New Insight into the Mechanism of Cardiovascular Dysfunction in the Elderly: Transfer Function Analysis

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This study sought to test the hypothesis that alterations in the relationships between (i) mean arterial pressure (MAP) and heart rate (HR), (ii) cardiac output (CO) and MAP, and (iii) total peripheral resistance (TPR) and MAP variability contribute to the diminished dynamic control of cardiovascular function with advanced age. Six-minute hemodynamic data were continuously recorded in 11 elderly (70 ± 2 years) and 11 young (26 ± 1 year) healthy volunteers under supine resting condition and during lower body negative pressure–induced orthostatic challenge. The data were converted using fast Fourier transform, and the ratio of cross-spectra to auto-spectra between two signals (i.e., MAP-HR, CO-MAP, TPR-MAP) was computed for transfer function analysis. In the low-frequency ranges (LF; 0.04–0.14 Hz) and high-frequency ranges (0.15–0.30 Hz), the gain and coherence of the transfer function describing the relationship between MAP-HR signals were significantly greater in younger than in older adults. The phase degree was significantly >0 in both groups under all conditions, suggesting that the MAP variability preceded the HR variability. In contrast, the coherence between CO-MAP signals in both age groups was <0.5, indicating that the beat-to-beat MAP variability was not significantly related to the CO signals. However, the transfer function gain and coherence of TPR-MAP signals were significantly greater in the young group (coherence ≥0.5 in the LF range), suggesting a more effective dynamic vasomotor control. In conclusion, the oscillations in CO-MAP signals are not significantly synchronized or not related in a simply linear fashion in both age groups. The MAP variability is more related to the oscillation of TPR signals in the young group only. Advanced age not only diminishes MAP-HR transfer function gain, but also weakens its coherence. Thus, alterations in the relationship between MAP-HR variability and TPR-MAP variability may significantly contribute to the diminished dynamic control of cardiovascular function manifest in the elderly. Exp Biol Med 230:549–557, 2005

Key words: cardiac output variability; coherence; regional cerebral O_2 saturation; LBNP

Introduction

The arterial baroreflex plays a pivotal role in the rapid reflex circulatory adjustments to acute cardiovascular stresses (e.g., standing upright from a supine or sitting position). As a negative feedback control system, the reflex responds to beat-to-beat changes in arterial blood pressure (ABP) by reflexively altering parasympathetic and sympathetic outflow. These autonomic neural adjustments affect ABP by altering heart rate (HR), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) in accordance with the following relationship: ABP = CO × TPR, where CO = HR × SV. It has been previously established that the ability of the arterial baroreflex to make these adjustments and thus regulate ABP is diminished with aging (1). This may explain, in part, the hemodynamic instability induced by an acute cardiovascular stress, such as an orthostatic challenge, in older individuals (2, 3). However, the mechanisms that underlie the inability of the baroreflex to effectively regulate ABP with aging remain largely unknown.

The detection of discrete changes in autonomic function can be considerably enhanced by the use of power spectral analyses. For example, using this technique we have documented in previous studies (3, 4) that decreases in the vagally mediated baroreflex control of HR significantly contribute to reductions in ABP regulation in the elderly.

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These findings were recapitulated in young adults by blocking muscarinic cholinergic parasympathetic nerves (i.e., simulated cardiac vagal dysfunction; Ref. 3). Further, in young adults, vagal blockade not only diminished the gain of the transfer function describing the relationship between mean arterial pressure (MAP) and HR, but also weakened its coherence around the respiration frequency (3), a finding that has yet to be reported in the elderly.

The use of power spectral analysis has been extended to quantify other hemodynamic relationships germane to beat-to-beat hemodynamic control mediated by baroreflex function. For example, the use of lower-body negative pressure (LBNP) to simulate an orthostatic challenge decreases CO without reducing MAP indicative of compensatory increases in TPR (5). Although MAP is relatively well maintained under these conditions, its variability (established using frequency-domain analysis) is substantially augmented (3). Using power spectral analysis, it has been reported that this increase in ABP variability is closely associated with the oscillation of sympathetic nerve activity (6). Supporting this relationship, removal of sympathetic influence by ganglionic blockade substantially diminishes the variability in ABP (7). However, the variability between CO and MAP signals using transfer function analysis (8) has yet to be elucidated in any age group. Thus, it is currently not clear if the variability determining the relationship between CO and MAP signals or between TPR and MAP signals is altered with aging. The current study was the first documented attempt to assess whether dynamic control of the beat-to-beat MAP variability was oscillated with CO or TPR variability.

The purpose of this study was to identify the potential mechanisms of baroreflex dysfunction that affect the normal regulation of ABP in the elderly using power spectral analysis techniques. Specifically, frequency domain and transfer function analyses were used to quantify the relationships between (i) MAP and HR, (ii) CO and MAP, and (iii) TPR and MAP in response to a simulated orthostatic challenge in both healthy young and elderly individuals. Although a previous study (2) has assessed HR variability or ABP variability individually in different age groups, the current study sought to test the hypothesis that dynamic control of beat-to-beat HR variability and ABP variability was less effective with advanced age in terms of the transfer function coherence and gain between these signals, which was significantly related to the baroreflex dysfunction manifest in the elderly.

Materials and Methods

Subjects. Eleven healthy elderly volunteers (7 men and 4 women; age, 69.8 ± 1.5 years) and 11 young volunteers (9 men and 2 women; age, 26.4 ± 1.2 years) gave written consent to participate in this study, which was approved by the Institutional Review Board for the Protection of Human Subjects at the University of North Texas Health Science Center at Fort Worth. There was no statistical difference in mean body mass index (26.4 ± 1.2 kg/m^2 vs. 23.9 ± 0.9 kg/m^2), weight (74.9 ± 4.1 kg vs. 73.1 ± 4.1 kg), or height (1.69 ± 0.03 m vs. 1.74 ± 0.02 m) between elderly and young groups, respectively. Subjects were required to pass a physical examination before being enrolled in the study. None of them had cardiovascular, metabolic, renal, or pulmonary diseases or were taking alpha-blockers, beta-blockers, or ganglionic blockers. In addition, each young female volunteer submitted a negative pregnancy test before the experimentation and was tested during the proliferative phase or secretory phase of her menstrual cycle.

Measurements. During the experiment, the subjects' HRs were monitored by a standard lead of electrocardiogram. Their ABP was measured from the radial artery tonometer (Model 7000 Tonometer; Colin, San Antonio, TX). We have previously reported that the tonometry was a reliable and accurate method for noninvasive measurement of ABP and that the radial ABP measured from the tonometry was compatible with the reading from the intraradial arterial catheter (3), which appeared to be supported by other documented reports (9–11). Regional cerebral oxygenation (RcO_2) was determined by near-infrared spectroscopy with sensor placed on right side of the forehead (Model 4100 INVOS Cerebral Oximeter; Somanetics, Troy, MI). The rationale for including this measurement in the study was that RcO_2 was paralleled with the cerebral blood flow (12) and that monitor of RcO_2 would provide an extra safety measure for testing the hemodynamic changes of the subjects, especially in the elderly, during orthostatic challenge. Systemic arterial oxygenation (SaO_2) was monitored from a pulse oximeter (OXY100C; BIOPAC, Santa Barbara, CA). Thoracic impedance (TI) was monitored by four tetra polar electrodes (13) with three-quarter-inch–wide Mylar tape strips placed around the neck and lower chest (EBI100C; BIOPAC). Previous data have confirmed that a change in TI is a reliable index for a change in central blood volume (14, 15) or stroke volume (16–19). The repeatability and trending ability to assess changes in cardiac output (CO) using this method have been confirmed in our laboratory (3, 20) and by the others (18, 21) as well, which appeared to be acceptable for noninvasive, beat-to-beat continuous monitoring of SV and CO in human subjects. These measurements were continuously recorded by a computer and were digitized online at 400 Hz. In addition, using TI measurements, beat-to-beat stroke volume (SV) was calculated off-line from the equation:

$$SV = \rho \cdot (L^2/Z_0^2) \cdot T \cdot (dZ_{max}/dt)$$

where ρ is the resistivity of blood (147 ohms/cm, a constant), L is the length or distance (in cm) between the second and third electrodes, Z_0 is thoracic impedance (ohms), T is one third of the HR interval in terms of left ventricular ejection time (sec), and dZ_{max}/dt is the

magnitude of the largest impedance change during systole (ohms/sec). Subsequently, beat-to-beat CO was determined from the product of HR and SV. The TPR was calculated from the ratio of MAP to CO. Figure 1 represents these measurements from one elderly subject.

Protocol. After instrumentation, each subject rested for a minimum of 30 mins in the supine position with his or her lower body sealed in an LBNP box. Subsequently, 6 mins of baseline data were continuously collected. In a graded fashion, the LBNPs of −15, −30, and −50 torr

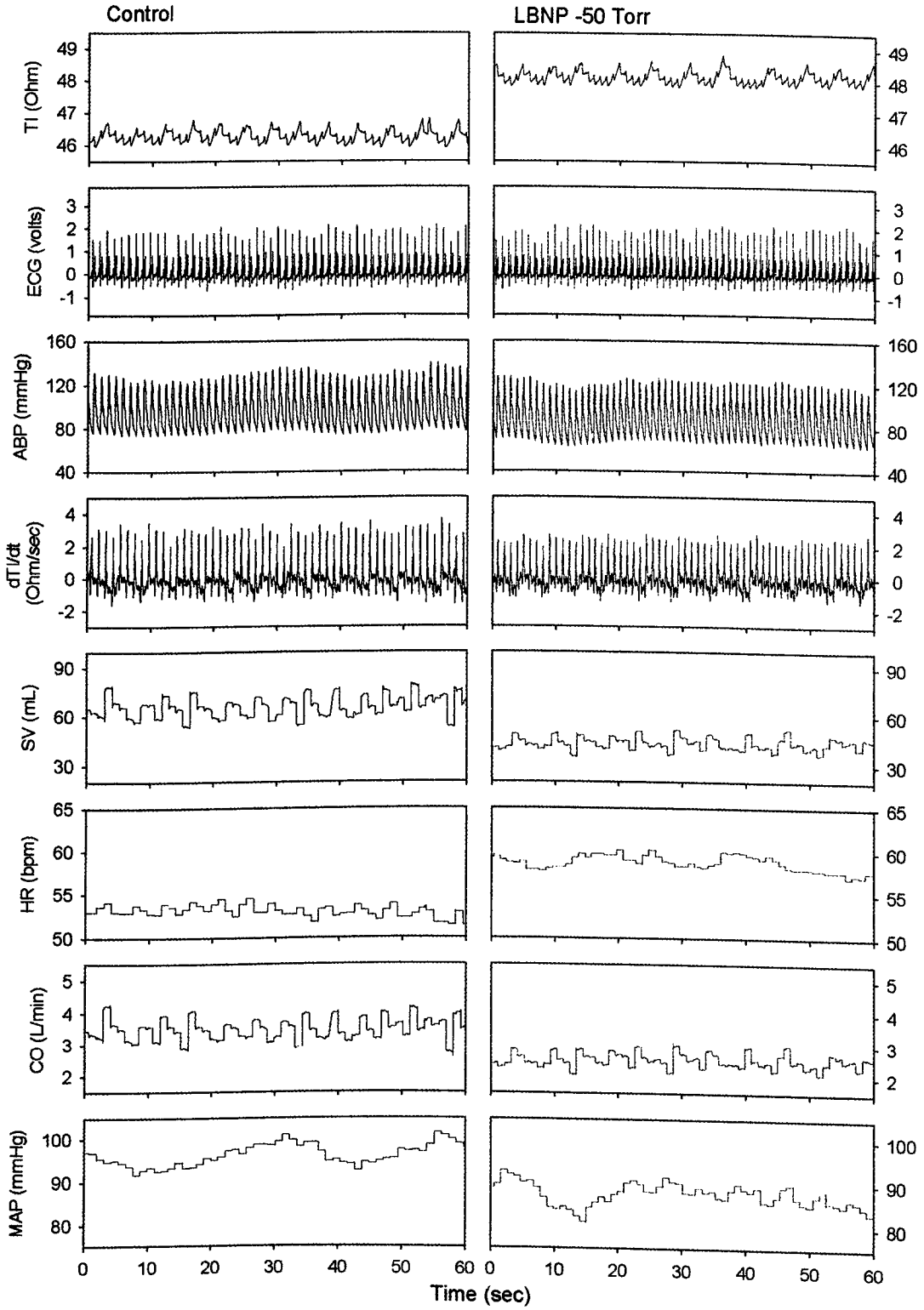

Figure 1. A 1-minute data section of cardiovascular measurements obtained in an elderly subject at rest (control; left panel) and during LBNP of −50 torr (right panel). The TI, electrocardiograph, ABP, rate of change in thoracic impedance (dTI/dt), and HR were continuously monitored online by a computer. The SV, CO, and MAP were computed off-line.

were then applied to the subjects' lower bodies. Each level of LBNP was maintained for a period of 6 mins. All subjects tolerated and completed LBNP at each of these levels.

Data Analyses and Statistics. Each 6-min data set was plotted and examined for variance. From the data set, a 5-min steady state continuous section exhibiting the least variation was selected. Ectopic or spurious beat among the continuous hemodynamic data were replaced by the interpolated beat from a beat before and after. The selected section of data was resampled at 2 Hz. Because the HR interval was much longer than 0.5 secs at rest and during LBNP in both elderly and young subjects, interpolation using this resampling frequency (2 Hz) should be adequate. After resampling, the data were fitted with third-order polynomial curve, and the variances were derived from the difference between the resampled and fitted data. The data then were divided into 128-point segments with 50% overlap for fast Fourier transform analysis. Figure 2 provides an example of this methodology from one elderly subject. These templates have been established in our previous studies (2, 3). Harmonic power spectra in the low frequency (LF) from 0.04–0.14 Hz and high frequency (HF) from 0.15–0.30 Hz were extracted. Because the magnitude of the power and the transfer function coherence become less significant near the end of HF spectrum and because the HF power peaks at the breath frequency (i.e., 0.20–0.25 Hz), we selected our HF range between 0.15–0.30 Hz. The gain, coherence, and phase degree of the transfer functions characterizing the relationships between MAP-HR signals, CO-MAP signals, and TPR-MAP signals were calculated using the Welch Spectral estimator as described by Zhang *et al.* (8, 22). The cross-spectra to auto-spectra ratio for any two cardiovascular signals was computed from the transfer function (3). A coherence value of <0.5 indicated that two signals were not significantly related or were not related in a simply linear fashion. Phase degree values significantly different from 0 indicated change in one variable preceded change in the second variable.

Data from both elderly and young subjects were reported as groups mean value ± SEM. Baseline data between the two age groups were compared using Student's *t* tests. Two-way ANOVA was applied to quantify the effects of age factor and LBNP factor on the cardiovascular responses and transfer function data. For ANOVA, a Duncan multiple comparison analysis was employed *post hoc* for repeated measure when the main factors were determined significant. The ANCOVA was used to compare the rate of change of cardiovascular variables during graded LBNP between two groups. Statistical analysis system (SAS) software was used for data analyses.

Results

Cardiovascular Responses to LBNP. Cardiovascular valuables at rest and during graded LBNP are presented in Table 1. Comparing age groups, resting HR, SV, and CO tended to be lower, while ABP and TPR were higher in the elderly subjects (Fig. 3). Both SaO_2 and RcO_2 appeared to be lower in the elderly than in the young individuals. In both young and elderly subjects, LBNP significantly increased TI and decreased SV, CO, and pulse

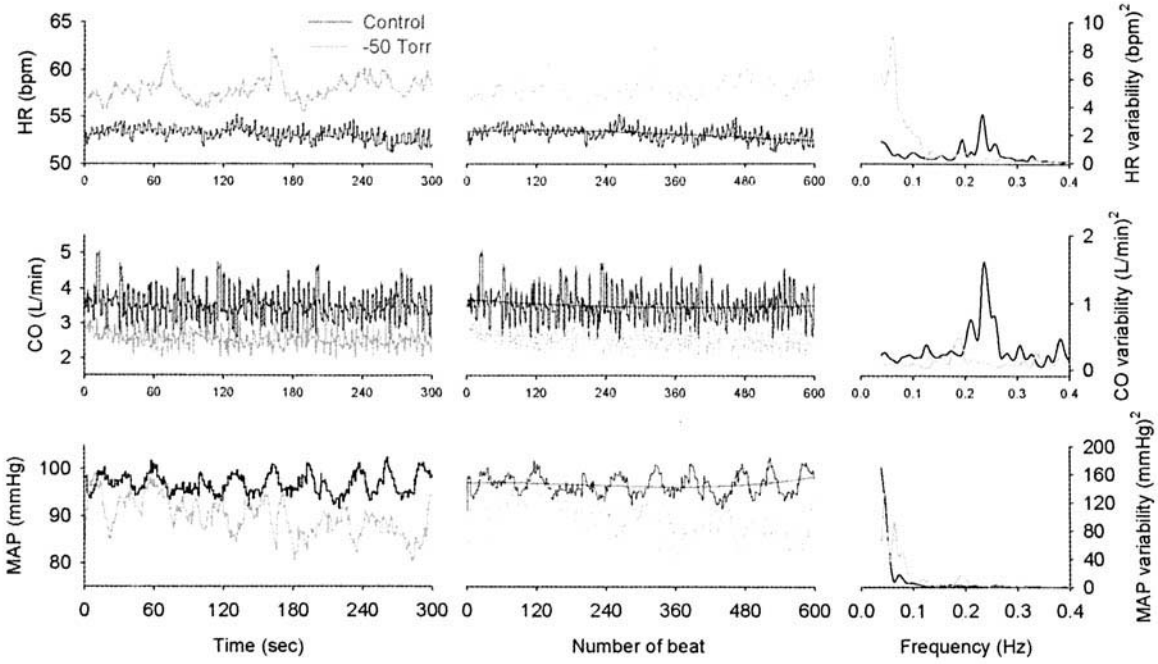

Figure 2. Transformation from time-domain data to frequency-domain data in one elderly subject. Left panels (from top to bottom): A 5-min continuous data section of HR, CO, and MAP at rest (black line) and during LBNP of –50 torr (gray line). Middle panels: The same data resampled at 2 Hz and detrended with third-order polynomial fitting. Right panels are the power spectral data derived for each variable.

Table 1. Cardiovascular Variables[a]

	LBNP (torr)	HR (bpm)	TI (ohm)	CO (l/min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	PP (mm Hg)	SaO_2 %
Elderly	0	58 ± 3	50.2 ± 4.0	3.31 ± 0.30	129 ± 3	73 ± 3	92 ± 3	56 ± 4	95.0 ± 0.5
	−15	58 ± 3	50.6 ± 4.0	2.95 ± 0.27[b]	125 ± 5	73 ± 3	90 ± 3	52 ± 5	94.4 ± 0.9
	−30	61 ± 3	51.2 ± 4.0 [b]	2.63 ± 0.26[b]	124 ± 4	72 ± 4	89 ± 3	51 ± 4	94.9 ± 0.6
	−50	69 ± 4[b]	51.3 ± 4.1[b]	2.46 ± 0.31[b]	120 ± 5	74 ± 6	89 ± 5	46 ± 3[b]	94.3 ± 0.7
Young	0	64 ± 2	41.4 ± 2.2	5.65 ± 0.49[c]	117 ± 3[c]	64 ± 3[c]	82 ± 3[c]	53 ± 2	96.1 ± 0.6[c]
	−15	65 ± 2	42.3 ± 2.3	5.27 ± 0.46[bc]	117 ± 3	64 ± 3	82 ± 3[c]	52 ± 2	96.4 ± 0.6
	−30	68 ± 2[c]	42.9 ± 2.4[b]	4.79 ± 0.41[bc]	115 ± 3	64 ± 3	81 ± 3[c]	51 ± 2	96.3 ± 0.6
	−50	78 ± 2[bc]	43.5 ± 2.4[b]	4.02 ± 0.38[bc]	109 ± 3	65 ± 3	80 ± 3	44 ± 3[b]	96.5 ± 0.4
P value	Age	0.001	0.013	0.001	0.001	0.001	0.001	0.499	0.001
	LBNP	0.001	0.001	0.001	0.107	0.984	0.845	0.003	0.992

[a] SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are group mean ± SE of the mean. *P* value indicates the ANOVA outcome.
[b] indicates a significant change from baseline (i.e., LNBP = 0).
[c] indicates a significant difference between groups.

pressure (PP) compared with baseline. Despite the reductions in SV and CO, MAP was maintained. This maintenance of ABP was most likely due to the significant increases in TPR induced by LBNP. Sustained LBNP had no effect on SaO_2 (Table 1), whereas RcO_2 was progressively decreased during the LBNP-induced central hypovolemia (Fig. 3). In terms of unit decrease in SV, the reductions in RcO_2 were more substantial in the elderly than in the young subjects (slopes of group RcO_2/SV in the elderly vs. the young: 0.268 ± 0.037%/ml vs. 0.127 ± 0.029%/ml; $P = 0.048$). Likewise, reductions in SV induced significantly greater increases in TPR in the elderly compared with the young (slopes of group TPR/SV in the elderly vs. the young: −0.570 ± 0.060 U/ml vs. −0.185 ± 0.007 U/ml; $P = 0.002$).

Power Spectra and Transfer Function Analyses. Table 2 presents spectral analyses characterizing LF and HF power. In both the LF and HF ranges, the power spectra of HR, SV, CO, and MAP variability tended to be greater in the young group than in the elderly group. However, TPR variability appeared to be greater in the elderly than in the young group. In both groups, LBNP appeared to augment MAP variability and TPR variability, but it did not significantly affect the variability in SV or CO.

Table 3 summarizes transfer function analyses between MAP-HR signals, CO-MAP signals, and TPR-MAP signals. The gain and the coherence of the transfer function characterizing MAP-HR signals appeared to be greater in the young than in the elderly subjects. The LBNP tended to decrease the HF transfer function gain of MAP-HR signals. In both the elderly and young groups, the transfer function coherence between CO-MAP signals was <0.5 at rest and during all levels of LBNP. The coherence of the transfer function between TPR-MAP signals was >0.5 in the LF range in the young group only. Age factor, but not LBNP factor, had a significant influence in the transfer function gain of TPR-MAP signals.

Discussion

Using LBNP to present an orthostatic challenge in both young and elderly subject populations, the present investigation elucidated several important findings including (i) in terms of unit decrease in SV, increases in TPR and reductions in RcO_2 were significantly greater in the elderly than in the young adults; (ii) in both the LF and HF ranges, the spectra of HR, SV, and CO variability were diminished, whereas the spectrum of TPR variability was augmented in the elderly compared with the young group; (iii) the gain and coherence of the transfer function characterizing variability of MAP-HR signals were significantly reduced in the elderly population; (iv) in terms of the transfer function coherence, the relationship between variability characterizing CO-MAP signals was not simply linear or significantly coherent in both age groups; (v) the gain and coherence of the transfer function characterizing variability of TPR-MAP signals were systematically greater in the LF than HF spectra; and (vi) in the elderly subjects, the transfer function coherence between TPR-MAP signals was <0.5 in both LF and HF spectra. Collectively, these findings suggest that the transfer function between MAP-HR signals and TPR-MAP signals, but not CO-MAP signals, is significantly diminished in elderly adults.

The MAP is determined by both CO and TPR, the latter of which is directly related to sympathetic nerve activity (SNA). Given this relationship, it is possible that the beat-to-beat variability in MAP signals may be closely associated with the beat-to-beat variability in either CO signals or TPR signals (a surrogate of SNA). It has been shown that MAP variability is directly related to the variability in SNA (6). Further, LBNP is known to induce concomitant increases in MAP variability (3), muscle SNA (23–31), and blood plasma norepinephrine (3, 32–37). As changes in SNA alter TPR, it has been postulated that the variability in MAP is dependent on the variability in TPR. In the present investigation, the relationship between MAP variability and CO variability

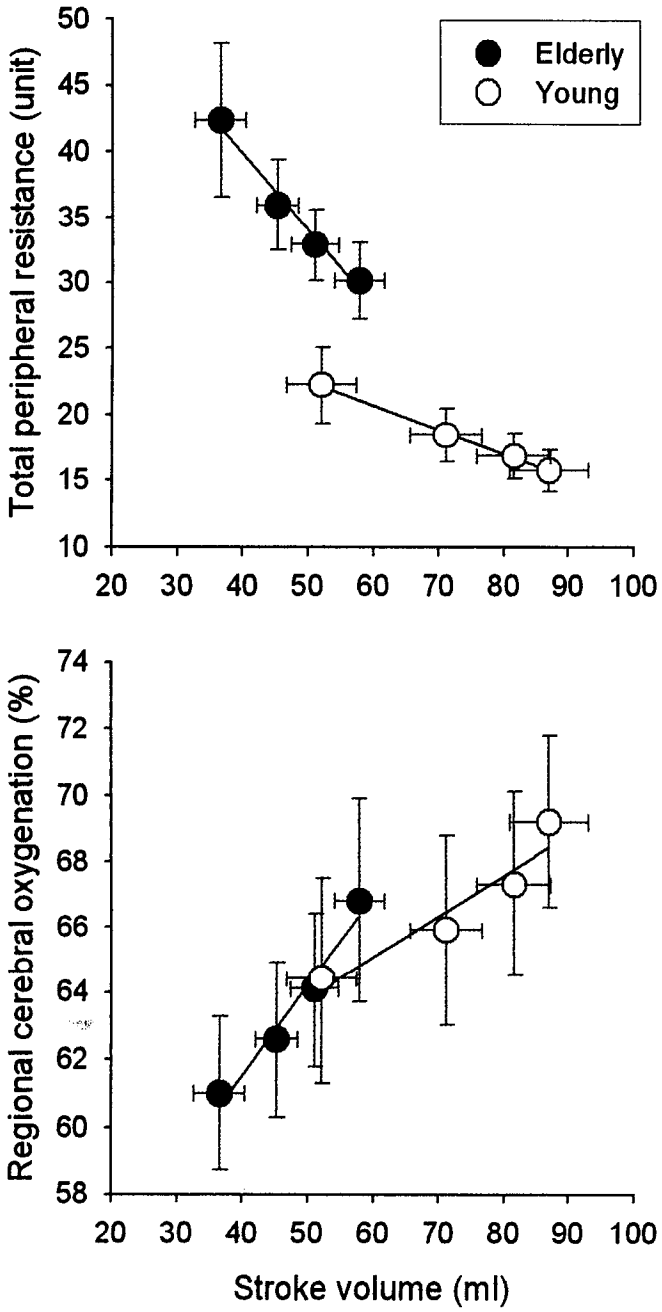

Figure 3. The association between TPR and SV (top panel) and between regional cerebral O_2 saturation and SV (bottom panel) during graded LBNP-induced central hypovolemia. In terms of per-unit decrease in SV, the augmentation of TPR and the reduction of RcO_2 were more significantly intensified in the elderly than in the young group.

found in the transfer function analysis was insignificant at rest and during LBNP as evidenced by coherence values of <0.5 in both the young and the elderly groups (Table 3). Further, LBNP-simulated orthostatic challenge augmented the power spectrum of the MAP variability but had no effect on the variability in the CO power spectrum (Table 2), demonstrating a degree of dissociation between the two variables. Additionally, this relationship between beat-to-beat CO-MAP variability determined at rest and during LBNP was not different between the young and the elderly individuals. However, the transfer function coherence between TPR-MAP signals was significantly greater in the young than in the elderly subjects (Table 3), which was ≥0.5 at the LF spectrum in the young group. Furthermore, the transfer function gain of the young adults between TPR-MAP signals was consistently greater compared with the elderly adults. These data implied that the beat-to-beat MAP variability was significantly oscillated with SNA modulation (i.e., TPR variability) at rest or during LBNP, and this dynamic vasomotor control was more effective in the young than in the elderly subject group. A significant association between TPR-MAP signals in the LF range appeared to be in agreement with the ontogenesis of the baroreflex-mediated SNA variability (6, 38). Nonetheless, a smaller (<0.5) transfer function coherence in the elderly group suggested a noncoherent and incompetent association of the beat-to-beat variability between TPR-MAP signals with advanced age. Collectively, this and previous reports indicated that the beat-to-beat variability in MAP signals could be more related to the variability in TPR signals rather than CO signals. To the best of our knowledge, the present investigation was the first documented study to demonstrate that there was no age-related difference in the transfer function between CO-MAP signals. However, the function of dynamic vasomotor control was significantly diminished in the elderly group in terms of the transfer function gain and coherence between TPR-MAP signals.

The present study confirmed that the power spectrum of HR variability was significantly diminished in the elderly compared with the young group (39). Furthermore, our data elucidated that both the power spectra of SV variability and CO variability were significantly smaller in the elderly than in the young adults (Table 2). This diminished SV variability or CO variability in the elderly group could be explained by a smaller HR variability, which was attributable to the age-related vagal cardiac dysfunction or diminished baroreflex function. Previously, it has been reported that the baroreflex-mediated tachycardiac response to LBNP is diminished in healthy, elderly people (2, 4, 37, 40). The present study confirmed that the gain of the transfer function characterizing the beat-to-beat dynamic relationship between MAP-HR signals (Table 3) tended to be diminished in the elderly group compared with the young group in both the LF and HF spectra. Furthermore, data analyses determined that the coherence of the transfer function describing MAP-HR variability was significantly lower in the elderly (Table 3). These findings suggest that the advanced age not only diminishes the gain of the transfer function characterizing MAP-HR variability, but also weakens the coherence of this relationship. Speculatively, these changes may contribute to the reductions in baroreflex sensitivity as well as the diminutions in HR variability that manifest in the elderly.

Although advanced age is known to diminish the sensitivity of the baroreflex, ABP was maintained during the LBNP-induced orthostatic challenge in the elderly subject

Table 2. *Power Spectral Data*[a]

		HR variability (bpm^2)		SV variability (ml^2)		CO variability (l/min^2)		MAP variability (mm Hg^2)		TPR variability (unit^2)	
	LBNP (Torr)	LF	HF	LF	HF	LF	HF	LF	HF	LF	HF
Elderly	0	2.3 ± 0.8	1.5 ± 0.8	8.4 ± 2.2	10.1 ± 2.2	0.05 ± 0.02	0.04 ± 0.01	2.5 ± 0.8	0.5 ± 0.2	2.9 ± 1.6	3.9 ± 2.3
	−15	1.6 ± 0.4	0.6 ± 0.1	6.5 ± 1.1	8.4 ± 1.7	0.03 ± 0.01	0.03 ± 0.01	3.0 ± 0.9	0.6 ± 0.1	4.1 ± 1.8	3.0 ± 1.0
	−30	2.5 ± 1.0	1.0 ± 0.5	6.7 ± 0.6	9.5 ± 2.0	0.05 ± 0.03	0.05 ± 0.02	3.1 ± 0.5	1.0 ± 0.2^b	4.9 ± 2.3	8.0 ± 4.1
	−50	1.8 ± 0.5	0.7 ± 0.3	6.3 ± 2.3	13.0 ± 4.9	0.06 ± 0.04	0.09 ± 0.05	3.6 ± 0.7	1.2 ± 0.3^b	10.2 ± 3.5^b	14.0 ± 4.7^b
Young	0	3.5 ± 0.7	3.9 ± 1.1^c	18.7 ± 4.9	26.8 ± 5.0^c	0.06 ± 0.02	0.09 ± 0.02^c	3.9 ± 0.6	0.8 ± 0.1	0.8 ± 0.4	0.7 ± 0.3
	−15	5.2 ± 1.0^c	3.5 ± 0.9^c	23.2 ± 5.3^c	26.8 ± 3.4^c	0.08 ± 0.02^c	0.10 ± 0.02^c	6.5 ± 1.3^c	1.3 ± 0.4^c	1.0 ± 0.5	0.8 ± 0.3
	−30	5.8 ± 1.1^{bc}	3.9 ± 1.5	22.6 ± 4.1^c	29.9 ± 5.6^c	0.09 ± 0.02^c	0.13 ± 0.03^c	8.5 ± 1.8^{bc}	1.3 ± 0.3^b	1.5 ± 0.5^b	1.1 ± 0.3^b
	−50	7.7 ± 1.1^{bc}	3.2 ± 1.2^c	14.9 ± 3.3^c	15.9 ± 4.1	0.07 ± 0.02	0.17 ± 0.08	8.1 ± 1.6^{bc}	1.5 ± 0.3^b	1.7 ± 0.5^{bc}	1.6 ± 0.4^{bc}
P value	Age	0.001	0.001	0.001	0.001	0.011	0.009	0.001	0.027	0.002	0.001
	LBNP	0.005	0.851	0.589	0.274	0.988	0.436	0.002	0.007	0.007	0.002

[a] LF, low frequency; HF, high frequency. *P* value indicates the ANOVA outcome.
[b] indicates a significant change from baseline (i.e., LNBP = 0).
[c] indicates a significant difference between groups.

Table 3. Transfer Function Data[a]

			Elderly				Young				*P* value	
	LBNP (torr)		0	−15	−30	−50	0	−15	−30	−50	Age	LBNP
MAP-HR transfer function	Gain (bpm/mm Hg)	LF	1.0 ± 0.3	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	1.0 ± 0.1	0.9 ± 0.1^b	0.8 ± 0.1	0.9 ± 0.1^b	0.019	0.472
		HF	1.1 ± 0.4	0.7 ± 0.1	0.6 ± 0.1	0.4 ± 0.1^c	1.7 ± 0.3	1.3 ± 0.2^b	1.3 ± 0.3^b	1.0 ± 0.2^{bc}	0.001	0.035
	Coherence (unit)	LF	0.50 ± 0.04	0.50 ± 0.05	0.49 ± 0.05	0.48 ± 0.04	0.55 ± 0.03	0.60 ± 0.03	0.62 ± 0.03^b	0.57 ± 0.03	0.002	0.788
		HF	0.40 ± 0.05	0.38 ± 0.03	0.41 ± 0.04	0.38 ± 0.03	0.52 ± 0.05	0.55 ± 0.03	0.52 ± 0.03	0.48 ± 0.04	0.001	0.852
	Phase (degree)	LF	63 ± 9	43 ± 6	58 ± 11	72 ± 5	67 ± 8	63 ± 8	73 ± 7	69 ± 9	0.116	0.189
		HF	42 ± 10	52 ± 9	57 ± 9	56 ± 9	54 ± 15	59 ± 12	59 ± 9	67 ± 12	0.284	0.616
CO-MA transfer function	Gain (mm Hg/l/min)	LF	13.5 ± 8.5	6.4 ± 0.9	7.6 ± 1.4	7.9 ± 1.7	4.9 ± 0.7	5.8 ± 0.9	6.3 ± 1.3	6.7 ± 1.0	—	—
		HF	11.2 ± 8.7	2.6 ± 0.4	3.1 ± 0.4	3.2 ± 0.7	2.3 ± 0.4	2.5 ± 0.4	2.4 ± 0.4	3.5 ± 0.8	—	—
	Coherence (unit)	LF	0.32 ± 0.02	0.31 ± 0.02	0.41 ± 0.09	0.33 ± 0.02	0.29 ± 0.02	0.30 ± 0.02	0.36 ± 0.03	0.31 ± 0.02	—	—
		HF	0.33 ± 0.02	0.31 ± 0.02	0.34 ± 0.02	0.33 ± 0.02	0.37 ± 0.02	0.36 ± 0.03	0.34 ± 0.03	0.35 ± 0.01	—	—
	Phase (degree)	LF	−1 ± 6	−12 ± 13	−2 ± 10	−7 ± 10	−8 ± 12	6 ± 10	−9 ± 7	4 ± 9	—	—
		HF	−1 ± 3	5 ± 8	−8 ± 9	7 ± 12	3 ± 12	16 ± 8	12 ± 11	5 ± 5	—	—
TPR-MAP transfer function	Gain (mm Hg/unit)	LF	0.7 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	1.7 ± 0.4^b	1.7 ± 0.4^b	2.0 ± 0.4^b	1.2 ± 0.2^b	0.001	0.351
		HF	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.9 ± 0.2^b	0.8 ± 0.1^b	1.1 ± 0.5	0.7 ± 0.1^b	0.001	0.612
	Coherence (unit)	LF	0.39 ± 0.03	0.40 ± 0.03	0.37 ± 0.03	0.37 ± 0.02	0.50 ± 0.04	0.50 ± 0.06	0.54 ± 0.06	0.52 ± 0.05	0.001	0.995
		HF	0.34 ± 0.02	0.32 ± 0.02	0.32 ± 0.02	0.34 ± 0.02	0.41 ± 0.03	0.41 ± 0.03	0.40 ± 0.04	0.43 ± 0.04	0.001	0.727
	Phase (degree)	LF	5 ± 7	3 ± 9	−7 ± 8	5 ± 5	0 ± 5	−1 ± 4	8 ± 4	2 ± 5	0.885	0.957
		HF	5 ± 7	−10 ± 8	−7 ± 6	−14 ± 8	−8 ± 8	−9 ± 5	−7 ± 8	10 ± 5	0.599	0.546

[a] LF, low frequency; HF, high frequency. *P* value indicates the ANOVA outcome.
[b] indicates a significant difference between groups.
[c] indicates a significant change from baseline (i.e., LNBP = 0).

group (Table 1). It appeared that this was accomplished *via* exaggerated increases in TPR (Fig. 3). Such a paradoxical augmentation in vasomotor tone may potentially compromise the distribution of blood flow to various organs, including the brain (7). This scenario may have materialized in the current study. For example, for a given unit decrease in SV, as indicative of central hypovolemia associated with orthostatic challenge, the reduction in RcO_2 appeared to be more significant in the elderly than in the young subjects (Fig. 3). As SaO_2 remained unchanged from baseline during sustained LBNP in both the young and elderly groups (Table 1), and because the metabolic rate was not altered by graded LBNP, brain O_2 consumption was assumed to be constant throughout the experiment. Thus, a progressive decrease in RcO_2 with LBNP may be indicative of a decrease in O_2 delivery to the brain (i.e., an underperfusion to the cerebral tissue; Ref. 41). In the clinical setting, drops in cerebral oxygenation indicate cerebral ischemia (42). Importantly, a greater than 10% decrease in RcO_2 may result in presyncope symptoms (e.g., lightheadedness, dizziness; Ref. 12) and increases the incidence of vasovagal syncope (43). Given the findings of the current study, the orthostatic intolerance commonly reported in elderly patients may be the consequence of cerebral underperfusion quantified by augmented decreases in RcO_2.

In summary, MAP variability at rest and during LBNP was not significantly related to CO variability. Importantly, this finding was reported for both the young and elderly populations and, therefore, occurred independent of age. The beat-to-beat MAP variability was significantly oscillated with the low-frequency TPR variability in the young group only. These data implied that dynamic vasomotor control at rest or during LBNP was modulated by sympathetic nerve activity, and advanced age compromised its coherence and efficacy in terms of the transfer function gain and coherence between TPR-MAP signals. Furthermore, the elderly individuals exhibited a diminution in HR variability that was associated not only with a reduction in the gain of the transfer function characterizing MAP-HR variability, but also with a decrease in the coherence between these two signals. The latter changes may contribute to the reductions in baroreflex sensitivity as well as the diminution in HR variability that manifest with aging, which is indicative of the development of vagal cardiac dysfunction. Augmentation of TPR during sustained central hypovolemia was more intensified in the elderly than in the young individuals. As a consequence, the paradoxically augmented vasomotor tone in the elderly appeared to compromise cerebral perfusion, as indicated by a greater drop in regional cerebral O_2 saturation per unit decrease in SV during orthostatic challenge. Clinically, the latter finding provides a mechanism by which the incidence of orthostatic intolerance is increased in the elderly adults. Our data elucidate that advanced age diminishes the efficacy and the coherence in dynamic control of beat-to-beat MAP variability and HR variability in terms of transfer function analysis.

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