Original Research *Highlight article*

Habitual physical activity improves vagal cardiac modulation and carotid baroreflex function in elderly women

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Impact Statement

A physically active lifestyle preserves carotid baroreflex function in elderly men, but the impact of habitual physical activity on the carotid baroreflex in elderly women is unknown. This study is among the first to demonstrate in elderly women that habitual physical activity enhances tonic vagal-cardiac modulation evident by increased heart rate variability at rest in both low- and high-frequency spectrum. Moreover, a physically active lifestyle enhanced dynamic vagal-cardiac response to a wide range of depressor and pressor challenges to the carotid baroreceptors. Regular physical activity may, in addition to increasing physical mobility, preserve cardiac autonomic control in elderly women, potentially protecting them from aging-associated vagal dysfunction and the resultant cardiac electrical and functional instability.

Abstract

The impact of habitual physical activity on vagal-cardiac function and baroreflex sensitivity in elderly women is poorly characterized. This study compared vagal-cardiac modulation and carotid baroreflex (CBR) function in eight physically active (67.6 ± 1.9 years; peak O_2 uptake 29.1 ± 2.5 mL/min/kg) versus eight sedentary (67.3 ± 1.8 years; peak O_2 uptake 18.6 ± 0.9 mL/min/kg) elderly women. Heart rate (HR) variabilities and maximal changes of HR and mean arterial pressure (MAP) elicited by 5-s pressure pulses between +40 and –80 mmHg applied to the carotid sinus were measured at rest and during carotid baroreceptor unloading effected by –15 mmHg lower-body negative pressure (LBNP). HR variability was greater in active than sedentary women in both low (0.998 ± 0.286 versus 0.255 ± 0.063 bpm^2; $P = 0.036$) and high (0.895 ± 0.301 versus 0.156 ± 0.045 bpm^2; $P = 0.044$) frequency domains. CBR-HR gains (bpm/mmHg) were greater (fitness factor $P < 0.001$) in active versus sedentary women at rest (–0.146 ± 0.014 versus –0.088 ± 0.011) and during LBNP (–0.105 ± 0.014 versus –0.065 ± 0.008). CBR-MAP gains (mmHg/mmHg) tended to be greater (fitness factor $P = 0.077$) in active versus sedentary women at rest (–0.132 ± 0.013 versus –0.110 ± 0.011) and during LBNP (–0.129 ± 0.015 versus –0.113 ± 0.013). However, LBNP did not potentiate CBR-MAP gains in either sedentary or active women (LBNP factor $P = 0.94$), and it depressed CBR-HR gains in both groups (LBNP factor $P = 0.003$). CBR-HR gains in the sedentary women did not differ (sex factor $P = 0.65$) from gains reported in age-matched sedentary men, although CBR-MAP gains tended to be greater (sex factor $P = 0.109$) in the men. Thus, tonic vagal modulation indicated by HR variability and dynamic vagal responses assessed by CBR-HR gain were augmented in physically active women. Enhanced vagal-cardiac function may protect against senescence-associated cardiac electrical and hemodynamic instability in elderly women.

Keywords: Carotid baroreflex, heart rate variability, physical fitness, vagal-cardiac function

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Introduction

Arterial baroreflex function diminishes with age, yet improves with physical fitness, in healthy men and women.[1] Thus, carotid baroreflex (CBR) sensitivity was augmented in physically active elderly men versus their age-matched healthy, sedentary counterparts.[2] Furthermore, vagal-cardiac modulation assessed from heart rate (HR) variability was greater in physically active versus sedentary post-menopausal women.[3] However, vagal-cardiac baroreflex sensitivity during Valsalva maneuvers was lower in exercise trained versus sedentary young women.[4] The question remained if a physically active lifestyle would enhance vagal-cardiac function in elderly women as it did in elderly men[2] or in post-menopausal, middle-aged women.[3] To define the effects of cardiorespiratory fitness on vagal-cardiac and CBR function

in elderly women, this study addressed the hypothesis that habitual physical activity augments HR variability and CBR control of HR and arterial pressure in healthy, elderly women.

Fu *et al.*[5] reported a diminished bradycardiac response to the hypertensive stimulus during phase IV of the Valsalva maneuver in young women versus men, although tachycardiac responses to the phase II hypotensive stimulus were similar in young women versus men. However, Kim *et al.*[6] reported greater CBR-mediated cardiac responses during neck-suction induced carotid hypertension, although not during neck-pressure induced carotid hypotension, in young women versus men. Although the mechanisms producing the divergent HR responses to hypertensive versus hypotensive stimuli, respectively, in young women versus men are unclear, a likely contributor is that brief pressure changes in the neck chamber selectively engage carotid baroreceptors,[6] while Valsalva maneuvers affect both carotid and aortic baroreceptors.[5] Another likely factor is sex-related differences in relative contributions from the carotid versus aortic baroreceptors. Okada *et al.*[7] found that compared to their male counterparts, elderly women had lower sympathetic baroreflex sensitivity assessed by spontaneous variations of muscle sympathetic nerve activity during beat-to-beat fluctuations of diastolic arterial pressure, as well as increased stiffness of the carotid artery and aortic arch.[7] However, tachycardiac responses to the hypotension during phase II of the Valsalva maneuver were similar in the elderly women and men, although the bradycardiac response to the phase IV hypertension was attenuated in the women. However, the impact of physical fitness on the selective CBR control of heart rate and arterial pressure in elderly women versus men is unknown. Thus, this study compared pressor and depressor responses during selective carotid hypotensive (neck-pressure) and hypertensive (neck-suction) stimuli, in sedentary versus physically active elderly women, and in these women versus the previously reported responses in elderly men.[2]

Cardiopulmonary baroreceptors exert tonic inhibition of the medullary cardiovascular center.[8–10] In young adults, attenuating this inhibition by applying lower-body negative pressure (LBNP) to unload the cardiopulmonary baroreceptors potentiated CBR control of HR,[11–13] arterial blood pressure,[11,13] vasoconstriction,[14] and muscle sympathetic nerve activity.[15] However, this central autonomic interaction between cardiopulmonary receptor unloading and CBR function is absent in elderly men, whether physically active or sedentary.[2] Therefore, this study also compared the facilitatory interaction of CBR function with LBNP-effected cardiopulmonary receptor unloading in sedentary elderly women versus their physically active counterparts with greater cardiorespiratory fitness.

Materials and Methods

Participants

Eight healthy sedentary and eight physically active elderly women participated in the study. The consent form and study protocol were reviewed and approved by the Institutional Review Board for the Protection of Human Subjects at the University of North Texas Health Science Center. After giving voluntary written informed consent, all subjects passed a physical examination and maximal stress test before enrollment in the study. Each subject was free of cardiovascular, metabolic, renal, or pulmonary diseases or symptoms. All women who self-reported engaging in ⩾60-min daily aerobic exercise for ⩾4 days/week over at least the past 15 consecutive years were assigned to the physically active group, and women who had not regularly participated in physical training or activities were assigned to the sedentary group. Power analysis was based on the analysis of our previous data from sedentary and physically active elderly men.[2] This previous report indicated that sample sizes of eight sedentary and eight physically active elderly subjects would be sufficient to detect the fitness-related difference in CBR function at $1-\beta=0.80$ and $\alpha=0.05$.

Mean age and height did not differ between the sedentary (67.3 ± 1.8 years old and 163 ± 2 cm) and physically active (67.6 ± 1.9 years old and 161 ± 2 cm) women, while body mass (80.5 ± 5.0 versus 63.5 ± 5.1 kg; $P=0.03$) and body mass index (BMI: 30.4 ± 1.8 versus 24.5 ± 1.6 kg/m^2; $P=0.03$) were greater in the sedentary women. Cardiorespiratory fitness, assessed from peak oxygen uptake (VO_{2peak}; Vacumed Vista VO_2 Lab, Ventura, CA, USA) during cycling at maximal capacity on a stationary bicycle, was greater ($P<0.01$) in the physically active (29.1 ± 2.5 mL//kg/min) than sedentary (18.6 ± 0.9 mL/kg/min) women. All subjects were oriented to the lab and familiarized with the experimental procedures and measurements before experiments.

Assessment of cardiovascular function

During the experiment, each subject's HR was continuously monitored by standard lead II electrocardiography. Radial arterial blood pressure (ABP) was continuously measured from the left arm using a tonometer (Model 7000 Tonometer Colin, San Antonio, TX, USA). We previously confirmed the reliability and accuracy of this non-invasive method by comparison with ABP directly measured via radial arterial catheter.[16] Stroke volume (SV) was estimated by thoracic impedance plethysmography[17] using tetrapolar electrodes placed on the neck and lower chest (EBI100C, BIOPAC, Santa Barbara, CA). Changes in bio-impedance reliably indicate changes in central blood volume[18,19] and SV.[20–22] Because of the between-group body mass difference, SV index (SVI) was taken as SV ÷ body surface area (DuBois formula). Forearm blood flow (FBF) was measured[13,23] with a double-strand mercury-in-Silastic strain gauge (Hokanson, Bellevue, WA, USA). All hemodynamic measurements were acquired on a computer and digitized online at 200 Hz. Cardiac output index (COI) equaled HR times SVI. Aortic compliance was estimated as SVI ÷ arterial pulse pressure. Total peripheral resistance index (TPRI) and forearm vascular resistance (FVR) equaled mean ABP (MAP) ÷ COI and MAP ÷ FBF, respectively.

CBR assessment

CBR function was evaluated as previously described.[2] Briefly, carotid baroreceptor activity was selectively altered using 5 sec pulses of neck-pressure (+40 and +20 mmHg)

and neck-suction (−20, −40, −60, and −80 mmHg) delivered in random order to a malleable lead chamber[24] around the anterior portion of the neck encompassing the carotid sinus region.[12,25] Neck-pressure or neck-suction was delivered during a breath-hold at the end of a normal expiration. The duration and timing of delivery of neck chamber pressures (NCP) were controlled by a computer equipped with custom-made software.[11] Brief (5 sec) pulses of neck pressure and suction as applied in this study selectively elicited the CBR with minimal or no influence from the aortic baroreceptors.[12,25–27] Changes in carotid sinus pressure (CSP) were estimated from the difference between the baseline MAP and the NCP. The ratios of the maximal responses of HR and MAP to the changes in CSP affected by neck pressure/neck suction, that is, ΔHR/ΔCSP and ΔMAP/ΔCSP, indexed the gains (sensitivities) of CBR control of cardiac and vasomotor responses, respectively.[2] The neck-pressure/neck-suction procedure was applied during quiet supine rest and during LBNP at an intensity (−15 mmHg) which produces central hypovolemia without imposing significant systemic hypotension that may disturb the high pressure side of the circulation.[28–30] Both neck-pressure/neck-suction[2,13,31] and LBNP[2,32–36] have been extensively applied in our previous studies.

Experiment protocol

The experiment was conducted with the subject supine and the lower body supported in an airtight LBNP box at 23 ± 2°C room temperature. After ⩾20-min supine rest, baseline HR, ABP and thoracic impedance were continuously recorded for 6 min, and four or five FBF readings were collected with a wrist cuff inflated to ~200 mmHg. After baseline cardiovascular data collection, neck-pressure and neck-suction pulses were delivered in random order to evaluate CBR function. Each neck-pressure/neck-suction series was repeated at least 3 times with ~60 s between trials for recovery of HR and MAP. If fewer than two of the expected tachycardiac and bradycardiac responses or pressor and depressor responses to neck-pressure induced carotid hypotension and neck-suction induced carotid hypertension, respectively, were detected, two more trials of the same NCP series were performed. After assessment of baseline CBR function, LBNP was applied, and after 2 min stabilization, the neck-pressure/neck-suction protocol was repeated at −15 mmHg LBNP. After recovery from the CBR assessment, SV and FBF were measured for ~2 min during LBNP without applying neck pressure or suction. One sedentary and three active subjects did not display the expected HR and MAP responses to NCP during LBNP; accordingly, data from these subjects during LBNP were excluded from analyses of CBR-HR and CBR-MAP gains.

Data analyses

A section of 5-min continuous data with minimal variance under supine resting control conditions was selected for frequency-domain analysis. Harmonic power of HR variability was analyzed using the procedure and templates that have been validated and repeatedly applied in our previous studies.[16,33–35] Low-frequency (0.05–0.149 Hz) and high-frequency (0.15–0.305 Hz) power were compared using *t*-tests for two independent samples. Because some of the individual data from the elderly subjects could not be fit to sigmoid function curves,[2] only group HR and MAP data were plotted against the estimated CSP at graded neck-pressure and neck-suction using logistical modeling techniques. The derived peak slope (i.e. the maximal gain) and standard error were calculated as described previously.[37] The significance of the difference in the maximal gains of the active versus sedentary groups was determined using the *z*-statistics.

Two-factor analysis of variance (ANOVA) was applied to determine the significance of the fitness and LBNP factor effects on the between-group differences in cardiovascular data at rest and during LBNP. Three-factor ANOVA was applied to assess the influences of fitness, LBNP and NCP on CBR-HR and CBP-MAP gains at rest and during LBNP. The fitness and LBNP factors were examined with the separation of positive NCP from negative NCP to test the differences in tachycardiac and pressor responses versus bradycardiac and depressor responses. Post hoc analysis with Tukey method was applied when the major factor attained statistical significance (i.e. P value ⩽ 0.05). To determine the effect of sex on CBR function, CBR-HR (ΔHR/ΔCSP) and CBR-MAP (ΔMAP/ΔCSP) gains during applications of −20 and 20 mmHg NCP were compared to previously reported[2] values in age-matched (68 ± 1 years old) men completing the same neck pressure/neck suction protocol. Chamber pressures of −20 and 20 mmHg were chosen because they elicited robust CBR gains for the bradycardiac/depressor and tachycardiac/pressor responses in both sexes. Data were reported as group mean values ± standard error of the mean (SEM). SigmaPlot and Statistical Analysis System (SAS, Cary, NC, USA) software were applied for figure preparation and statistical analysis.

Results

Cardiovascular variables

At rest, HR was lower ($P = 0.01$), while SVI and COI were higher ($P = 0.01$) in the physically active versus sedentary elderly women (Table 1). Although arterial blood pressures were not significantly different between the groups, TPRI was higher ($P = 0.01$) in the sedentary than physically active women (Table 1). As expected, application of −15 mmHg LBNP decreased ($P = 0.01$) SVI and COI. However, arterial blood pressure was unchanged during LBNP, suggesting a compensatory reflex vasoconstriction. A lower COI, reflecting a reduced venous return or central hypovolemia, at a constant arterial blood pressure indicated that −15 mmHg LBNP predominantly unloaded the cardiopulmonary baroreceptors with minimal disturbance of the arterial baroreceptors. There were no fitness-related differences in the responses of cardiovascular variables during the mild central hypovolemia elicited by −15 mmHg LBNP (Table 1). The SVI/arterial pulse pressure ratio, a measure of aortic compliance, was higher in the physically active women than their sedentary counterparts (fitness factor $P = 0.03$), and fell slightly during LBNP (LBNP factor $P = 0.05$) in both active and sedentary women (Table 1).

Table 1. Cardiovascular variables in sedentary and physically active subjects.

	Baseline		LBNP		*P* value	
	Sedentary	Active	Sedentary	Active	Fitness	LBNP
HR (bpm)	71 ± 4	54 ± 3*	72 ± 4	54 ± 2*	0.01	0.87
SVI (mL/m^2)	21.8 ± 2.8	33.9 ± 3.9*	18.8 ± 2.5†	31.8 ± 4.0*	0.01	0.01
COI (L/min/m^2)	1.54 ± 0.28	1.82 ± 0.21	1.34 ± 0.18†	1.69 ± 0.19	0.01	0.01
SBP (mmHg)	127 ± 6	131 ± 4	130 ± 6	130 ± 4	0.35	0.60
DBP (mmHg)	67 ± 3	68 ± 2	68 ± 3	66 ± 3	0.78	0.72
MAP (mmHg)	87 ± 4	89 ± 2	89 ± 3	88 ± 2	0.79	0.97
PP (mmHg)	60 ± 4	63 ± 4	62 ± 6	64 ± 5	0.19	0.36
SVI/PP (mL/m^2/mmHg)	0.37 ± 0.04	0.55 ± 0.06*	0.31 ± 0.04†	0.50 ± 0.05*	0.03	0.05
TPRI (unit)	66.9 ± 12.5	54.1 ± 6.9	75.1 ± 10.3	58.1 ± 8.3	0.01	0.01
FBF (mL/min/100cc)	5.59 ± 1.11	5.26 ± 0.71	4.73 ± 0.84†	4.27 ± 0.56†	0.13	0.01
FVR (unit)	24.2 ± 6.7	19.0 ± 2.4	27.9 ± 9.0	23.3 ± 3.3	0.03	0.06

LBNP: lower-body negative pressure; HR: heart rate; SVI: stroke volume index; COI: cardiac output index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; TPRI: total peripheral resistance index; FBF: forearm blood flow; FVR: forearm vascular resistance.
Values are group means ± SEM from eight sedentary and eight physically active subjects.
Aortic compliance was estimated as SVI/PP. P values for fitness and LBNP factors were generated by two-factor ANOVA. Post hoc analysis: *$P < 0.05$ versus sedentary; †$P < 0.05$ versus group baseline.

Heart rate variability

Figure 1(A) summarizes group HR variability power spectra under supine resting condition and Figure 1(B) presents group and individual low- and high-frequency spectral densities of HR variability. Both low- (0.05–0.15 Hz) and high-frequency (0.15–0.31 Hz) HR variability densities were significantly greater in the physically active versus sedentary women (low-frequency: 0.998 ± 0.286 versus 0.255 ± 0.063 bpm^2, $P = 0.036$; high-frequency: 0.895 ± 0.301 versus 0.156 ± 0.045 bpm^2, $P = 0.044$). One active woman had extremely high HR variability (Figure 1(B)). Excluding this data point lowered the mean HR variabilities in the active group to 0.728 ± 0.111 bpm^2 in the low-frequency and 0.625 ± 0.156 bpm^2 in the high-frequency powers. These active group HR variabilities remained significantly greater than those of the sedentary group in both low ($P = 0.002$) and high frequencies ($P = 0.009$).

Carotid baroreflex function

Overall CBR-HR gains at rest were significantly greater (fitness factor $P < 0.001$) in the physically active (−0.146 ± 0.014 bpm/min) than sedentary (−0.088 ± 0.011 bpm/mmHg) women (Figure 2(A)). LBNP lowered the CBR-HR gains (LBNP factor $P < 0.003$) to −0.105 ± 0.014 and −0.065 ± 0.008 bpm/mmHg in the physically active and sedentary women, respectively (Figure 2(B)). Post hoc analysis revealed that the fitness-related difference ($P < 0.01$) in overall CBR-HR gain persisted during −15 mmHg LBNP. The fitness factor remained significant ($P < 0.01$) on the separate tachycardiac response to positive NCP and the bradycardiac response to negative NCP. Furthermore, the LBNP factor was also significant on the tachycardiac ($P = 0.035$) and bradycardiac responses ($P = 0.043$). With the stratifications of LBNP and NCP, the CBR-HR gains were significantly different ($P = 0.024$) between the physically active (−0.075 ± 0.019 bpm/mmHg) and sedentary (−0.024 ± 0.008 bpm/mmHg) groups with NCP of 40 mmHg during LBNP. There were no significant interactions between the NCP and fitness factors ($P = 0.63$) or the NCP and LBNP factors ($P = 0.77$) on the CBR-HR gains.

The fitness factor approached significance ($P = 0.077$) on overall CBR-MAP gains at rest (active −0.133 ± 0.014 mmHg/mmHg versus sedentary −0.110 ± 0.011 mmHg/mmHg; Figure 2(C)) and at −15 mmHg LBNP (active −0.129 ± 0.015 mmHg/mmHg versus sedentary −0.113 ± 0.013 mmHg/mmHg; Figure 2(D)). The LBNP factor did not impact ($P = 0.94$) but NCP significantly influenced ($P < 0.01$) the CBR-MAP gains. Furthermore, there was a significant interaction between the NCP and fitness factors ($P < 0.01$) on the CBR-MAP gains. Overall, the fitness-related differences in CBR-MAP gains at rest and during LBNP appeared to be more substantial in the pressor responses to positive NCP-induced carotid hypotension ($P < 0.01$) than the depressor responses to negative NCP-induced carotid hypertension ($P = 0.63$). Post hoc analysis with Tukey test indicated a significant difference in the CBR-MAP gains in response to the carotid hypotension induced by 20 mmHg neck-pressure between the sedentary and physically active groups at rest, that is, −0.113 ± 0.020 versus −0.239 ± 0.054 mmHg/mmHg ($P = 0.046$), while this group difference in the CBR-MAP gains during LBNP, that is, −0.133 ± 0.039 versus −0.235 ± 0.055 ($P = 0.151$) was not statistically significant. The LBNP factor did not impact the pressor ($P = 0.82$) or depressor ($P = 0.87$) responses.

Figure 3 presents the group HR and MAP responses to estimated carotid sinus pressures elicited by neck-pressure and neck-suction. Only baseline group CSP-HR response curves could be fit using logistic modeling in both the sedentary and physically active women (Figure 3(A)). During LBNP, the CSP-HR response in the sedentary group was not sigmoidal (Figure 3(B)). Furthermore, the CSP-MAP response curve could not be logistically modeled in the sedentary women at rest (Figure 3(C)) or in the physically active women during −15 mmHg LBNP (Figure 3(D)). The derived maximal gains of the estimated CSP-HR response

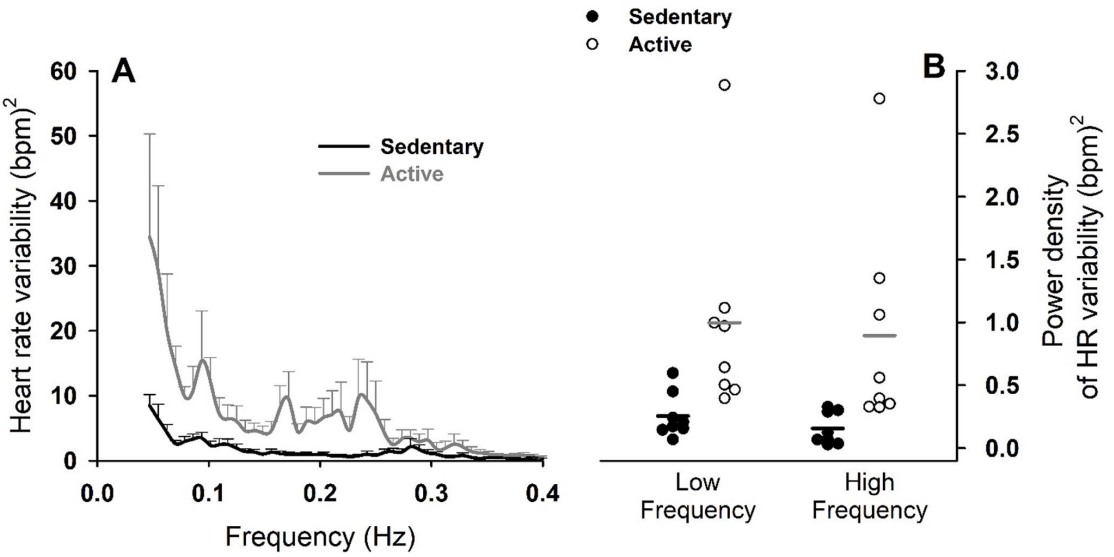

Figure 1. Power spectrum analysis of heart rate variability at pre-LBNP baseline. Panel (A): frequency-domain analysis of heart rate variabilities (mean ± SEM) in sedentary (black line) and physically active elderly women (gray line) during supine rest. Panel (B): low-frequency (0.05–0.15 Hz) and high-frequency (0.15–0.31 Hz) power densities of heart rate variabilities.
Circles and horizontal bars indicate individual values and group means, respectively. Power densities of heart rate variability in both low and high frequency domains were significantly greater in physically active versus sedentary elderly women, with and without the high outlier in the physically active group.

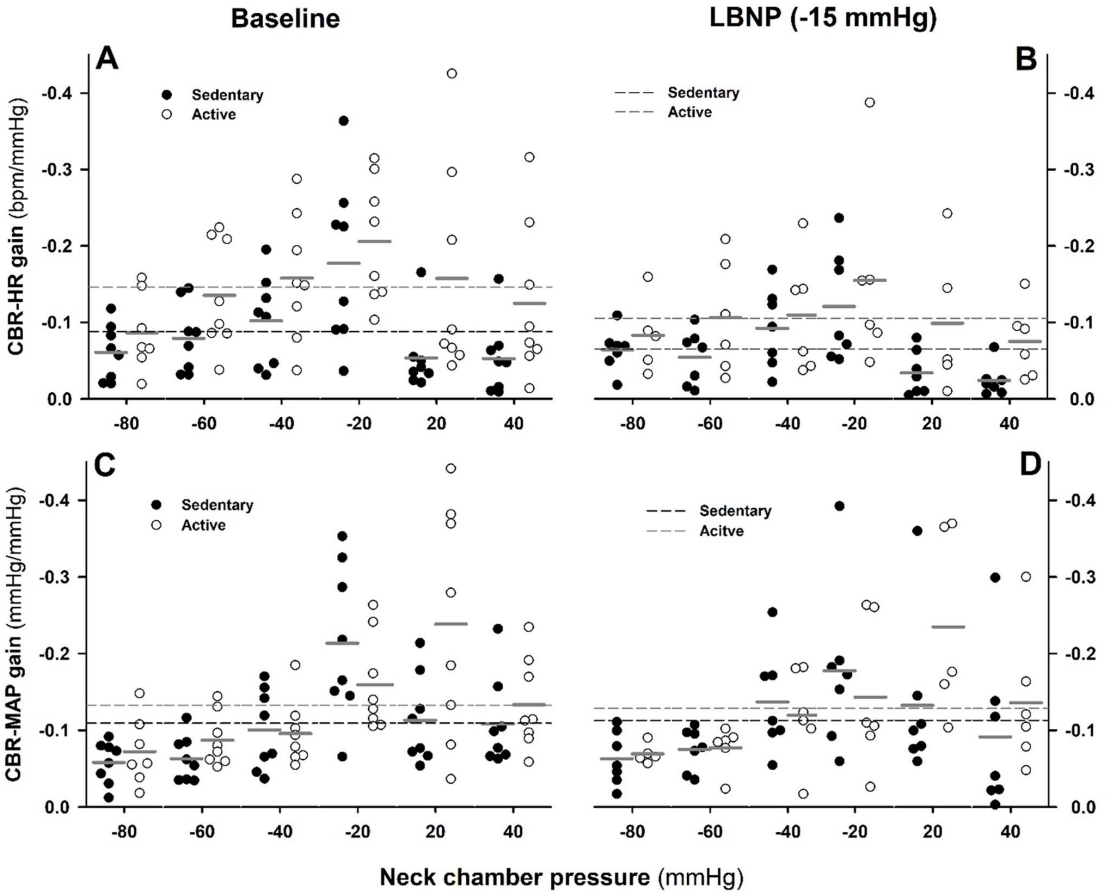

Figure 2. Carotid baroreflex control of heart rate and mean arterial pressure. Carotid baroreflex gains for control of heart rate (Panels (A) and (B): CBR-HR gain) and mean arterial pressure (Panels (C) and (D): CBR-MAP gain) at rest and during −15 mmHg lower body negative pressure (LBNP) are plotted as functions of neck chamber pressure. The fitness factor is statistically significant ($P < 0.01$) on CBR-HR gain, indicating more robust carotid baroreflex control of heart rate in the physically active versus sedentary women. LBNP tended to decrease CBR-HR gain (LBNP factor $P < 0.01$). Overall CBR-MAP gains trended upward in the physically active versus sedentary women (fitness factor $P = 0.077$). When data are subdivided into positive and negative chamber pressures, the fitness factor is significant on CBR-MAP gains during positive ($P < 0.01$) but not negative neck chamber pressures. LBNP did not alter CBR-MAP gains (LBNP factor $P = 0.94$). Closed and open symbols represent individual data of the sedentary and physical active women, respectively. Gray bars denote the group means. Black and gray broken lines indicate grand group means of carotid baroreflex gains in the sedentary and physically active elderly women, respectively.

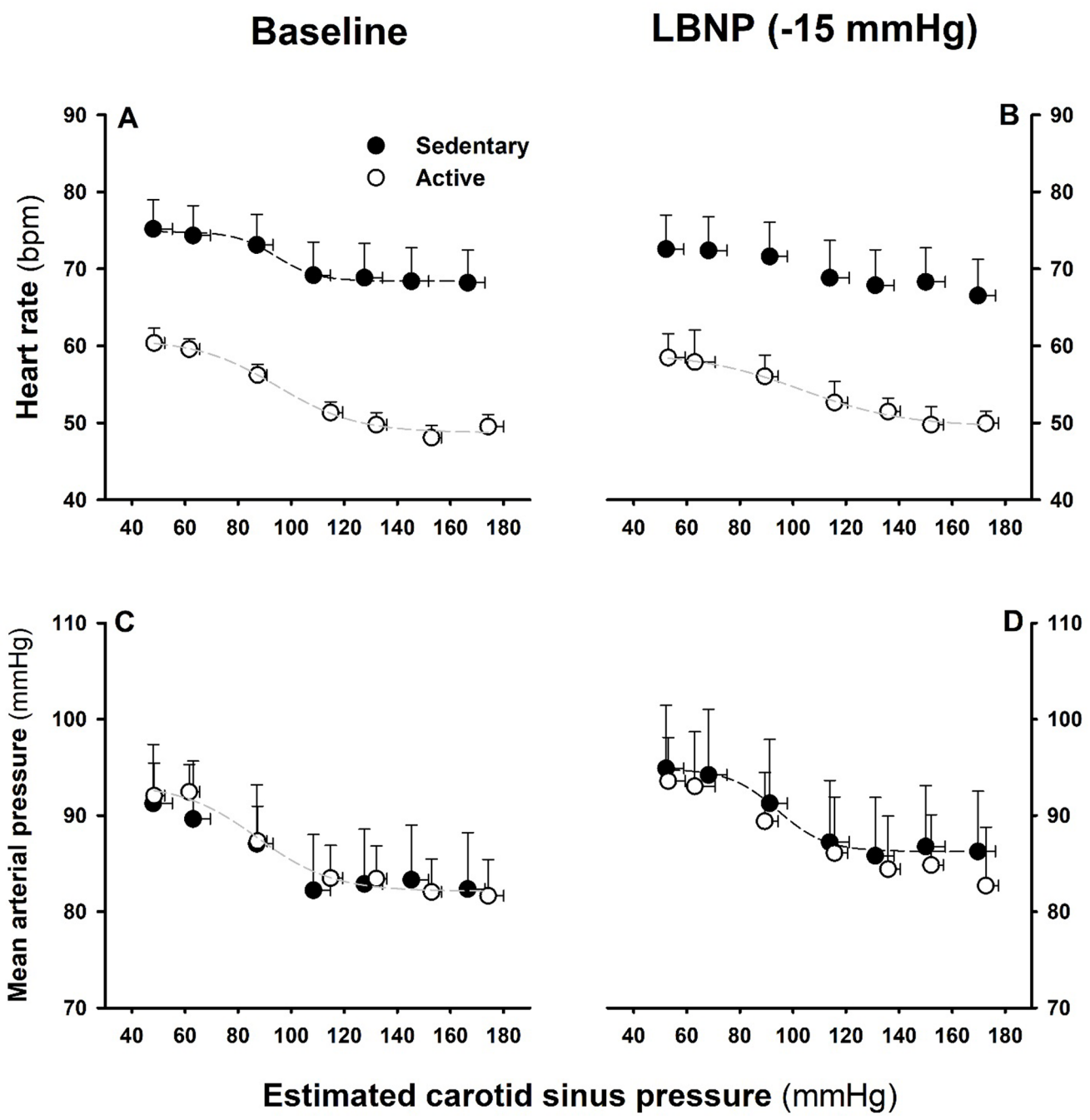

Figure 3. Heart rate and mean arterial pressure as functions of carotid sinus pressure. Mean values ± SEM and logistic modeling (broken lines) in sedentary (closed circles) and physically active (open symbols) elderly women. Panels (A) and (B): heart rate versus estimated carotid sinus pressure (CSP) during pre-LBNP baseline (Panel (A)) and at −15 mmHg LBNP (Panel (B)), Panels (C) and (D): mean arterial pressure versus estimated carotid sinus pressure during pre-LBNP baseline (Panel (C)) and at −15 mmHg LBNP (Panel (D)).
Broken lines are omitted when the data could not be logistically modeled. Baseline maximal gain of the heart rate response to CSP is significantly increased ($P < 0.01$) in the physically active (−0.454 ± 0.057 bpm/mmHg) versus sedentary (−0.123 ± 0.024 bpm/mmHg) women.

curves differed ($P < 0.01$) in the sedentary (−0.123 ± 0.024 bpm/mmHg) versus physically active (−0.454 ± 0.057 bpm/mmHg) groups at rest.

Carotid baroreflex function in elderly men versus elderly women

Carotid baroreflex control of HR (CBR-HR gain), that is, the bradycardiac response to the carotid hypertension induced by −20 mmHg neck-suction and the tachycardiac response to the carotid hypotension induced by 20-mmHg neck-pressure did not differ (sex factor $P = 0.65$) in elderly women versus men (Figure 4(A)), although the response of CBR-HR gain to physically active lifestyle differed in men versus women (fitness factor $P = 0.019$). The sex-related difference in carotid baroreflex control of MAP (CBR-MAP gain), that is, depressor response during −20 mmHg neck-suction and pressor response during 20 mmHg neck-pressure showed a trend

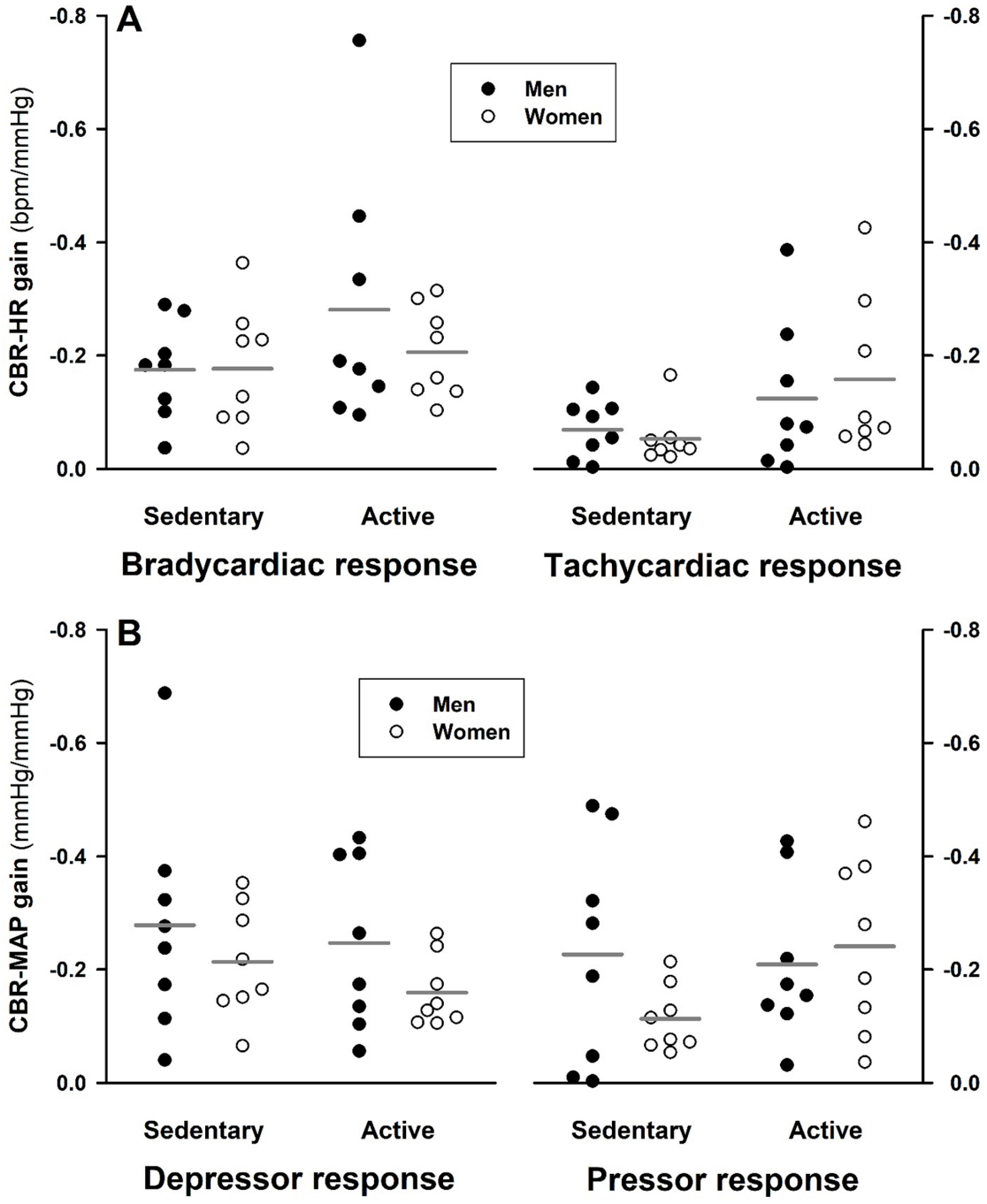

Figure 4. Carotid baroreflex control of heart rate (A) and mean arterial pressure (B) during carotid hypertension induced by –20 mmHg neck-suction and carotid hypotension induced by +20 mmHg neck-pressure in elderly men versus elderly women.
Individual (symbols) and group mean values (gray bars) from sedentary and physically active elderly women (open symbols) and age-matched men (closed symbols) during pre-LBNP baseline are shown. Panel A: Carotid baroreflex control of heart rate (CBR-HR gain) did not differ between the genders; however, the fitness factor was statistically significant on CBR-HR gain. Panel B: carotid baroreflex control of mean arterial pressure (CBR-MAP gain) trended higher in the elderly men versus women ($P = 0.109$), except the pressor response to 20 mmHg neck pressure, where the trend was absent in physically active subjects. The fitness factor on CBR-MAP gain is not statistically significant. Values in the elderly men were reported previously.[2]

(sex factor $P = 0.109$) toward greater sensitivity in the elderly men than women (Figure 4(B)); however, fitness did not impact the CBR-MAP gain (fitness factor $P = 0.86$).

Discussion

This study is among the first to document in elderly women that habitual physical activity augments HR variability in both low- and high-frequency domains of the power spectrum, indicating increased tonic cardiac parasympathetic modulation (Figure 1). Our data confirmed that maintaining a physically active lifestyle could preserve autonomic control of the heart as women transition from middle age to senescence.[1,3] This study also demonstrated over a broad hypotensive–hypertensive range that the carotid baroreceptor reflex control of HR was more robust in physically active

elderly women than their sedentary counterparts (Figure 2). These findings in elderly women are concordant with a previous study in which physically active elderly men showed enhanced CBR-HR gains versus age-matched sedentary men.[2] Collectively, the present findings demonstrate appreciable enhancements of both tonic vagal modulation (manifested by HR variability in the high-frequency domain) and dynamic vagal-cardiac response (represented by CBR-HR gain) in the hearts of elderly women who maintained a physically active lifestyle. Thus, the age-related weakening of parasympathetic control of cardiac function could be mitigated by habitual physical activity and improved cardiorespiratory fitness in elderly women.

Carotid baroreflex enhancement by physical activity: potential mechanisms

The enhancement of carotid baroreflex sensitivity by exercise training has been proposed to be related to an augmented compliance in central arteries[38,39] where the arterial baroreceptors are located. Concordant with that proposal, in this study aortic compliance estimated from the ratio of stroke volume index to arterial pulse pressure (Table 1) was greater in the physically active than sedentary women. Furthermore, enhancement of the efferent limb of the vagal-cardiac baroreflex arc also could contribute substantively to the augmented CBR-HR sensitivity previously reported in physically active versus sedentary elderly men.[2]

However, the question remains whether the carotid baroreceptor mediated afferent pathway or autonomic nervous efferents and the innervated end-organs are the primary contributors to the enhancement of carotid baroreflex sensitivity in physically fit, elderly women. Were the change in baroreceptor sensitivity the sole mechanism, both CBR-HR and CBR-MAP gains would be similarly enhanced in the physically active versus sedentary women. However, only overall CBR-HR gains at rest and during LBNP were significantly higher in the physically active women, while overall CBR-MAP gains trended higher in the active women, but did not attain statistical significance. This observation implies that the age-related change in vagal-cardiac function could be more profoundly affected by improved cardiorespiratory fitness in elderly women than the change in sympathovasomotor function. The different responses of the CBR-HR and CBR-MAP gains to active lifestyles also implied that the relative contribution of carotid baroreflex mediated cardiac response to CBR-MAP gain exceeded the contribution of the vasomotor response. Although CBR-HR gain might contribute to the augmentation of MAP or CBR-MAP gain in physically active elderly women, the reflex vasomotor response is likely to be the more important contributor.

The fitness-related differences in carotid baroreflex function appeared to be more robust during tachycardiac responses to the suppression of carotid baroreceptors by positive neck pressures at rest and during LBNP (Figure 2). In addition to CBR-HR gain, CBR-MAP gain during pressor response to the carotid hypotension induced by positive neck pressure tended to be augmented in the physically active versus sedentary elderly women. Collectively, these findings suggested that carotid baroreflex control of both vagal-cardiac function (represented by the HR response) and probably sympathetic-vasomotor function (represented by the MAP response) were enhanced in elderly women maintaining a physically active lifestyle.

Gender-related differences in CBR enhancement by physical activity

We previously reported physical activity did not affect CBR-MAP gains in elderly men,[2] but in this study physical activity increased CBR-MAP gain in the pressor response in elderly women (Figure 4(B)). The divergent findings in elderly men versus women may be ascribed to the trend toward a lower pressor response CBR-MAP gain in sedentary elderly women versus men (Figure 4(B)). When CBR-MAP gains in physically active elderly women were compared with those in physically active and sedentary elderly men, the sex disparity was absent during the pressor response to 20-mmHg neck-pressure. The lower CBR-MAP gains in the sedentary elderly women were consistent with previous reports of lower arterial baroreflex sensitivity[1,7,40] and orthostatic tolerance[41,42] in women versus men. The present findings suggest that a physically active lifestyle could prevent the sex-related diminution of CBR-MAP gains, and thus, improve orthostatic intolerance in elderly women.

Carotid baroreflex function is pivotal to short-term regulation and control of cardiovascular homeostasis. Baroreflex sensitivity was inversely correlated with plasma norepinephrine concentration (a measure of sympathetic control) in healthy subjects[1,43] and in patients with acute myocardial infarction.[44] Chronic activation of carotid baroreceptors improved survival of dogs with heart failure, in association with reflexive suppression of plasma norepinephrine and angiotensin II.[45] Arguably, the enhanced carotid baroreflex function and HR variability in physically active elderly women may serve to preserve cardiovascular homeostasis. However, a facilitatory interaction of carotid baroreflex function with cardiopulmonary baroreceptor unloading was absent in both physically active and sedentary elderly women (Figure 2). This finding indicated that aging and senescence may impair a central autonomic interaction in women regardless of their physical fitness, concordant with previous observations in elderly sedentary and physically active men.[2] Furthermore, similar hemodynamic responses to mild central hypovolemia elicited by −15 mmHg LBNP in sedentary and physically active elderly women suggested the reflex cardiopulmonary baroreceptor response to minimal unloading was unaffected by physical fitness.

Study limitations and perspectives

The main limitation of this study is that the healthy, sedentary elderly women were heavier than their physically active counterparts. Indumathy *et al.*[46] reported decreased frequency-domain and time-domain HR variability and baroreflex sensitivity in pre-obese and obese young adults versus normal weight controls. In morbidly obese patients, decreases in BMI 3 and 6 months after gastric bypass or sleeve gastrectomy were associated with increased frequency-domain HR variability and baroreflex sensitivity.[47] However, the impacts of weight factor or BMI versus fitness

factor on HR variability and carotid baroreflex function in elderly women is unknown. Studies addressing this question will require sedentary groups with the same body mass as the physically active groups. In addition, this study utilized a cross-sectional rather than longitudinal design, so it does not provide information regarding the age at which a woman must begin exercising in order to enjoy its cardiovascular benefits later in life. Indeed, endurance exercise training can improve cardiovascular function and peak aerobic capacity even in elderly men and women,[48] suggesting that one is never too old to benefit from exercise training.

Cardiovascular function appears to be more adversely affected by aging in sedentary women than men. Active physical lifestyle or habitual physical activity enhances HR variability (a tonic vagal modulation) and CBR-HR gain (a dynamic vagal response) in elderly women, thereby preventing an age-related vagal cardiac dysfunction and providing more robust cardioprotection against ventricular arrhythmia or fibrillation.[49,50] Furthermore, the augmented CBR-MAP gain in the physically active versus sedentary elderly women suggests that habitual exercise may help improve carotid baroreflex function and, thereby, hemodynamic stability. Chronic exercise training not only maintains and enhances physical mobility in the elderly, it also prevents or slows the cardiovascular deterioration associated with primary aging.

Conclusions

This study demonstrated that habitual physical activity improves vagal-cardiac modulation and reflex function mediated by carotid arterial baroreceptors in elderly women, although there is no facilitatory interaction between unloading cardiopulmonary baroreceptor and carotid baroreflex function. This fitness related improvement in carotid baroreflex control of HR and arterial pressure effects a particularly robust pressor response to decreased carotid sinus pressure.

AUTHORS' CONTRIBUTIONS

MC, HW, and XS conceived and planned study. XS performed experiments. MC, HW, and XS analyzed data. MC, HW, SR, SD, GK, YD, RM, and XS interpreted results of experiments. MC, HW, GK, YD, RM, and XS prepared figures and drafted manuscript. MC, HW, SR, SD, GK, YD, RM, and XS edited the manuscript. MC, HW, SR, SD, GK, YD, RM, and XS approved final version of manuscript.

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DECLARATION OF CONFLICTING INTERESTS

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