

Physically Active Lifestyle Enhances Vagal-Cardiac Function but Not Central Autonomic Neural Interaction in Elderly Humans

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The cause of the age-related impairment of arterial baroreflex function remains ill-defined; moreover, it is unknown whether this impairment results from aging per se or from an inactive lifestyle associated with aging. In this study, we sought to: 1) determine whether elderly individuals who maintained an active lifestyle had an enhanced carotid baroreflex function as compared with their sedentary counterparts; and 2) determine whether this difference was due in part to altered function of the arterial baroreceptor and/or altered central modulation. Eight healthy, sedentary (SED, 68 ± 2 yr) and eight physically active (ACT, 68 ± 1 yr) elderly men with peak O_2 consumption 25.5 ± 1.2 vs 35.7 ± 2.4 ml/min/kg ($P < 0.01$), respectively, were assessed with carotid baroreceptor (CBR) function using 5s pulses of neck pressure or suction (ranging from +40 to -80 Torr) delivered to the carotid sinus region at rest and during lower body negative pressure (LBNP) of -15 and -40 Torr. Changes in heart rate (HR) and mean arterial pressure (MAP) were assessed for CBR-HR and CBR-MAP gains, respectively. Overall CBR-HR gains in a range of ~120 mmHg of carotid sinus pressure were greater ($P < 0.01$) in ACT than SED at rest and during LBNP. The derived peak CBR-HR slopes between ACT and SED at rest were -0.32 ± 0.07 vs -0.11 ± 0.02 bpm/mmHg ($P = 0.007$), respectively. However, there was no statistical difference ($P = 0.37$) in CBR-MAP gains between the groups. Neither CBR-MAP ($P = 0.08$) nor CBR-HR ($P = 0.41$) gain was

augmented by LBNP in the elderly. **Conclusion:** Active lifestyle enhances the CBR-HR reflex sensitivity as a result of the improved vagal-cardiac function in elderly people. Aging is associated with an absence of central autonomic interaction in the control of blood pressure regardless of physical fitness. *Exp Biol Med* 233:209–218, 2008

Key words: aging; arterial baroreflex gain; carotid sinus pressure; central autonomic dysfunction; lower body negative pressure

Introduction

Mounting evidence indicates that healthy aging is associated with a diminished arterial baroreflex control of heart rate (HR) and an increased incidence of autonomic dysfunction. Furthermore, it is apparent that a sedentary lifestyle, or chronic physical inactivity, appears to be a major factor involved in the diminished arterial baroreflex function of the elderly (11, 24, 25). The underlying evidence supporting this contention is that the responsiveness of the arterial baroreflex control of HR or R-R interval (RRI) was enhanced in physically active (ACT) older people when compared to their sedentary (SED) counterparts (11), or in a group of SED older adults following a period of regularly performed aerobic exercise training (24, 25). Thus it is an established tenet that a physically active lifestyle is essential to prevent the diminished arterial baroreflex control of the HR in older adults. Nonetheless, it remains elusive as to whether the aerobic exercise training related enhancement of the sensitivity of the arterial baroreflex control of the HR of the elderly is also manifest in the arterial baroreflex control of the vasculature or arterial blood pressure (ABP). Therefore, one aim of this study was to test the hypothesis that there were differences in the carotid arterial baroreflex control of both ABP and HR between SED and ACT elderly adults.

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Table 1. Subjects' Physical and Physiological Characteristics^a

Variables	Sedentary	Active	<i>P</i> value ^b
Age (yr)	67.5 ± 1.9	68.0 ± 1.3	0.835
Weight (kg)	83.9 ± 6.9	79.9 ± 3.3	0.606
Height (cm)	173 ± 3	178 ± 2	0.190
BMI (unit)	27.9 ± 1.5	25.4 ± 1.3	0.231
VO _{2peak} (ml/min/kg)	25.2 ± 1.2	35.7 ± 2.4	0.001
HR (bpm)	62 ± 3	53 ± 2	0.031
SV (ml)	47.8 ± 3.6	71.6 ± 10.2	0.056
TI (Ohm)	48.3 ± 3.4	44.2 ± 3.8	0.433
CO (L/min)	2.93 ± 0.20	3.68 ± 0.48	0.167
SBP (mmHg)	128 ± 4	117 ± 4	0.051
DBP (mmHg)	70 ± 5	64 ± 3	0.334
MAP (mmHg)	89 ± 4	82 ± 3	0.140
PP (mmHg)	58 ± 5	52 ± 3	0.298
TPR (unit)	32.1 ± 3.9	24.7 ± 2.9	0.155
FBF (ml/min/100cc)	5.08 ± 0.72	4.10 ± 0.56	0.300
FVR (unit)	19.48 ± 1.99	22.91 ± 3.44	0.404

^a BMI, body mass index; VO_{2peak}, peak O₂ uptake; HR, heart rate; SV, stroke volume; TI, thoracic impedance; CO, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; TPR, total peripheral resistance; FBF, forearm blood flow; FVR, forearm vascular resistance.

^b *P* value is the outcome of t-test with two independent samples. N = 8 in each subject group.

It has been found in young adults that the carotid baroreflex control of HR or RRI (33, 35, 40), ABP (33, 40), vasoconstriction (51), and muscle sympathetic nerve activity (12) is augmented during lower body negative pressure (LBNP) elicited reductions in central blood volume or central hypovolemia. This enhanced arterial baroreflex sensitivity during central hypovolemia associated with the simulated orthostasis appears to be an important physiologic mechanism in defending against orthostatic hypotension, or syncope. However, the facilitatory interaction between carotid baroreflex responsiveness and decreases in central blood volume in healthy older adults appears to be absent (40). Based upon the recent evidence identifying the beneficial effects of aerobic exercise training on the maintenance of autonomic function and vascular function (8, 9, 11, 24, 25, 31, 42, 47) and on the alterations in central neural control of the circulation (16, 26), we hypothesized that the interaction of the carotid baroreflex control of HR and ABP with cardiopulmonary baroreceptor would be impaired in SED and preserved or improved in ACT elderly subjects as compared with their SED counterparts.

Therefore, in a cross-sectionally designed experiment we investigated the effect of a physically active lifestyle on the changes in the carotid baroreflex function as well as its interaction with unloading of the cardiopulmonary baroreceptor in healthy elderly adults. Graded positive (+20 and +40 Torr) and negative (−20, −40, −60, and −80 Torr) pressures were briefly (5 sec) delivered to the carotid sinus region to elicit open-loop reflex control of HR and mean arterial pressure (MAP) to changes of carotid sinus transmural pressures. Furthermore, the carotid baroreflex control of HR and MAP was superimposed on central hypovolemia during mild to moderate LBNP of −15 and −40 Torr to

assess the impact of physical fitness on the interaction of carotid baroreceptor (CBR) with decreases in central blood volume of the elderly.

Methods

Subjects. Eight healthy, average fit SED and 8 high fit ACT elderly volunteer men (see Table 1 for the physical characteristics) provided written consent to participate in the study. The study was approved by the Institutional Review Board for the Protection of Human Subjects at UNT Health Science Center at Fort Worth. All subjects passed a physical examination and stress test prior to being enrolled in the study. Each subject was clinically confirmed to be free of cardiovascular, metabolic, renal, or pulmonary diseases and symptoms. Physical fitness was determined by measurement of the subject's peak oxygen uptake (VO_{2peak}) using Vista VO₂ Lab (Vacumed, Ventura, CA) during cycling on a stationary bicycle. Physical activity history was obtained from the subjects' self-report on their medical history questionnaire. All ACT elderly subjects had been continuously engaged in regular aerobic exercise ≥60 minutes/day ≥4 days/week each year for a period of the past 15 consecutive years or more; whereas SED elderly subjects had not regularly participated in physical training or activities. Before the experimental testing, all subjects had an orientation session to familiarize them with the experimental procedures and measurements to be used in the study.

Measurements. During the experiment, the subject's HR was monitored from a standard lead of the electrocardiogram. Radial arterial blood pressure (ABP) was measured using a tonometer (Model 7000 Tonometer Colin, San Antonio, TX). We have previously validated this method with directly measured ABP from an intra-radial

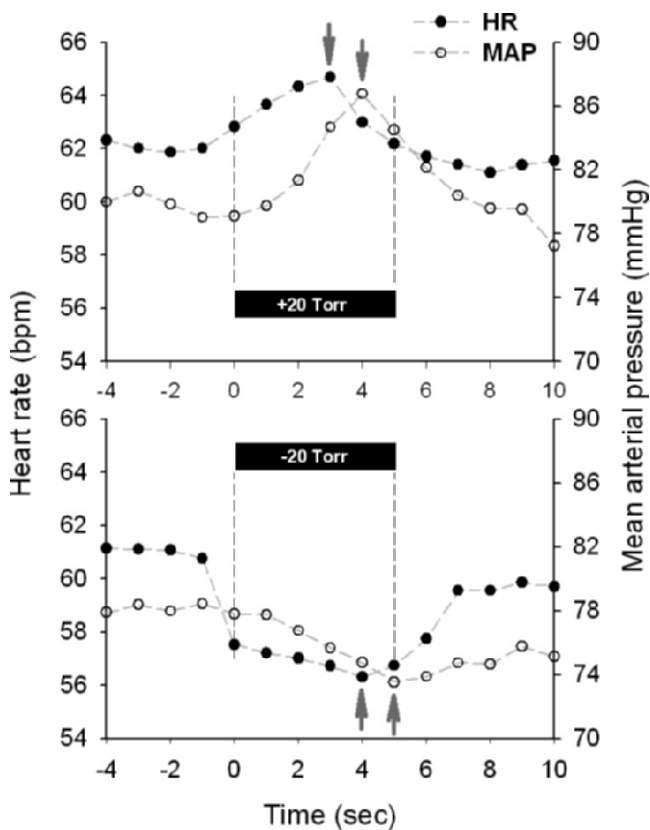


Figure 1. Heart rate (HR) and mean arterial pressure (MAP) responses to +20 Torr neck pressure (top panel) and -20 Torr neck suction (bottom panel) in one representative subject. Arrows indicate their peak responses to neck chamber pressures. Solid bar denotes the duration of the application of neck chamber pressure.

arterial catheter and found it to be a reliable and accurate non-invasive measurement of ABP (52). Thoracic impedance (TI) was monitored by four tetra polar electrodes (18), 3/4 inch wide Mylar tape strips, placed around the neck and lower chest (EBI100C, BIOPAC, Santa Barbara, CA). Previous data have confirmed that a change in the bio-impedance is a reliable index of changes in central blood volume (4, 32) or stroke volume (5, 28, 49). Forearm blood flow (FBF) was measured using a double strand mercury-in-Silastic strain gauge (Hokanson, Bellevue, WA) (40). All hemodynamic measurements were interfaced to a computer and were digitized on-line at 200 Hz. Total peripheral resistance (TPR) and forearm vascular resistance (FVR) were calculated off-line from the ratio of MAP to cardiac output (CO) and MAP to FBF, respectively.

Carotid baroreflex function was assessed using a method modified by Potts et al (35, 36). Five-sec pulses of neck pressure (+40 and +20 Torr) and suction (-20, -40, -60, and -80 Torr) were delivered in random order to a malleable lead chamber (6) that encompassed the carotid sinus region of the subject's anterior portion of the neck. The neck pressure or suction was delivered during quiet supine rest and during LBNP of -15 and -40 Torr when the subject held their breath at the end of normal expiration. The duration and

timing of delivery of neck chamber pressure was controlled by a PC computer loaded with custom-made software as described previously (33). Brief (5s) neck pressure and suction as applied in the present study selectively elicit the CBR responses with minimal or no influence from aortic arterial baroreceptor (15, 29, 35, 36). Changes in carotid sinus pressure (CSP) were estimated from the difference between the baseline MAP and the neck chamber pressure delivered. The ratio of the peak responses of HR and MAP to the changes in CSP during neck pressure and suction were identified and calculated for the gain (or sensitivity) of CBR control of cardiac (i.e., $\Delta\text{HR}/\Delta\text{CSP}$) and ABP or vasomotor (i.e., $\Delta\text{MAP}/\Delta\text{CSP}$) responses, respectively (Fig. 1).

Procedure. The experiment was carried out with the subject supine and the lower body supported in an air-tight LBNP box at a room temperature of 24°C–25°C. After 20 minutes of supine rest, each subject's baseline HR and ABP data were continuously recorded for 6 min. Following the collection of the control cardiovascular data, graded neck pressure and suction was delivered in random order to estimate the CBR responsiveness. Each neck pressure and suction was repeated at least 3 times separated by 60 sec between each trial to enable the recovery of HR and MAP from the preceding neck pressure or suction stimulus. After assessment of the control CBR function, LBNP was stabilized at -15 Torr for ~2 min prior to the data collection. The graded neck pressure and suction protocol was applied again during the sustained LBNP of -15 Torr followed by application of -40 Torr with each grade neck pressure (+40 and +20 Torr) and suction (-20, -40, -60, and -80 Torr) repeated ≥ 3 times. However, LBNP of -40 Torr was interrupted for ~5 min after completion of 3 graded neck pressure and/or suction to prevent the subject from experiencing orthostatic intolerance or pre-syncope. Subsequently, -40 Torr LBNP was resumed and application of another remained 3 graded neck pressure and/or suction was completed during sustained LBNP of -40 Torr. After recovery from the assessment of the carotid baroreflex function, SV and FBF at rest and during LBNP were measured without application of neck pressure or suction. The measurement of SV was continuously monitored; meanwhile 4 to 5 FBF readings were collected within 2 minutes after a wrist cuff was inflated to ~200 mmHg for ≥ 45 s under the resting control condition and during graded LBNP, respectively.

Data Analyses. The gain (or sensitivity) of CBR-HR and CBR-MAP was calculated from $\Delta\text{HR}/\Delta\text{CSP}$ and $\Delta\text{MAP}/\Delta\text{CSP}$ at each neck pressure and suction, respectively. In addition, group data of mean HR and MAP were plotted against the estimated carotid sinus pressure at graded neck pressure and suction using logistical modeling technique (33, 35, 36). The peak slopes (i.e., the maximal gains) of the two fitness groups were derived from the group curves because not all individual data fit to sigmoid function curves.

Difference in baseline data between the groups was determined by t-test procedure with two-independent-

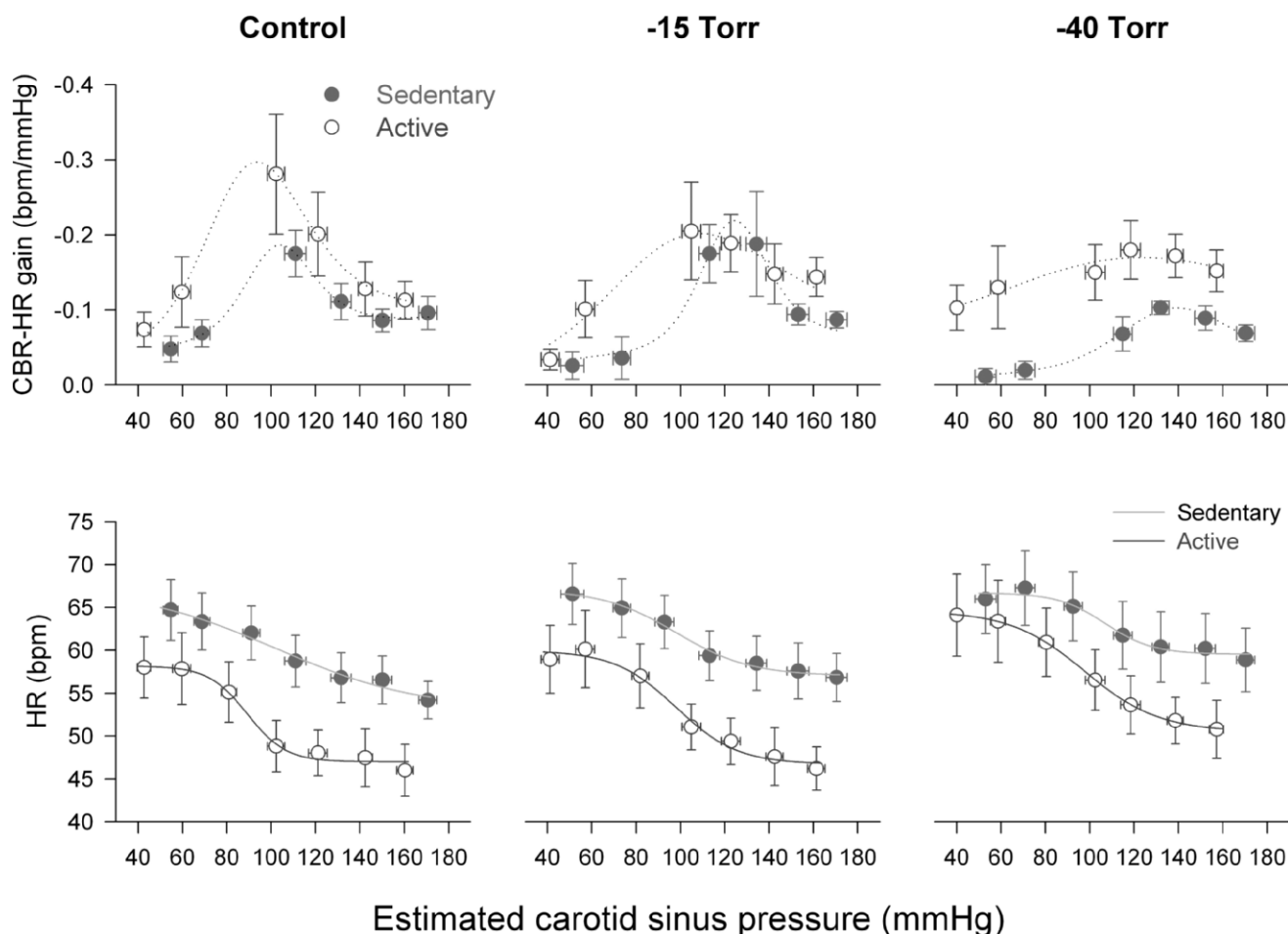


Figure 2. Top panels summarize the gain (i.e., sensitivity) of the carotid baroreflex control of heart rate (CBR-HR gain) at various carotid sinus transmural pressures elicited by graded neck pressure (+40 and +20 Torr) and suction (−20, −40, −60, and −80 Torr) under the supine resting control condition and during lower body negative pressure (LBNP) of −15 and −40 Torr. The CBR-HR gains are consistently greater ($P < 0.01$) in the physically active (open circle) than sedentary (closed circle) group. With stratification of LBPN, ANOVA P value is 0.011, 0.14, and 0.001 at the control, −15, and −40 Torr LBPN, respectively (top panels). However, LBPN factor has no significant influence on the CBR-HR gains ($P = 0.41$). Bottom panels illustrate the relationship between group heart rate (HR) and estimated carotid sinus pressure during graded application of neck chamber pressures. The derived peak slopes (i.e., maximal gains) between the sedentary vs physically active groups are -0.110 ± 0.024 vs -0.320 ± 0.074 bpm/mmHg ($P = 0.0066$), -0.150 ± 0.027 vs -0.240 ± 0.069 bpm/mmHg ($P = 0.166$), and -0.166 ± 0.060 vs -0.210 ± 0.006 bpm/mmHg ($P = 0.46$) at rest and during LBPN of −15 and −40 Torr, respectively.

samples analysis. Three-way analysis of variance (ANOVA) was applied to determine the effects of fitness, LBPN and positive (neck pressure) or negative (neck suction) neck chamber pressure on the gains of CBR-HR and CBR-MAP with repeated measurements, respectively. Changes in cardiovascular variables during LBPN were compared between the two fitness groups using two-way ANOVA. Post-hoc analysis ANOVA with Scheffe's option was applied when the major factor reached a significant difference, i.e., when P value was ≤ 0.05 . Data were reported as group mean and the mean of standard error (SE). Software package of Statistic Analysis System (Cary, NC) was applied for data treatment and analysis.

Results

At supine resting (i.e., control) condition, HR was lower ($P = 0.031$) and SV was greater ($P = 0.056$) in ACT

than SED elderly men (Table 1). The CBR-HR gains within a range of ~ 120 mmHg of the changes in carotid sinus transmural pressure were significantly ($P < 0.01$) greater in ACT Subjects (Figure 2, top panel). Comparison across LBPN indicates that the group differences in the CBR-HR gains remained statistically significant during the control condition ($P = 0.011$) and during −40 Torr LBPN ($P = 0.001$), but not during −15 Torr LBPN ($P = 0.14$). The derived peak slopes (i.e., maximal gains) from the group data were smaller in SED than ACT groups, i.e., -0.110 ± 0.024 vs -0.320 ± 0.074 bpm/mmHg ($P = 0.007$) at rest, but not significantly different during LBPN of −15 (-0.150 ± 0.027 vs -0.240 ± 0.069 bpm/mmHg, $P = 0.166$) or −40 Torr (-0.166 ± 0.060 vs -0.210 ± 0.006 bpm/mmHg, $P = 0.459$), respectively (Fig. 2, bottom panel). The LBPN factor on the CBR-HR reflex function did not show a significance ($P = 0.41$) in these elderly subjects.

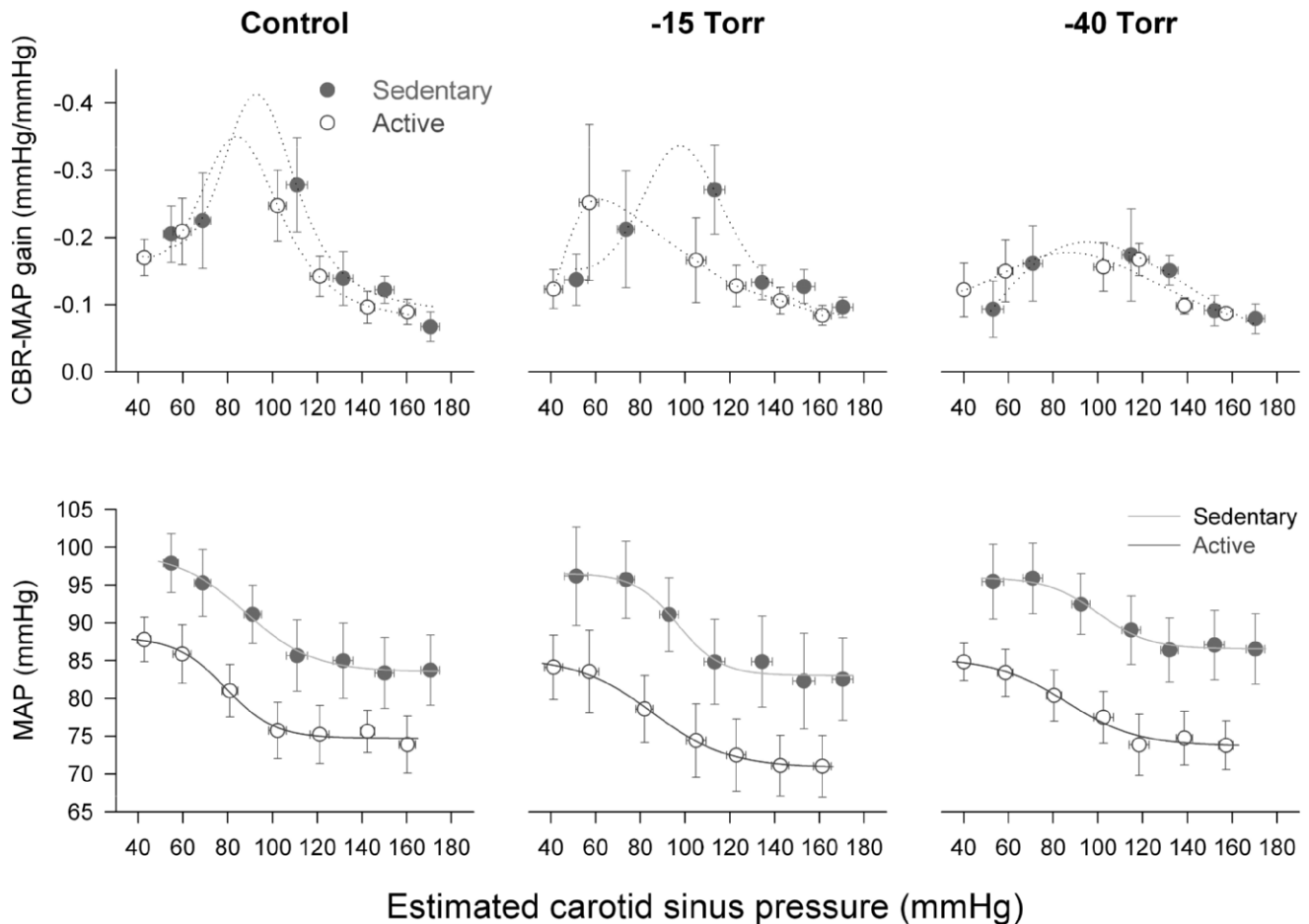


Figure 3. Top panels summarize the gain (i.e., sensitivity) of the carotid baroreflex control of mean arterial pressure (CBR-MAP gain) at various carotid sinus transmural pressures elicited by graded neck pressure (+40 and +20 Torr) and suction (−20, −40, −60, and −80 Torr) under the supine resting control condition and during lower body negative pressure (LBNP) of −15 and −40 Torr. Fitness factor ($P = 0.37$) has no significant influence on the CBR-MAP gains and LBNP factor ($P = 0.08$) does not facilitatively augment the CBR-MAP gains. Bottom panels illustrate the relationship between group mean arterial pressure (MAP) and estimated carotid sinus pressure during graded application of neck chamber pressures at rest and during LBNP. The derived peak slopes (i.e., maximal gains) between the sedentary vs physically active groups are -0.259 ± 0.083 vs -0.306 ± 0.097 mmHg ($P = 0.713$), -0.307 ± 0.110 vs -0.188 ± 0.031 mmHg/mmHg ($P = 0.300$), and -0.209 ± 0.068 vs -0.182 ± 0.077 mmHg/mmHg ($P = 0.793$) at rest or during LBNP of −15 and −40 Torr, respectively.

The CBR-MAP gains were not significantly influenced by the fitness factor ($P = 0.37$). Furthermore, the LBNP factor did not augment ($P = 0.08$) the CBR-MAP gains of SED and ACT subjects as well (Fig. 3).

There was a significant difference between the gains of the tachycardiac and bradycardiac responses elicited by +20 Torr and −20 Torr neck chamber pressures ($P = 0.003$) in both ACT and SED subjects (see Table 2), indicating that the optimal operating point (or *set-point*) of the CBR-HR gain was located within the bradycardiac response side rather than in tachycardiac response side in these elderly subjects (Fig. 2, top panel). However, the CBR-MAP gains at −20 Torr and +20 Torr of neck chamber pressures were not significantly different ($P = 0.78$), see Table 2 and Figure 3, top panel. During the hypertensive stimulus (or depressor response) elicited by −20 Torr neck chamber pressure, the magnitude of relative changes in HR vs MAP (i.e., $\% \Delta \text{HR}$ vs

$\% \Delta \text{MAP}$) was not significantly different in both the groups at rest or during LBNP (Fig. 4). During the hypotensive stimulus (or pressor response) elicited by +20 Torr neck chamber pressure, the magnitude of $\% \Delta \text{HR}$ vs $\% \Delta \text{MAP}$ ($P = \text{n.s.}$) remained similar in the physically active group. However, the magnitude of $\% \Delta \text{HR}$ in the sedentary group during the hypertensive stimulus was less compared to that of $\% \Delta \text{MAP}$ at rest ($P = 0.099$) or during LBNP of −15 ($P = 0.044$) and −40 ($P = 0.049$) Torr, respectively.

During LBNP of −15 and −40 Torr CO and SV were significantly decreased in both elderly groups, suggesting a reduction in venous return or central hypovolemia (see Table 3). The decreases in CO appeared to be compensated for by vasoconstriction, as evidenced by a significant increase in TPR and FVR (Table 3). Therefore, MAP was maintained despite the reduction in CO or central hypovolemia. The LBNP elicited increases in TI indicated

Table 2. Comparison of the Carotid Baroreflex Gains During Positive and Negative Neck Chamber Pressures^a

		Control		−15 Torr		−40 Torr	
		Sedentary	Active	Sedentary	Active	Sedentary	Active
CBR-HR gain (bpm/mmHg)	+20 Torr	−0.070	−0.124	−0.036	−0.101	−0.020	−0.130
		±0.018	±0.046	±0.028	±0.038	±0.012	±0.054
	−20 Torr	−0.175	−0.282	−0.175	−0.205	−0.068	−0.150
		±0.003	±0.079	±0.039	±0.064	±0.022	±0.036
The effect of fitness: $P = 0.0046$; the effect of LBNP: $P = 0.1032$; and the effect of neck chamber pressure: $P = 0.0003$.							
		Control		−15 Torr		−40 Torr	
		Sedentary	Active	Sedentary	Active	Sedentary	Active
CBR-MAP gain (mmHg/mmHg)	+20 Torr	−0.225	−0.209	−0.212	−0.252	−0.161	−0.150
		±0.071	±0.049	±0.087	±0.116	±0.056	±0.046
	−20 Torr	−0.278	−0.247	−0.271	−0.166	−0.174	−0.136
		±0.070	±0.053	±0.066	±0.063	±0.069	±0.036
The effect of fitness: $P = 0.4262$; the effect of LBNP: $P = 0.1455$; and the effect of neck chamber pressure: $P = 0.7838$.							

^a The gains (i.e., sensitivity) of carotid baroreflex control of heart rate (CBR-HR) and mean arterial pressure (CBR-MAP) are summarized from the data in Figures 2 and 3 (top panels), respectively.

a peripheral pooling, or central hypovolemia. This increase in TI appeared to be greater in ACT than SED (Table 3). However, the magnitude of increases in TPR or FVR in terms of the changes in SV or TI was not statistically different between the two groups (Table 4).

Discussion

The present study provides three major novel findings. First, the carotid baroreflex control of HR was more sensitive in ACT than SED elderly men during a broad range of hypotensive and hypertensive changes in carotid

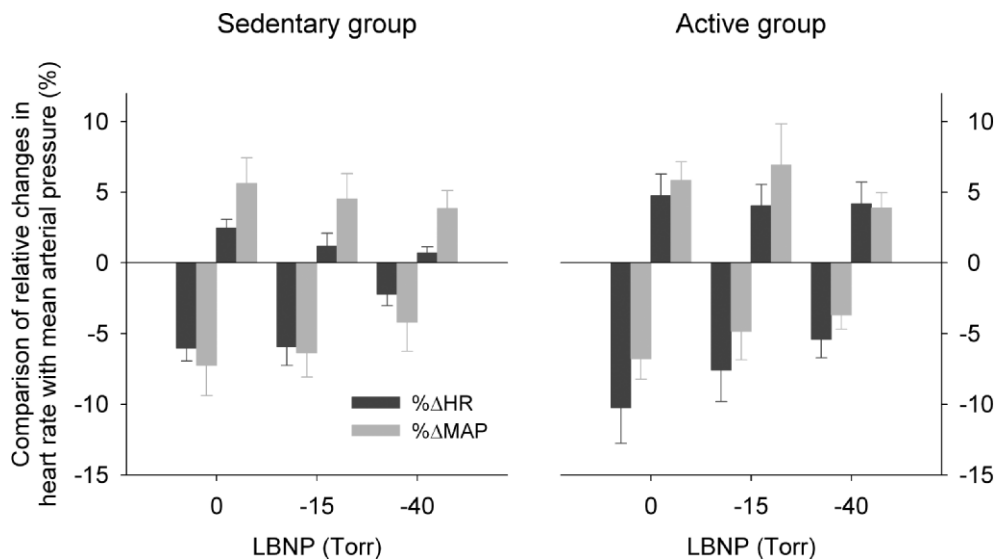


Figure 4. compares the magnitude of relative changes in heart rate (%ΔHR) and mean arterial pressure (%ΔMAP) during the pressor and depressor responses (or hypotensive and hypertensive stimuli) elicited by positive (+20 Torr neck pressure) and negative (-20 Torr neck suction) neck chamber pressures, respectively, in the groups of sedentary (left panel) and physically active (right panel) older subjects at rest and during lower body negative pressure (LBNP) of -15 and -40 Torr. Neck pressure of +20 Torr elicits tachycardiac-pressor responses as indicated by increases in HR and MAP, whereas neck suction of -20 Torr elicited bradycardiac-depressor responses as indicated by decreases in HR and MAP. The magnitude of %ΔHR (dark bar) is significantly greater in the physically active than sedentary group during both neck pressure ($P = 0.005$) and suction ($P = 0.032$). However, this fitness factor on %ΔMAP (gray bar) is not significant during either neck pressure ($P = 0.62$) or suction ($P = 0.55$). During the depressor response (i.e., hypertensive stimulus) elicited by neck suction of -20 Torr, decrease in MAP appears to be more dependent on a bradycardiac response (or vasodilator response appears to be less dominant) in both the sedentary and physically active groups, as the difference in the magnitude of decreases in HR and MAP (i.e., %ΔHR vs %ΔMAP) was not statistically different in both subject groups at rest and during LBNP. During the pressor response (i.e., hypotensive stimulus) elicited by neck pressure of +20 Torr, increase in MAP remains to be more dependent on HR response in the physically active group (i.e., no significant difference between %ΔHR and %ΔMAP), whereas this tachycardiac contribution becomes less dominant in the sedentary group (i.e., %ΔHR vs %ΔMAP: $P = 0.099$, 0.044 , and 0.049 at rest and during LBNP -15 and -40 Torr, respectively).

Table 3. Cardiovascular Response to Lower Body Negative Pressure (LBNP)

		Sedentary		Physically active		<i>P</i> value ^a	
		–15 Torr	–40 Torr	–15 Torr	–40 Torr	LBNP	Fitness
Δ HR	bpm	+1.8 ± 0.5	+4.1 ± 1.0 ^b	+2.5 ± 1.0	+8.2 ± 0.8 ^{b,c}	0.001	0.012
	%	+3.0 ± 1.0	+6.5 ± 1.5 ^b	+4.6 ± 1.9	+15.5 ± 1.1 ^{b,c}	0.001	0.001
Δ SV	ml	–4.7 ± 1.0 ^b	–12.0 ± 1.6 ^b	–9.1 ± 2.2 ^b	–21.5 ± 2.9 ^{b,c}	0.001	0.003
	%	–9.6 ± 1.7 ^b	–25.1 ± 2.5 ^b	–12.4 ± 2.2 ^b	–31.2 ± 3.7 ^b	0.001	0.096
Δ TI	Ohm	+0.43 ± 0.10 ^b	+1.04 ± 0.22 ^b	+1.06 ± 0.29 ^b	+2.16 ± 0.53 ^b	0.014	0.012
	%	+0.8 ± 0.2 ^b	+2.2 ± 0.4 ^b	+2.2 ± 0.5 ^{b,c}	+4.6 ± 0.9 ^{b,c}	0.002	0.002
Δ CO	L/min	–0.21 ± 0.05 ^{b*}	–0.60 ± 0.09 ^b	–0.34 ± 0.13 ^b	–0.72 ± 0.14 ^b	0.001	0.25
	%	–7.0 ± 1.5 ^b	–20.4 ± 2.4 ^b	–8.2 ± 3.5 ^b	–20.6 ± 4.4 ^b	0.001	0.83
Δ TPR	PRU	+2.3 ± 0.8 ^b	+8.8 ± 1.9 ^b	+2.2 ± 1.0 ^b	+8.1 ± 2.7 ^b	0.001	0.80
	%	+8.8 ± 3.3 ^b	+28.0 ± 6.0 ^b	+10.5 ± 4.1 ^b	+30.1 ± 7.9 ^b	0.001	0.73
Δ MAP	mmHg	+0.7 ± 2.0	+0.8 ± 1.9	+0.4 ± 2.0	+0.7 ± 1.7	0.88	0.91
	%	+1.0 ± 2.6	+1.1 ± 2.3	+0.7 ± 2.3	+1.1 ± 2.1	0.83	0.95
Δ SBP	mmHg	–1.6 ± 1.6	–5.7 ± 2.7	–0.7 ± 2.2	–3.2 ± 2.1	0.037	0.41
	%	–1.2 ± 1.4	–4.2 ± 2.0	–0.4 ± 1.8	–2.4 ± 1.8	0.065	0.47
Δ DBP	mmHg	+1.8 ± 2.4	+4.4 ± 1.8	+0.9 ± 2.0	+2.6 ± 1.7	0.123	0.55
	%	+3.2 ± 3.9	+6.2 ± 2.8	+1.2 ± 2.9	+4.2 ± 2.7	0.126	0.57
Δ PP	mmHg	–3.4 ± 1.4 ^b	–9.7 ± 1.9 ^b	–1.6 ± 1.0	–5.8 ± 1.6 ^b	0.001	0.062
	%	–5.9 ± 2.6	–15.6 ± 2.7 ^b	–3.2 ± 1.9	–11.1 ± 3.4 ^b	0.001	0.185
Δ FBF	ml/min/100cc	–0.73 ± 0.18 ^b	–1.06 ± 0.19 ^b	–0.83 ± 0.25 ^b	–1.04 ± 0.28 ^b	0.001	0.86
	%	–13.7 ± 2.8 ^b	–24.2 ± 5.2 ^b	–20.1 ± 4.6 ^b	–24.6 ± 5.2 ^b	0.001	0.45
Δ FVR	PRU	+3.6 ± 1.6 ^b	+8.4 ± 2.5 ^b	+6.9 ± 2.6 ^b	+9.0 ± 3.3 ^b	0.001	0.44
	%	+18.4 ± 6.4 ^b	+37.7 ± 9.9 ^b	+29.4 ± 8.9 ^b	+38.6 ± 9.7 ^b	0.001	0.50

^a *P* value indicates the outcome of two-way ANOVA.

^b and ^c denote a significant change and a significant difference between the groups, respectively. N = 8 in each subject group.

sinus pressure (~120 mmHg). However, the CBR-MAP gains were not statistically different between the groups. These data suggest that the alteration of the CBR function was more likely related to a change in the efferent to effector-organ arm of the baroreflex arc as a result of adaptation to habitual exercise in the elderly people. Second, neither the CBR-HR gain nor the CBR-MAP gain was increased by LBNP of –15 and –40 Torr in both fitness groups. The absence of a facilitative interaction between the CBR with unloading of the cardiopulmonary baroreceptors (or central hypovolemia) in the elderly indicates that an age-related alteration in the central autonomic neural integrative control of the vagal-cardiac reflex and the sympathetic-vasomotor reflex was present and was independent of differences in physical activity lifestyles. Third, in both SED and ACT elderly subjects under supine resting condition, the CBR-HR gains appeared to peak around neck suction of –20 Torr,

whereas the peak CBR-MAP gain was located between neck chamber pressures +20 Torr and –20 Torr. These data demonstrate that the circulatory homeostasis during hypotensive and hypertensive stimuli was equally protected by the carotid baroreceptor. However, the carotid baroreflex mediated tachycardiac response was less sensitive when compared to the bradycardiac response in the elderly subjects.

The mechanisms for the fitness-related difference among these elderly subjects appear to be related to an improved vagal-cardiac function resulting from the habitual exercise. It has become a prevailing view that the HR reflex response to changes in ABP is primarily mediated by the parasympathetic nervous system (7, 30) and is independent of the sympathetic nervous system's influence on the heart. The present study identified that chronic physical activity of elderly adults was associated with a resting bradycardia. This adaptive change in the vagal-cardiac function with

Table 4. Ratios of the Normalized Changes

		LBNP				<i>P</i> value	
		–15 Torr		–40 Torr		LBNP	Fitness
		Sedentary	Physically active	Sedentary	Physically active		
% Δ HR/% Δ SV		–0.3 ± 0.1	–0.7 ± 0.4	–0.3 ± 0.1	–0.6 ± 0.1	0.73	0.11
% Δ HR/% Δ TI		4.0 ± 1.3	3.0 ± 1.8	4.6 ± 1.5	4.2 ± 0.6	0.53	0.58
% Δ TPR/% Δ SV		–0.9 ± 0.3	–0.9 ± 0.4	–1.1 ± 0.2	–0.8 ± 0.2	0.82	0.71
% Δ TPR/% Δ TI		12.3 ± 5.7	6.9 ± 2.5	17.2 ± 4.8	7.1 ± 1.9	0.53	0.06
% Δ FVR/% Δ SV		–2.4 ± 0.8	–4.4 ± 1.9	–1.6 ± 0.4	–1.4 ± 0.4	0.09	0.42
% Δ FVR/% Δ TI		24.6 ± 6.7	22.1 ± 9.0	21.0 ± 8.1	10.0 ± 2.7	0.27	0.34

habitual exercise is consistent with an elevated parasympathetic neural activity or control (41, 43). In addition, arterial baroreflex control of HR was improved in the ACT subjects and was shown to contribute significantly to the circulatory homeostasis that occurred during both pressor and depressor responses elicited by hypotensive and hypertensive stimuli, respectively (Fig. 4).

Decrease in central arterial compliance has been related to a diminished baroreflex sensitivity associated with age (14, 24). Although baseline TPR was not statistically different between the groups, an estimated compliance of the aortic artery calculated from the ratio of SV to PP was greater in ACT than SED (1.38 ± 0.27 vs 0.83 ± 0.12 ml/mmHg, $P = 0.049$) elderly adults. Physiologically, more compliant conduit arteries would enable greater mechanical deformation per arterial pulse wave. These data confirm that an age-related decrease in central arterial compliance may be prevented through habitual exercise in the elderly. However, the CBR-MAP gain was not statistically different between SED and ACT elderly subjects. These findings suggest that the mechanical transmission of the neck pressure and suction stimuli was not a significant contributing factor (11), because any substantial mechanical change originating in the baroreceptor as a result of differences in physically activity lifestyles would have affected the vasomotor responsiveness. Furthermore, it has been reported that the impact of exercise training on baroreceptor-afferent nerve traffic activity in rats appeared to be minimal (38). Although muscle sympathetic nerve activity is elevated in exercise trained older adults, the responses of neurotransmitter or alpha-adrenergic receptor in terms of increases in blood plasma norepinephrine concentration or Δ MAP (i.e., the vasomotor responsiveness) during cold stress and isometric handgrip is similar between the trained and untrained older subjects (27). Collectively, these data suggest that chronic physical activity primarily enhances the parasympathetic control of the heart without changing the baroreceptor mediated sympathetic reflex control of vasomotion in the elderly.

Changes within the central nervous system associated with advanced age are characterized by a loss of neural integrative components or coupling in the neuronal networks (44). Although there is no documented study to elucidate the mechanism for an age-related change in central autonomic integration, it has been recognized that human cerebral atrophy in the healthy aging brain (3) involving loss of neurons in the autonomic nervous system (37) begins in the fifth to sixth decades of life with no significant clinical manifestation. It has been suggested that the age-related alteration in central autonomic interaction may be a result of chronic interaction of reactive oxygen species (including nitric oxide, superoxide, and peroxynitrite) on the neurons in the *cardiovascular center* during aging (2). A higher electrical resistance of some neurons in the nucleus tractus solitarius has been observed in the senescent rat (13). The cardiopulmonary baroreceptors exert a tonic inhibitory influence on the cardiovascular center (1, 10, 17, 22, 23, 34),

which includes the nucleus ambiguus and the dorsal vagal nucleus, i.e., the vagal-cardiac center (20, 45), as well as the nuclei in the rostral ventrolateral medulla and ventromedial medulla, i.e., the sympathetic-vasomotor center (19, 39, 45). Previous studies have indicated that the CBR responsiveness of young adults is augmented with the central hypovolemia elicited by LBNP (12, 33, 35, 40), which presumably removes the inhibitory influence of the cardiopulmonary baroreceptor. However, this facilitative interaction is absent in older adults (40). Data from the current study confirmed that the facilitative interaction arising from a decrease in central blood volume during mild to moderate LBNP with the carotid baroreflex function was absent in both ACT and SED elderly groups (Figs. 2 and 3). Since aging *per se* has no significant effect on the cardiopulmonary baroreflex sensitivity (40, 46), and since unloading of the cardiopulmonary baroreceptor during LBNP of -15 and -40 Torr elicited similar increases in FVR and TPR between the groups, we suggest that a possible mechanism responsible for lack of the interaction of CBR with the cardiopulmonary baroreceptor in the elderly people is likely related to an age-associated alteration in the central autonomic neural interaction. This interaction may involve the reflex circuits of the central interneurons, which are associated directly (19, 20, 45) or indirectly (19, 39, 45) with the second-order sensory (or baroreceptor) neurons in the medial or dorsomedial nucleus tractus solitarius, and provide the synapses for the sympathetic-vasomotor neurons and the preganglionic vagal motoneurons of the medulla (19, 39, 45). This postulation appears to be coincident with the finding that both the CBR-HR gains and the CBR-MAP gains are not sensitized or augmented by mild or moderate LBNP stimuli in the elderly with sedentary or physically active lifestyles.

The present study has some potentially important clinical and physiological implications. First, it confirms that the cardiovascular aging related vagal-cardiac dysfunction can be prevented or delayed in the elderly adults who maintain a physically active lifestyle. This physical fitness-related improvement in the vagal-cardiac function not only increases the safety margin for cardiac protection, but also appears to help maintain the cardiovascular homeostasis during orthostatic challenge by improving the CBR mediated HR response in the elderly people. This improved vagal-cardiac function is especially important to the elderly whose baroreflex function is unable to be sensitized during the LBNP simulated orthostatic stress. Second, a central autonomic dysfunction, as indicated by the absent interaction between the carotid baroreflex and the cardiopulmonary baroreceptors, develops during healthy aging regardless of lifestyle or physical fitness of the elderly. This central autonomic neurodegenerative alteration in the modulation of the cardiovascular reflex function may also explain, in part, an increase in the susceptibility of the elderly to orthostatic intolerance.

A possible study limitation that may confound interpretation of the data includes the use of a cross-sectional comparison between SED and ACT groups and,

therefore, does not exclude genetic factors, which may potentially influence the arterial baroreflex function. Additionally, because of the experimental testing on healthy humans, we cannot anatomically determine vagal and sympathetic outflows (21) and pinpoint the exact *central* mechanism or location for the age-related lack of the interaction between the carotid baroreflex and the cardiopulmonary baroreceptor. Because the trend of the difference in the CBR-HR gains, or the non-difference in the CBR-MAP gains, were persistent between the two groups during graded LBNP (Figs. 2 and 3), we suggest that neither the CBR-afferent pathway nor the individual efferents to effector-organs were likely to be the significant factor responsible for the absence of the baroreflex interaction. Moreover, unloading of the cardiopulmonary baroreceptor mediated vasomotor response (including the vagal sensory fiber and the sympathetic-vasomotor response in the baroreflex pathway) was not different between younger and older individuals (40, 50) or between the elderly men with different levels of physical fitness. Taken together, these data appear to support the interpretation that an alteration may occur in the central autonomic interaction (involving both the interneurons in the central baroreflex pathway and the nuclei in the vagal-cardiac center and sympathetic-vasomotor center) of elderly people. Lastly, the application of mild LBNP (−15 Torr) with or without significant systemic hypotension may not be selectively limited to the unloading of the cardiopulmonary baroreceptor. A spill-over influence on the arterial baroreceptors during LBNP has been reported (48). However, steady-state LBNP of −15 and −40 Torr, with or without significant systemic hypotension or involvement of unloading of the arterial baroreceptors, appears to have no significant impact on the expected functional change in the CBR mediated HR and MAP reflex responsiveness in these elderly people.

In conclusion, the carotid baroreflex control of HR measured across a wide range of hypotensive and hypertensive changes in carotid sinus pressure is significantly more sensitive in physically active than sedentary elderly men. The underlying mechanism is primarily related to an improved vagal-cardiac function associated with habitual exercise. This improved function appears to help maintain the circulatory homeostasis during both depressor and pressor responses mediated by the rapid, open-loop carotid arterial baroreflex. How exercise training produces this effect remains to be determined. However, central autonomic integrative function appears to be absent in both healthy sedentary and physically active elderly men. This finding suggests a central autonomic dysfunction occurs during the normal healthy aging process, which may be unaffected by a change in lifestyle or aerobic fitness condition.

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