Table 1. *Subject demographics and hemodynamics during baseline*

	Masters athletes (n = 11)	Sedentary elderly (n = 12)
Gender (M/F)	8/3	7/5
Age (yr)	73 ± 6	71 ± 6
Body mass index	23 ± 3	24 ± 3
$\dot{V}O_{2max}$ (ml·kg^{-}·min^{-})	42 ± 5	24 ± 4*
Heart rate (beats/min)	58 ± 8	69 ± 6*
Respiratory rate (breaths/min)	15 ± 4	14 ± 3
Mean CBFV (cm/s)	38 ± 9	49 ± 18
MBP (mmHg)	85 ± 6	88 ± 15
SBP (mmHg)	128 ± 14	136 ± 22
DBP (mmHg)	65 ± 6	67 ± 12
$EtCO_2$ (mmHg)	38 ± 4	37 ± 3

Values are means ± SD. $\dot{V}O_{2max}$, maximal oxygen uptake; CBFV, cerebral blood flow velocity; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; $EtCO_2$, end-tidal CO_2. *$P < 0.05$ compared with Masters athletes.

sum test was performed. Correlations between $\dot{V}O_{2\,max}$, baroreflex function, and dCA were performed using Pearson Product Moment. Data are presented as means ± SD. A value of $P < 0.05$ was considered statistically significant.

RESULTS

All subjects underwent baseline measurements, but one Masters athlete did not perform sit-stand maneuvers due to technical issues. The two groups were similar in age, body mass index (BMI), respiratory rate, CBFV, BP, and $EtCO_2$. As expected, $\dot{V}O_{2\,max}$ was higher and HR was lower in the Masters athletes (Table 1). Of note, $\dot{V}O_{2\,max}$ of Masters athletes was lower than would be expected of young elite endurance athletes because of the decline in $\dot{V}O_{2\,max}$ with age, even when maintaining a similar level of training (42). There were no gender differences within or between groups (data not shown), thus we present pooled data.

Baroreflex function. Baroreflex gain between spontaneous changes in BP and R-R interval was higher in Masters athletes than in sedentary elderly (Table 2) at the LF range (0.05–0.15 Hz). As expected, under these baseline (resting) conditions, the spectral power of SBP and R-R interval were relatively small (Fig. 1, Fig. 2, Table 2). Forced BP changes at 0.05 Hz induced by repeated sit-stand maneuvers augmented VLF spectral power in both groups, however, R-R interval variability increased more in Masters athletes. Although this suggests higher baroreflex sensitivity, which is consistent with findings at LF, estimation of VLF transfer function gain did not differ significantly between groups (Table 2).

Table 2. *Power spectral and transfer function analysis of baroreflex function during spontaneous changes in SBP and R-R interval (LF) and repeated sit-stand maneuvers at 0.05 Hz (VLF)*

	Masters athletes (n = 11)	Sedentary elderly (n = 12)
Power Spectrum		
Baseline LF PS SBP ($mmHg^2$)	6.5 ± 4.5	8.9 ± 9.8
Sit-stand VLF PS SBP ($mmHg^2$)	168 ± 140	88 ± 70
Baseline LF PS R-R interval (ms^2)	411 ± 424	157 ± 161
Sit-stand VLF PS R-R interval (ms^2)	2757 ± 3578	769 ± 770*
Transfer Function		
Baseline LF gain (ms/mmHg)	7.69 ± 7.95	3.18 ± 1.29*
Baseline LF phase (rad)	−1.01 ± 0.35	−1.29 ± 0.41
Baseline LF coherence (units)	0.50 ± 0.16	0.53 ± 0.19
Sit-stand VLF gain (ms/mmHg)	3.47 ± 1.59	2.77 ± 1.49
Sit-stand VLF phase (rad)	−0.86 ± 0.64	−1.27 ± 0.52
Sit-stand VLF coherence (units)	0.67 ± 0.09	0.61 ± 0.09

Values are means ± SD. PS, power spectral; SBP, systolic blood pressure; LF, low frequency (0.05–0.15 Hz). VLF, very low frequency (0.02–0.07 Hz). *$P < 0.05$ compared with Masters athletes.

Cerebral autoregulation. Power spectral analysis (Fig. 3, Table 3) showed no differences in spontaneous or induced MBP and CBFV variability between the two groups. Transfer function analysis (Fig. 4, Table 3) showed a lower absolute, but not normalized VLF gain in the Masters athletes during baseline. There were no differences in phase, gain, or coherence between the two groups during sit-stand maneuvers. However, a trend toward increases in BP oscillations was observed in Masters athletes compared with sedentary elderly (Fig. 3, Table 3).

No correlations were observed between dCA and baroreflex gain either during baseline or sit-stand maneuvers.

DISCUSSION

The main findings of this study are twofold. First, we did not find significant differences in dCA between the Masters athletes and sedentary elderly. Second, we found that cardiac

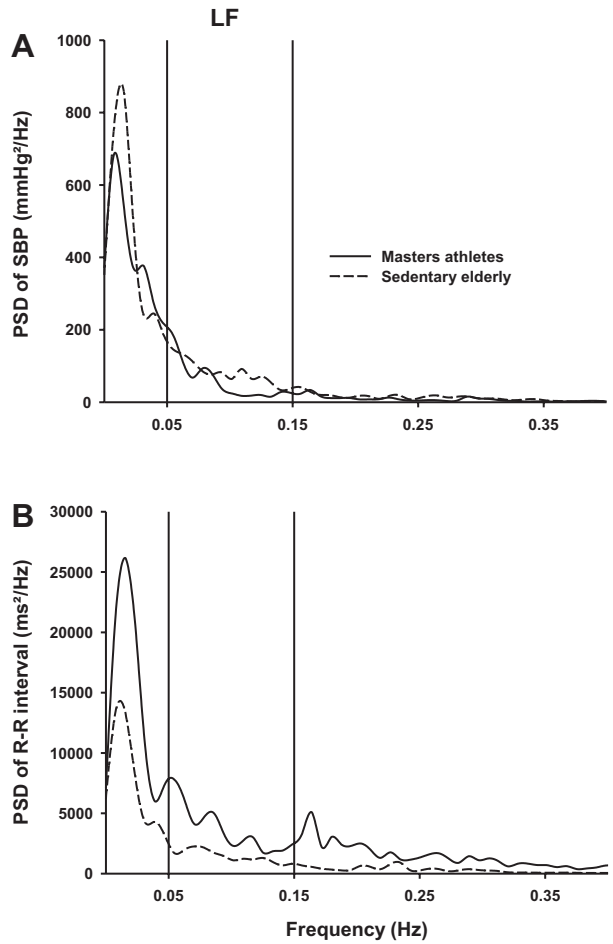

Fig. 1. Group-averaged power spectral density of spontaneous changes in systolic blood pressure (SBP) (*A*) and R-R interval (*B*).

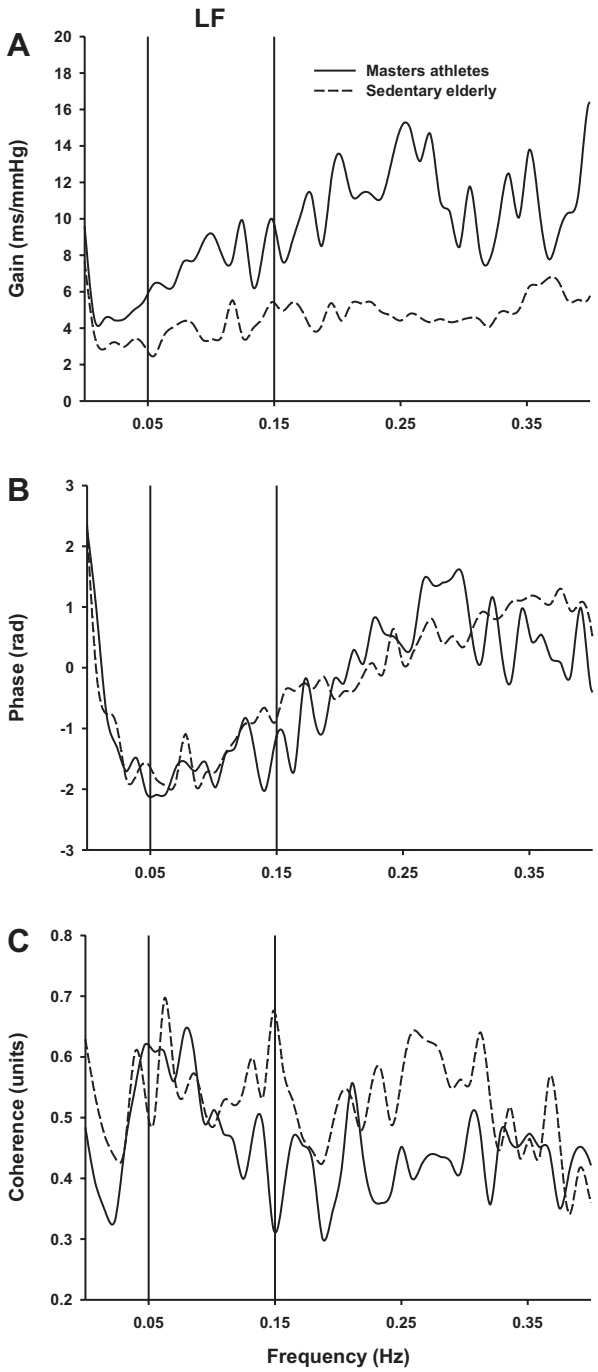

Fig. 2. Group-averaged transfer function gain (*A*), phase (*B*), and coherence (*C*) between spontaneous changes in systolic blood pressure (SBP) and R-R interval.

baroreflex gain was more than doubled in the Masters athletes compared with sedentary elderly. Moreover, no correlations were observed between the estimates of baroreflex gain and dCA. Collectively, these findings suggest that lifelong endurance training improves cardiac baroreflex function, but it does not alter dCA in older adults.

Effect of endurance training on cardiac baroreflex function. Previous studies suggest that endurance training improves (6, 13, 23, 26, 32, 38) and aging reduces (8, 14, 18, 40) cardiac baroreflex function. The combined effects of exercise and aging are therefore interesting.

Our finding that Masters athletes had a higher cardiac baroreflex gain than that observed in sedentary elderly during spontaneous BP changes is consistent with previous studies showing that endurance training from several months to a year reduced the age-related decline in baroreflex function (6, 13, 32).

The underlying mechanisms through which exercise improves cardiac baroreflex function are not completely understood. Exercise training may increase tonic vagal activity, which could explain the higher cardiac baroreflex gain found in the Masters athletes (41, 45). Consistent with this hypothesis, Masters athletes had a higher R-R interval variability and lower resting heart rate than sedentary elderly, indeed suggesting increased vagal activity. Alternatively, exercise training may reduce age-related arterial stiffening and increase stroke volume, changing the transduction of mechanical stimuli to the baroreceptors, which in turn, may increase cardiac baroreflex gain (20). Finally, increases in cardiac cholinergic responsiveness associated with exercise training may lead to increases in baroreflex sensitivity (31).

R-R interval variability was higher in Masters athletes during the augmented BP oscillations induced by repeated sit-stand maneuvers than it was in sedentary elderly. However,

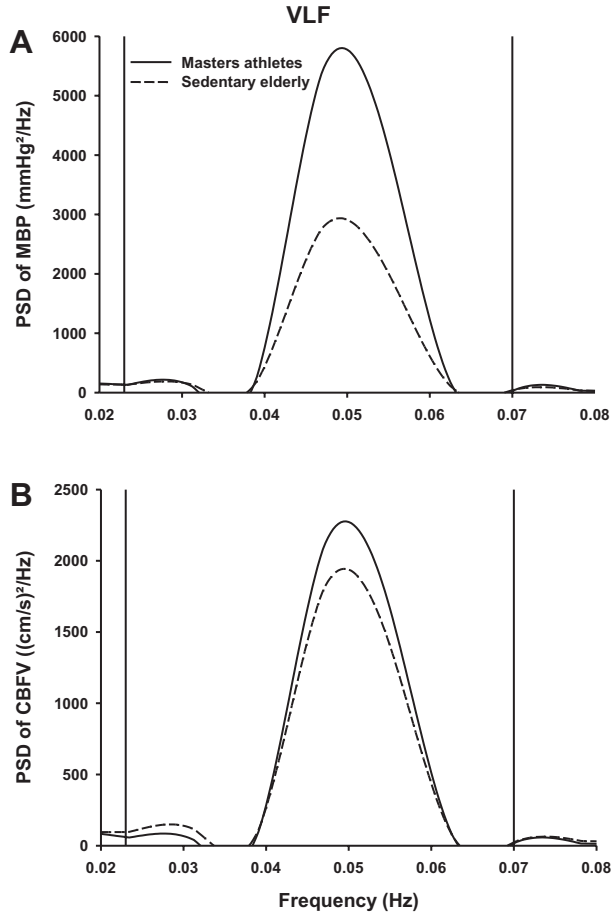

Fig. 3. Group-averaged power spectral density of mean blood pressure (MBP) (*A*) and cerebral blood flow velocity (CBFV) (*B*) during repeated sit-stand maneuvers at 0.05 Hz.

Table 3. *Power spectral and transfer function analysis of dynamic cerebral autoregulation during spontaneous changes in MBP and CBFV (VLF, LF, and HF) and repeated sit-stand maneuvers at 0.05 Hz (VLF)*

	Masters athletes (n = 11)	Sedentary elderly (n = 12)
Power Spectrum		
Baseline PS CBFV (cm/s)^2		
VLF	2.13 ± 1.8	2.98 ± 1.3
LF	1.43 ± 0.8	1.97 ± 1.7
HF	0.41 ± 0.6	0.74 ± 0.8
Baseline PS MBP (mmHg^2)		
VLF	5.41 ± 4.5	4.04 ± 1.9
LF	1.71 ± 1.2	2.19 ± 2.5
HF	0.31 ± 0.4	0.39 ± 0.2
Sit-stand PS CBFV VLF (cm/s)^2	30.8 ± 29.1	27.1 ± 23.4
Sit-stand PS BP VLF (mmHg^2)	77.2 ± 55.2	39.8 ± 29.3
Transfer Function		
Baseline		
VLF gain (cm·s^{-}·mmHg^{-})	0.50 ± 0.13	0.66 ± 0.18*
VLF normalized gain (%/mmHg)	1.31 ± 0.25	1.43 ± 0.34
VLF phase (rad)	0.84 ± 0.38	0.68 ± 0.63
VLF coherence	0.57 ± 0.14	0.58 ± 0.21
LF gain	0.86 ± 0.15	1.00 ± 0.40
LF normalized gain	2.30 ± 0.40	2.12 ± 0.80
LF phase	0.57 ± 0.17	0.47 ± 0.19
LF coherence	0.68 ± 0.15	0.64 ± 0.19
HF gain	1.00 ± 0.32	1.08 ± 0.37
HF normalized gain	2.61 ± 0.52	2.33 ± 0.76
HF phase	0.10 ± 0.18	0.20 ± 0.17
HF coherence	0.67 ± 0.15	0.66 ± 0.15
Sit-stand		
VLF gain	0.57 ± 0.24	0.73 ± 0.25
VLF normalized gain	1.50 ± 0.56	1.56 ± 0.42
VLF phase	0.78 ± 0.20	0.72 ± 0.27
VLF coherence	0.73 ± 0.10	0.70 ± 0.10

Values are means ± SD. PS, power spectral; CBFV, cerebral blood flow velocity; MBP, mean blood pressure; VLF, very low frequency (0.02–0.07 Hz); LF, low frequency (0.07–0.20 Hz); HF, high frequency (0.20–0.35 Hz). *$P < 0.05$ compared with Masters athletes.

calculation of baroreflex gain was not significantly higher in the Masters athletes. In view of the high interindividual variance, this may reflect a lack of power for assessing baroreflex gain at the VLF range.

The higher SBP variations during repeated sit-stand maneuvers in the Masters athletes may be explained by the training-related changes in cardiovascular mechanics (28). A greater peripheral vascular distensibility or left ventricular distensibility alone or in combination, together with a steeper slope of the Starling relationship between the left ventricular filling pressure and stroke volume may result in large oscillations in stroke volume, and therefore SBP, during sit-stand maneuvers in the Masters athletes. This is consistent with the observation that athletes are more susceptible to orthostatic hypotension (28).

Effect of endurance training on cerebral autoregulation. Several studies have investigated the acute effects of aerobic exercise on cerebral circulation and dCA (7, 36, 37). Brys et al. (7) observed that dCA was maintained during stepwise ergometric challenge at 50, 100, and 150 W. However, Ogoh et al. (36) observed that dCA was impaired during ergometry at a mean workload of 168 W continued to exhaustion. In addition, Ogoh et al. (37) found an unchanged normalized transfer function gain between MBP and mean CBFV and between SBP and systolic CBFV, but an increased gain between DBP and diastolic CBFV during cycling at a heart rate of 150 beats/min, indicating reduced dCA during diastole. Both CBF and CBFV may increase during aerobic exercise (19, 21, 37, 47). However, it has been argued that increases in CBFV during exercise may reflect cerebral vasoconstriction of the insonated artery rather than increases in blood flow (19). Clearly, differences in exercise intensity, duration, and mode used in these studies may have contributed to the above discrepancies. However, collectively, these studies do suggest

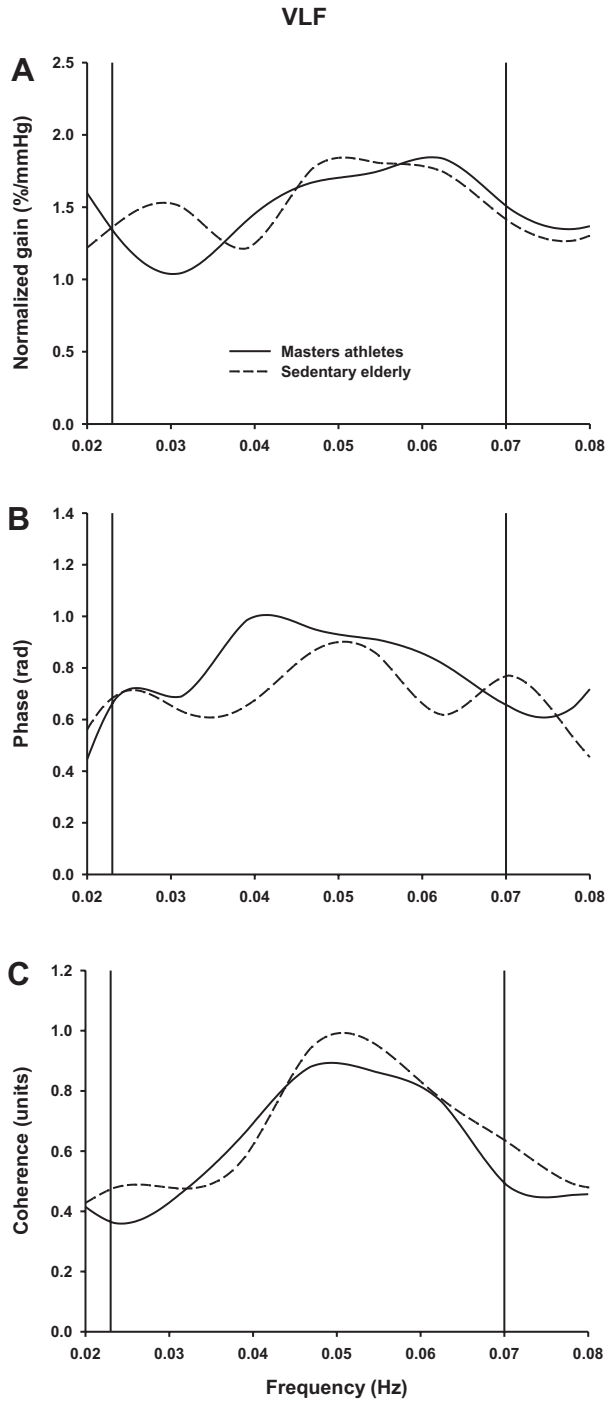

Fig. 4. Group-averaged transfer function gain (*A*), phase (*B*), and coherence (*C*) between mean blood pressure (MBP) and cerebral blood flow velocity (CBFV) during repeated sit-stand maneuvers at 0.05 Hz.

the possible presence of acute effects of exercise on brain perfusion (7, 19, 21, 36, 37, 47).

Few studies have determined the effects of exercise training on CBF regulation. In a cross-sectional study, Ainslie et al. (1) showed that high aerobic fitness was associated with a higher baseline CBFV, suggesting that exercise training may ameliorate age-related decline in CBF. Consistent with the proposed salutary effects of exercise training on brain perfusion, endurance training for 3 mo reduced cerebrovascular resistance in women >60 yr of age (57) and increased cerebral vasomotor reactivity in stroke survivors, but did not change baseline CBFV (22). Interestingly, Lind-Holst et al. (29) found that dCA was less effective in endurance-trained young adults relative to their sedentary controls.

Contrary to these findings, baseline CBFV was not higher in Masters athletes than in sedentary elderly. In addition, no group differences in dCA were observed. Confounding factors such as the limitations of cross-sectional study, differences in the study population, and uncertainty about a potential dose-response relationship of exercise training and CBF regulation all may have contributed to these inconsistent findings. However, the present study provides evidence that dCA was not compromised in the Masters athletes who had participated in lifelong endurance exercise training.

Relationship between cardiac baroreflex function and dCA. Short-term stability of the cerebral circulation is maintained primarily by two mechanisms: the baroreflex control of arterial pressure and dCA regulation of CBF (51). Whether a fundamental relationship exists between these regulatory mechanisms is unclear. Tzeng et al. (50) found an inverse correlation between cardiac baroreflex function and dCA in young individuals. These findings have been interpreted to indicate that there is a negative interaction between BP and CBF regulation (50), with higher baroreflex sensitivity associated with less effective dCA.

In the present study, we did not observe any correlations between estimates of cardiac baroreflex and dCA gain in Masters athletes or in sedentary elderly. Consistently, Masters athletes had a higher cardiac baroreflex gain, but a similar dCA to that of sedentary elderly. These findings indicate that higher baroreflex sensitivity is not necessarily associated with a reduction in dCA in the elderly. These findings also suggest that the overall effects of exercise on cerebral hemodynamics are positive, with enhanced BP regulation combined with an unaffected regulation of CBF.

Study limitations. The major limitations of the present study are its cross-sectional design and the limited sample size. A causal relationship between lifelong endurance training in Masters athletes and changes in baroreflex function and dCA cannot be determined. However, conducting a longitudinal study to address these questions would be difficult, if not impossible, to implement. The small sample size was due to the low prevalence and hence difficulty to recruit Masters athletes. However, on the basis of previous work (52), we had >80% power to detect a difference of 0.4 radians at VLF between the groups as an index of impaired dCA.

There are no gold standard methods to assess baroreflex function or dCA. Therefore, direct comparisons between different studies are challenging. However, the transfer function methods used in the present study are widely accepted and the results of this study could be compared with a large number of studies using similar methods to assess cardiac baroreflex function and dCA.

Our sedentary elderly do not reflect typically sedentarism as the chosen cut-off level for physical activity may still have been relatively high. In addition, the elderly subjects did not have hypertension, used no cardiovascular medication, and did not have other comorbidities that typically are associated with sedentarism. Therefore, the sedentary elderly in this study most likely reflect the normal aging of healthy controls. Thus, the findings of this study primarily reflect the differences in cardiac baroreflex function and dCA between normal aging and lifelong exercise training of Masters athletes. Using a more sedentary control group could have enhanced contrasts between groups, but it would also have complicated comparisons because comorbidities might have confounded the results.

Finally, as with all studies using transcranial Doppler ultrasonography to assess dCA, the assumption that changes in CBFV reflect changes in CBF is valid only if the insonated middle cerebral artery (MCA) diameter did not change during the experimental conditions. The MCA diameter is unlikely to change under resting conditions or during moderate changes in BP induced during repeated sit-stand maneuvers (16, 34). However, lifelong endurance training may lead to vasodilation in the basal cerebral arteries, including the MCA (17). If this is the case, a lower CBFV observed in the Masters athletes may underestimate CBF. To reduce the effect of this potential limitation on the assessment of dCA, we normalized transfer function gain.

In summary, in this cross-sectional study, we found that cardiac baroreflex gain was more than doubled in Masters athletes compared with sedentary elderly; however, estimates of dCA were similar between the two groups. Furthermore, no correlations were observed between the estimates of baroreflex gain and dCA. Taken together, these findings suggest that lifelong endurance training improves cardiac baroreflex function, but does not alter dCA in older adults. Thus beneficial effects of exercise training on BP regulation can be achieved in older adults without compromising dynamic regulation of CBF.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: V.L.A. analyzed data; V.L.A., J.A.C., and R.Z. interpreted results of experiments; V.L.A. prepared figures; V.L.A. and J.A.C. drafted manuscript; V.L.A., J.A.C., B.D.L., and R.Z. edited and revised manuscript; J.A.C. and R.Z. approved final version of manuscript; B.D.L. and R.Z. conceived and designed research; B.D.L. and R.Z. performed experiments.

REFERENCES

1. **Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, Thomas KN, Williams MJ, Atkinson G.** Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J Physiol* 586: 4005–4010, 2008.
2. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799–1805, 2004.
3. **Balke B, Nagle FJ, Daniels J.** Altitude and maximum performance in work and sports activity. *JAMA* 194: 646–649, 1965.
4. **Battisti-Charbonney A, Fisher J, Duffin J.** The cerebrovascular response to carbon dioxide in humans. *J Physiol* 589: 3039–3048, 2011.
5. **Bishop CC, Powell S, Rutt D, Browse NL.** Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. *Stroke* 17: 913–915, 1986.
6. **Bowman AJ, Clayton RH, Murray A, Reed JW, Subhan MF, Ford GA.** Baroreflex function in sedentary and endurance-trained elderly people. *Age Ageing* 26: 289–294, 1997.
7. **Brys M, Brown CM, Marthol H, Franta R, Hilz MJ.** Dynamic cerebral autoregulation remains stable during physical challenge in healthy persons. *Am J Physiol Heart Circ Physiol* 285: H1048–H1054, 2003.
8. **Burkhart CS, Rossi A, Dell-Kuster S, Gamberini M, Mockli A, Siegemund M, Czosnyka M, Strebel SP, Steiner LA.** Effect of age on intraoperative cerebrovascular autoregulation and near-infrared spectroscopy-derived cerebral oxygenation. *Br J Anaesth* 107: 742–748, 2011.
9. **Carey BJ, Eames PJ, Blake MJ, Panerai RB, Potter JF.** Dynamic cerebral autoregulation is unaffected by aging. *Stroke* 31: 2895–2900, 2000.
10. **Claassen JA, Levine BD, Zhang R.** Dynamic cerebral autoregulation during repeated squat-stand maneuvers. *J Appl Physiol* 106: 153–160, 2009.
11. **Cornelissen VA, Fagard RH.** Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* 46: 667–675, 2005.
12. **Cornelissen VA, Goetschalckx K, Verheyden B, Aubert AE, Arnout J, Persu A, Rademakers F, Fagard RH.** Effect of endurance training on blood pressure regulation, biomarkers and the heart in subjects at a higher age. *Scand J Med Sci Sports* 21: 526–534, 2011.
13. **Deley G, Picard G, Taylor JA.** Arterial baroreflex control of cardiac vagal outflow in older individuals can be enhanced by aerobic exercise training. *Hypertension* 53: 826–832, 2009.
14. **Fisher JP, Ogoh S, Ahmed A, Aro MR, Gute D, Fadel PJ.** Influence of age on cardiac baroreflex function during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 293: H777–H783, 2007.
15. **Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD.** Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation* 122: 1797–1805, 2010.
16. **Giller CA, Bowman G, Dyer H, Mootz L, Krippner W.** Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 32: 737–741; discussion 741–732, 1993.
17. **Green DJ, Spence A, Rowley N, Thijssen DH, Naylor LH.** Vascular adaptation in athletes: Is there an "Athlete's Artery"? *Exp Physiol* 97: 295–304, 2011.
18. **Gribbin B, Pickering TG, Sleight P, Peto R.** Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* 29: 424–431, 1971.
19. **Hellstrom G, Wahlgren NG.** Physical exercise increases middle cerebral artery blood flow velocity. *Neurosurg Rev* 16: 151–156, 1993.
20. **Hunt BE, Farquhar WB, Taylor JA.** Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? *Circulation* 103: 2424–2427, 2001.
21. **Ide K, Horn A, Secher NH.** Cerebral metabolic response to submaximal exercise. *J Appl Physiol* 87: 1604–1608, 1999.
22. **Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF.** Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. *Stroke* 42: 1994–2000, 2011.
23. **Iwasaki K, Zhang R, Zuckerman JH, Levine BD.** Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit? *J Appl Physiol* 95: 1575–1583, 2003.
24. **James MA, Potter JF.** Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects. *Age Ageing* 28: 522–530, 1999.
25. **Kenny RA, Kalaria R, Ballard C.** Neurocardiovascular instability in cognitive impairment and dementia. *Ann N Y Acad Sci* 977: 183–195, 2002.
26. **Komine H, Sugawara J, Hayashi K, Yoshizawa M, Yokoi T.** Regular endurance exercise in young men increases arterial baroreflex sensitivity through neural alteration of baroreflex arc. *J Appl Physiol* 106: 1499–1505, 2009.
27. **La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ.** Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 351: 478–484, 1998.
28. **Levine BD.** Regulation of central blood volume and cardiac filling in endurance athletes: the Frank-Starling mechanism as a determinant of orthostatic tolerance. *Med Sci Sports Exerc* 25: 727–732, 1993.
29. **Lind-Holst M, Cotter JD, Helge JW, Boushel R, Augustesen H, Van Lieshout JJ, Pott FC.** Cerebral autoregulation dynamics in endurance-trained individuals. *J Appl Physiol* 110: 1327–1333, 2011.
30. **Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, Reneman RS, Hoeks AP, Hofman A, Witteman JC.** Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. *J Hypertens* 25: 1421–1426, 2007.
31. **Monahan KD.** Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol* 293: R3–R12, 2007.
32. **Monahan KD, Dinenno FA, Tanaka H, Clevenger CM, DeSouza CA, Seals DR.** Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men. *J Physiol* 529 *Pt* 1: 263–271, 2000.
33. **Motoyama M, Sunami Y, Kinoshita F, Kiyonaga A, Tanaka H, Shindo M, Irie T, Urata H, Sasaki J, Arakawa K.** Blood pressure lowering effect of low intensity aerobic training in elderly hypertensive patients. *Med Sci Sports Exerc* 30: 818–823, 1998.
34. **Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR.** Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke* 25: 793–797, 1994.
35. **Ogoh S, Ainslie PN.** Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol* 107: 1370–1380, 2009.
36. **Ogoh S, Dalsgaard MK, Yoshiga CC, Dawson EA, Keller DM, Raven PB, Secher NH.** Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J Physiol Heart Circ Physiol* 288: H1461–H1467, 2005.
37. **Ogoh S, Fadel PJ, Zhang R, Selmer C, Jans O, Secher NH, Raven PB.** Middle cerebral artery flow velocity and pulse pressure during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 288: H1526–H1531, 2005.
38. **Okazaki K, Iwasaki K, Prasad A, Palmer MD, Martini ER, Fu Q, Arbab-Zadeh A, Zhang R, Levine BD.** Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors. *J Appl Physiol* 99: 1041–1049, 2005.
39. **Panerai RB, White RP, Markus HS, Evans DH.** Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. *Stroke* 29: 2341–2346, 1998.
40. **Parati G, Frattola A, Di Rienzo M, Castiglioni P, Pedotti A, Mancia G.** Effects of aging on 24-h dynamic baroreceptor control of heart rate in ambulant subjects. *Am J Physiol Heart Circ Physiol* 268: H1606–H1612, 1995.
41. **Raczak G, Daniłowicz Szymanowicz L, Kobuszewska-Chwirot M, Ratkowski W, Figura-Chmielewska M, Szwoch M.** Long-term exercise training improves autonomic nervous system profile in professional runners. *Kardiol Pol* 64: 135–140; discussion 141–132, 2006.
42. **Robinson S.** Experimental studies of physical fitness in relation to age. *Eur J Appl Physiol Occup Physiol* 10: 251–323, 1938.
43. **Robinson TG, James M, Youde J, Panerai R, Potter J.** Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke* 28: 1671–1676, 1997.
44. **Sammons EL, Samani NJ, Smith SM, Rathbone WE, Bentley S, Potter JF, Panerai RB.** Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation. *J Appl Physiol* 103: 369–375, 2007.
45. **Smith ML, Hudson DL, Graitzer HM, Raven PB.** Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* 21: 40–44, 1989.

46. **Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR.** Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 102: 1270–1275, 2000.
47. **Thomas SN, Schroeder T, Secher NH, Mitchell JH.** Cerebral blood flow during submaximal and maximal dynamic exercise in humans. *J Appl Physiol* 67: 744–748, 1989.
48. **Tsai JC, Chang WY, Kao CC, Lu MS, Chen YJ, Chan P.** Beneficial effect on blood pressure and lipid profile by programmed exercise training in Taiwanese patients with mild hypertension. *Clin Exp Hypertens* 24: 315–324, 2002.
49. **Tsai JC, Yang HY, Wang WH, Hsieh MH, Chen PT, Kao CC, Kao PF, Wang CH, Chan P.** The beneficial effect of regular endurance exercise training on blood pressure and quality of life in patients with hypertension. *Clin Exp Hypertens* 26: 255–265, 2004.
50. **Tzeng YC, Lucas SJ, Atkinson G, Willie CK, Ainslie PN.** Fundamental relationships between arterial baroreflex sensitivity and dynamic cerebral autoregulation in humans. *J Appl Physiol* 108: 1162–1168, 2010.
51. **van Beek AH, Claassen JA, Rikkert MG, Jansen RW.** Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab* 28: 1071–1085, 2008.
52. **van Beek AH, Olde Rikkert MG, Pasman JW, Hopman MT, Claassen JA.** Dynamic cerebral autoregulation in the old using a repeated sit-stand maneuver. *Ultrasound Med Biol* 36: 192–201, 2010.
53. **Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME.** Initial orthostatic hypotension: review of a forgotten condition. *Clin Sci (Lond)* 112: 157–165, 2007.
54. **Zhang R, Claassen JA, Shibata S, Kilic S, Martin-Cook K, Diaz-Arrastia R, Levine BD.** Arterial-cardiac baroreflex function: insights from repeated squat-stand maneuvers. *Am J Physiol Regul Integr Comp Physiol* 297: R116–R123, 2009.
55. **Zhang R, Zuckerman JH, Giller CA, Levine BD.** Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol Heart Circ Physiol* 274: H233–H241, 1998.
56. **Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, Levine BD.** Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation* 106: 1814–1820, 2002.
57. **Zhu YS, Parker R, Tseng BY, Van Erkelens A, Coles G, Brunk E, Armstrong K, Rodrigue K, Kennedy K, Park D, Zhang R.** Exercise training decreases arterial stiffness and improves brain perfusion in sedentary elderly women (Abstract). *Circulation* 124: A16151, 2011.