Significant role of the cardiopostural interaction in blood pressure regulation during standing

Xu D, Verma AK, Garg A, Bruner M, Fazel-Rezai R, Blaber AP, Tavakolian K. Significant role of the cardiopostural interaction in blood pressure regulation during standing. Am J Physiol Heart Circ Physiol 313: H568–H577, 2017. First published June 16, 2017; doi:10.1152/ajpheart.00836.2016.—Cardiovascular and postural control systems have been studied independently despite the increasing evidence showing the importance of cardiopostural interaction in blood pressure regulation. In this study, we aimed to assess the role of the cardiopostural interaction in relation to cardiac baroreflex in blood pressure regulation under orthostatic stress before and after mild exercise. Physiological variables representing cardiovascular control (heart rate and systolic blood pressure), lower limb muscle activation (electromyography), and postural sway (center of pressure derived from force and moment data during sway) were measured from 17 healthy participants (25 ± 2 yr, 9 men and 8 women) during a sit-to-stand test before and after submaximal exercise. The cardiopostural control (characterized by baroreflex-mediated muscle-pump effect in response to blood pressure changes, i.e., muscle-pump baroreflex) was assessed using wavelet transform coherence and causality analyses in relation to the baroreflex control of heart rate. Significant cardiopostural blood pressure control was evident counting for almost half of the variable total variance in blood pressure changes that observed in the cardiac baroreflex (36.6–72.5% preexercise and 34.7–53.9% postexercise). Thus, cardiopostural input to blood pressure regulation should be considered when investigating orthostatic intolerance. A reduction of both cardiac and muscle-pump baroreflexes in blood pressure regulation was observed postexercise and was likely due to the absence of excessive venous pooling and a less stressed system after mild exercise. With further studies using more effective protocols evoking venous pooling and muscle-pump activity, the cardiopostural interaction could improve our understanding of the autonomic control system and ultimately lead to a more accurate diagnosis of cardiopostural dysfunctions.

NEW & NOTEWORTHY We examined the interaction between cardiovascular and postural control systems during standing before and after mild exercise. Significant cardiopostural input to blood pressure regulation was shown, suggesting the importance of cardiopostural integration when investigating baroreflex hypotension. In addition, we observed a reduction of baroreflex-mediated blood pressure regulation after exercise.

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THE ORTHOSTATIC HYPOTENSION frequently experienced in the elderly (38, 48) and in patients with neurodegenerative diseases (4, 56) is largely associated with autonomic dysfunction (15). Astronauts also suffer from orthostatic intolerance after spaceflight (6) due to a reduction in blood volume and impairment of cardiac function and heart rate (HR) responses (77). In addition, astronauts often experience postflight gait and postural instabilities due to in-flight adaptive alterations to sensory-motor control (34). Upon standing, gravitational effects cause a downward displacement of thoracic blood volume to the regions below the diaphragm (65, 69). In addition, the central blood volume declines after a rise in fluid filtration into the interstitial spaces in the upright position (39). As a consequence, the venous return falls leading to a reduction in stroke volume, cardiac output, and arterial blood pressure, which, if not compensated for, will result in systemic hypotension that could further lead to cerebral hypoperfusion and syncope (20, 64, 68).

Maintaining postural and cardiovascular stability in the upright posture involves complex physiological regulations among which the autonomic nervous system plays a central role (66).Orthostatic stress evokes a number of physiological responses including the arterial baroreflex elevating HR and peripheral vascular resistance (30, 59, 75) and skeletal muscle-pump effect propelling the pooled blood back to the heart (18, 24, 45).

Upon standing, decreased aortic and carotid blood pressure unload the baroreceptors located in the aortic arch and carotid sinuses resulting in a rapid increase of HR via vagal withdrawal and slower elevation of HR and peripheral vascular resistance through sympathetic activation to maintain arterial blood pressure (59). Nevertheless, the baroreflex-mediated sympathetic nerve activity has little effect on venous tone in the lower limbs due to scarce sympathetic innervation in the veins within limb muscles (16, 60). As a consequence, quiet standing results in extensive venous pooling in the legs in the absence of skeletal muscle-pump effect. Contraction of muscles in the lower limbs pumps the pooled venous blood back to the heart and increases venous return and cardiac output (21, 24, 41, 70a). It is well recognized that the skeletal muscle pump plays a major role in blood pressure regulation under
orthostatic stress especially in patients with autonomic failure who have difficulties elevating vascular resistance (66). In addition, the slight postural sway during standing resulted from lower limb muscle activities also serves as an important contributor in promoting venous return (1, 29, 50).

Although it has been long known that the skeletal muscle pump helps maintain blood pressure (21), the cardiovascular and postural reflexes have been primarily investigated as independent control mechanisms (13, 55, 81). Recent research has been conducted to focus on the control relationship between the musculoskeletal and cardiovascular systems. Novak et al. (52) proposed a conceptual model of cardiocirculatory coupling during walking. In this model, the authors hypothesized that forces generated by muscle contraction during walking act as a pump, propelling venous blood to the right atrium with a step synchronized rhythm. Studies conducted by Claydon and Hainsworth (8, 9) showed the link between postural sway and prevention of syncope in which participants who had poor table orthostatic tolerance but never fainted during normal standing showed greater postural sway than patients who experienced frequent syncopal episodes (9). These observations demonstrate the importance of the skeletal muscle-pump effect in cardiovascular regulation under physiological conditions of insufficient vascular control. In addition to the mechanical effect of muscle pump on blood pressure, it is reasonable to hypothesize the existence of a feedback baroreflex-mediated muscle-pump activation in response to blood pressure changes (i.e., muscle-pump baroreflex), which forms a closed control loop analogous to the well-known closed-loop model between HR and blood pressure. That is, the muscle-pump baroreflex responds to blood pressure changes via baroreceptors, like the arterial baroreflex, and activates skeletal muscle contractions through central neural pathways to compensate blood pressure perturbations.

The integrative model shown in Fig. 1 has recently been proposed by our group describing the interactions between cardiovascular and postural control systems related to orthostatic tolerance through the skeletal muscle-pump effect (2). In this model, the novel component is the muscle-pump baroreflex in response to blood pressure changes through a central cardiopostural integration. This muscle-pump baroreflex, combined with the well-known mechanical effect of the muscle pump on cardiovascular systems, forms a closed control loop between the cardiovascular and postural systems (cardiopostural control). In addition, the blood pressure regulation through cardiac baroreflex control of HR and the limb muscle activation in response to the sensory perception of the foot during postural sway through somatosensory control system (i.e., postural control) are also integrated into the model. In the present study, the emphasis is on the newly proposed muscle-pump baroreflex mechanism.

The cardiopostural integration was characterized based on a wavelet-based technique in our previous studies that showed evidence of significant coherent behavior between the two systems (17, 18). However, the directionality of the information flow between the systems remains to be understood. Such information will aid in monitoring system performance under various physiological conditions. Decline or deviation in the strength of causality from well-established baseline values could be an indicator of system impairment. Causal interactions between cardiovascular and postural control systems were explored in our previous work (71–74).

In this study, we investigated the role of cardiopostural control (the muscle-pump baroreflex in particular) in relation to cardiac baroreflex in blood pressure regulation under orthostatic stress. Participants were exposed to controlled external perturbation in the form of submaximal exercise, and signals representing cardiovascular control [HR and systolic blood pressure (SBP)], lower limb muscle activation [electromyography (EMG)], and postural sway [center of pressure (COP), derived from force and moment data during sway] were measured before and after exercise. Mild exercise has been reported to decrease blood pressure during postexercise standing (31, 33, 40) as a consequence of excessive venous pooling induced by vasodilatation of the leg muscles (22). We hypothesized that 1) the cardiopostural control plays a significant role in blood pressure regulation in response to orthostatic challenge and 2) the muscle-pump baroreflex mechanism will be further activated and have a greater contribution to blood pressure regulation after exercise.

**MATERIALS AND METHODS**

**Protocols.** Data were collected from 20 participants (age: 26 ± 2 yr, height: 173 ± 8 cm, weight: 67 ± 11 kg, 10 men and 10 women) with no history of cardiovascular, respiratory, or neurological disease, major musculoskeletal injuries, or hormone imbalance. The use of prescription medications and naturopathic remedies was reported. Participants taking any substance that could alter cardiovascular regulation or postural stability were excluded. Before the experiments, participants’ height, weight, general medical history, and present medications were recorded. Female participants were asked to report the use of prescription contraceptives and were not tested during a particular phase of the menstrual cycle. All participants were instructed to refrain from exercise and caffeine consumption for 24 h before the experiment. The experiment protocol was approved to be of minimal risk by Simon Fraser University’s Research Ethics Board, in compliance with the Tri-Council policy on research ethics (TCPS 2). Written informed consent was obtained from each participant before the experiment.
The experiment protocol consisted of three parts: preexercise sit-to-stand test, submaximal cycle ergometer exercise, and postexercise stand test. All tests were conducted in a sensorily-minimized environment: a dark room with black drapes in front of the participants with minimal ambient noise. During the sit-to-stand test, participants were seated quietly with arms relaxed by their sides for 5 min, after which assistance was provided to transition into upright stance on a force platform for an additional 6 min to induce orthostatic stress. Participants’ feet were placed parallel and 5 cm apart on the center of the force platform. They were instructed to keep their eyes closed, maintain imaginary eye-level gaze, and not to alter foot placement.

After the sit-to-stand test, participants were seated comfortably on a cycle ergometer to carry out a 12-min submaximal exercise protocol. The exercise protocol consisted of a 2-min warm-up at 25 W, followed by 10 min at 80 or 100 W for female and male participants, respectively. Participants were instructed to maintain 70 rpm throughout the duration of the exercise protocol. This protocol was designed to induce mild stress on the cardiovascular system without crossing the aerobic threshold and limited the risk of musculoskeletal fatigue. No data were collected during the exercise period.

Immediately upon cessation of exercise, a 6-min stand test was conducted with eyes closed (forward gaze) and identical pretest foot placement on the force platform. Approximately 30 s elapsed in the transition from the cycle ergometer to the force platform and initiation of data acquisition.

**Data collection.** During the preexercise sit-to-stand test and postexercise stand test, electrocardiography (ECG) was acquired with custom equipment from LifePak 8 (Medtronic) in a standard Lead II electrode configuration. Continuous blood pressure was monitored through a noninvasive photoplethysmography finger cuff from Finometer Model 1 (FMS, Amsterdam, The Netherlands). Surface EMG signals were measured from four bilateral lower leg muscles of both legs: tibialis anterior, lateral soleus, and medial and lateral gastrocnemius. Transdermal differential recording of the signals was performed using the Bagnoli-8 (Delsys) EMG system. The sites for surface EMG sensor placement were chosen based on recommendations from the SENIAM project (25). Postural sway data, in the form of COP coordinates (medial-lateral sway (COPx) and anteroposterior sway (COPy)), were derived from force and moment data obtained with an Accusway Plus force platform (AMTI). The exercise protocol was performed on a digital Jaeger ER 800 cycle ergometer (Wuerzburg, Germany). Data were acquired at a sampling rate of 1,000 Hz through a National Instruments PCI-6229 16-bit data acquisition platform and Labview 8.2 software (National Instruments). Data analysis. Data analyses were performed in MATLAB (MathWorks). The last 5 min of the quiet stance phase were used for analysis. QRS complex was first detected from ECG based on Pan-Tompkins algorithm (54), which yielded the time series of heart beat period (i.e., RR interval). Beat-by-beat time series of SBP were then obtained from the maximum pressure values of the blood pressure waveform within each RR interval while the diastolic blood pressure (DBP) time series were constructed by identifying the minimum blood pressure values before the SBP peak of the following beat. The beat-by-beat mean arterial pressure (MAP) was then calculated by averaging the blood pressure waveform between two adjacent DBP valleys.

Aggregate EMG was obtained by addition of rectified EMG signals from all individual leg muscles to represent the overall muscle activities (17, 18). The EMG envelope was then captured by a moving average filter whose cutoff frequency was recommended by the SENIAM project to be within 5–20 Hz (25). Considering the low-frequency response of cardiopostural control (<0.5 Hz) (2, 5, 76), a cutoff frequency of 5 Hz was used for the filter in EMG envelope extraction to minimize the estimation uncertainty (25). Finally, analogous to the impulse of force, the area under the EMG envelope within each heart beat [i.e., EMG impulse (EMGimp)] was calculated to represent the muscle contraction strength on a beat-by-beat basis. The concept of impulse was used because, in a beat-by-beat perspective, the strength of muscle contraction over a heart beat would be related to the time period of that beat. That is, a brief strong contraction can be considered to be equivalent to weaker contractions over a longer period and the same contraction level would produce higher overall strength over a longer heart beat. The resultant COP (COPr) was obtained from COPx and COPy (i.e., COPr = \sqrt{COPx^2 + COPy^2}) and the change rate of COPr (COPrv) was calculated as the first derivative of COPr and averaged within each beat. The resultant COPv time series represent the beat-by-beat postural sway velocity (44, 82). All beat-by-beat time series were resampled to 10 Hz using spline interpolation before the wavelet transform and causality analysis.

**Wavelet transform coherence analysis.** The wavelet transform coherence (WTC) method was proposed and has been explained in detail by Torrence and Compo (70). Briefly, the Morlet wavelet was applied to obtain time-frequency distributions of WTC (17, 18) for the following signal pairs: SBP ↔ RR (cardiac baroreflex), SBP ↔ EMGimp (muscle-pump baroreflex), SBP ↔ COPr (baroreflex-mediated postural sway), and COPrv ↔ EMGimp (postural control). For each pair of signals, the threshold of significant coherence was obtained from the WTC of 500 pairs of surrogate data as the 90th percentile of the coherence sampling distribution at each scale/frequency through the Monte Carlo method (19). The surrogate data were generated with a first-order autoregressive model with coefficients estimated from the actual signals. Three frequency bands were considered to reflect the common range of possible responses to perturbations of both the cardiovascular and postural control systems (2, 5, 76): very low frequency (VLF; 0.03 – 0.07 Hz), low frequency (LF; 0.07 – 0.15 Hz), and high frequency (HF; 0.15 – 0.5 Hz).

The percentage of significant coherence (%SC) was computed as the area of significant WTC in each frequency band divided by the total area of that frequency band from the time-frequency distribution of WTC (18). The gain values (G) of each signal pair were computed from the cross wavelet transform of the two signals (19) and averaged over regions of significant WTC within each frequency band.

**Causality analysis.** The causality between the acquired signals was studied using the nonlinear convergent cross mapping (CCM) method (35, 67). The efficacy of the CCM method toward detecting causality between physiological signals and its superior performance over Granger causality with signals of nonlinear nature have been demonstrated in the literature (26, 61, 62, 67, 74). To infer a causal relationship between two variables (X and Y), first, the state space reconstruction (shadow manifold) for both variables were performed. Next, the correspondence between the original variable and its estimate using the shadow manifold of the other variable was quantified using Pearson correlation coefficient (varying from 0 to 1) to assert the causal information flowing from one variable to another. The mathematical representation of causal relationship is presented in the Appendix, and the detailed explanation of the CCM method is presented in the work done by Sugihara et al. (their Supplementary Materials in Ref. 67).

The bidirectional causalities were investigated between the following signal pairs: SBP ↔ RR (cardiac baroreflex vs. heart rate effect on blood pressure), SBP ↔ EMGimp (muscle-pump baroreflex vs. blood pressure regulation via mechanical muscle-pump effect), COPrv ↔ EMGimp (posture control vs. muscle contraction induced postural sway), and SBP ↔ COPr (baroreflex-mediated postural sway vs. blood pressure regulation via postural sway). For each signal pair, if there existed a significant difference in a population-wide mean causality values between the two causal directions (X → Y and Y → X), then one was considered to have a dominant causal behavior on another. This behavior was representative of a system being a regulator or regulated through other physiological processes (muscle-pump driven, baroreflex driven, or postural sway driven). All
CCM results presented in this paper were calculated using an embedding dimension (E) of 4, chosen based on false nearest neighbor’s algorithm (32) using CRP toolbox in MATLAB (43), at a delay (τ) of 10 samples to capture physiological alterations within a heart beat range.

Spontaneous baroreflex sensitivity. Spontaneous baroreflex sensitivity (BRS) was estimated to characterize the autonomic regulation of HR in response to blood pressure changes using the beat sequence method (27, 55). Briefly, beat-by-beat SBP and RR interval sequences were selected when the SBP and RR interval increased or decreased in the same direction for three or more beats and the absolute change in SBP between beats was <0.5 mmHg. Regression slopes (∆RR/∆SBP) were calculated for each selected beat sequence and averaged over the entire 5-min data to obtain the overall BRS.

The timescale used in BRS calculation (i.e., ±3 heart beats) implies that the frequency information carried in BRS is mostly in accordance with the HF band in WTC analysis (0.15–0.5 Hz). As a conventional indicator of cardiac baroreflex regulation, BRS, therefore, provides reference values for the WTC-derived SBP → RR gain values in HF band. The correlation of the two techniques was evaluated by linear regression and Bland-Altman method (3) using the pooled BRS estimates and SBP → RR gain values in HF band from all participants pre- and postexercise.

Statistics. Statistical analyses were performed with JMP 12 software (SAS Institute). Two-factor (pre-/postexercise and men/women) ANOVA with repeated measures on one factor (pre-/postexercise) was used followed by Tukey’s honestly significant difference post hoc test. Residual of the ANOVA model was tested for normality using Shapiro-Wilk test. Data that failed the test of normality were analyzed using nonparametric Friedman’s test instead. Significance was accepted at P < 0.05, but given the limited number of participants, P < 0.1 is reported to reveal possible trends. Results are presented as means ± SD.

RESULTS

The collected data were carefully reviewed, and data from three participants were excluded due to the low signal quality of the continuous blood pressure measurements. As a consequence, data from 17 participants (9 men and 8 women, age: 25 ± 2 yr (men: 26 ± 2 yr and women: 25 ± 3 yr, P = 0.36), height: 174 ± 9 cm (men: 180 ± 4 cm and women: 168 ± 7 cm, P < 0.001), weight: 69 ± 11 kg (men: 77 ± 9 kg and women: 61 ± 4 kg, P < 0.001)] were used in the analysis.

Cardiovascular and postural variables. Averaged values of cardiovascular and postural variables are shown in Table 1. HR increased (P = 0.002) and SBP decreased (P = 0.049) after exercise, whereas DBP and MAP remained unchanged (P = 0.42 and 0.17, respectively). EMG and EMGimp were reduced postexercise (P = 0.009 and 0.004, respectively). Male participants tended to have greater COPrv (i.e., larger postural sway) than female participants (P = 0.09). No significant interaction effects (exercise × sex) were found in mean values.

Cardiopostural coupling and spontaneous BRS. Results describing cardiopostural coupling and spontaneous BRS are shown in Table 2. The averaged percentage times of cardiopostural coupling (SBP → EMGimp, muscle-pump baroreflex) before and after exercise were 21.1% and 18.8% (P = 0.52) in the HF band, 35.8% and 31.4% (P = 0.61) in the LF band, and 25.3% and 15.6% (P = 0.04) in the VLF band. %SC values for the cardiac baroreflex (SBP → RR) before and after exercise were 56.8% and 54.2% (P = 0.38) in the HF band, 76.3% and 79.6% (P = 0.40) in the LF band, and 46.5% and 31.6% (P = 0.006) in the VLF band. The linear coupling (%SC) between SBP and EMGimp was reduced after exercise in the VLF band and the SBP → EMGimp gain values (i.e., the muscle-pump BRS) decreased across all three frequency bands. The interaction between SBP and RR showed a similar pattern with a reduction of %SC in the VLF band and decreased SBP → RR gain values in all frequency bands. In the VLF band, the reduction of SBP → RR gain values was only found in female participants. The %SC and gain values from SBP to COPrv were not altered by mild exercise, but a sex difference (men > women) in %SC was observed at LF. Neither exercise nor sex had effects on %SC or gain values from COPrv to EMGimp. These results are also shown in Fig. 2.

The spontaneous BRS derived from beat sequence method declined postexercise, which is in accordance with the WTC results. Linear regression between BRS estimates and SBP → RR gain values in HF band showed a correlation coefficient r of 0.96 and regression slope of 1.07 (P < 0.0001), and the Bland-Altman plot indicated that the differences between the two methods were within the 95% limits of agreement except for one data point, showing a close agreement between the two methods with a systemic bias of 1.8 ms/mmHg (Fig. 3). The two data points with the largest BRS values (Fig. 3) were from the same participant with low HR (49 beats/min preexercise and 56 beats/min postexercise). This observation is consistent with the positive correlation between RR interval and BRS previously reported, suggesting a higher level of parasympathetic activity in the participant (27). Therefore, in a physiological sense, the two data points were treated as normal rather than outliers and included in the analysis.

Causality. Causality results are shown in Table 3. Bidirectional causality between SBP and RR (SBP ↔ RR) was not affected by either exercise or sex. In terms of cardiopostural control, the causality results revealed significantly stronger causal driving control from EMGimp → SBP, COPrv → SBP, and COPrv → EMGimp compared with causality values in reverse directions (P < 0.05). This dominant control pattern remained unchanged after exercise with a further reduction of nondominant causality of SBP → EMGimp, SBP → COPrv, and EMGimp → COPrv along with decreased COPrv → EMGimp causality.

Table 1. Averaged cardiovascular and postural variables during standing before and after mild exercise

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<tr>
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<th>Exercise</th>
<th>Sex</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
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<tr>
<td>HR, beats/min</td>
<td>77.1 ± 10.2</td>
<td>88.5 ± 15.4*</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>106.2 ± 9.7</td>
<td>102.7 ± 9.4*</td>
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<td>DBP, mmHg</td>
<td>66.7 ± 5.4</td>
<td>65.9 ± 6.5</td>
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<tr>
<td>MAP, mmHg</td>
<td>81.6 ± 6.6</td>
<td>79.9 ± 6.9</td>
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<tr>
<td>EMG, μV</td>
<td>50.0 ± 27.4</td>
<td>39.0 ± 24.4*</td>
</tr>
<tr>
<td>EMGimp, μV·s</td>
<td>40.3 ± 24.3</td>
<td>37.8 ± 19.2*</td>
</tr>
<tr>
<td>COPrv, mm/s</td>
<td>32.3 ± 13.6</td>
<td>33.5 ± 11.9</td>
</tr>
<tr>
<td>COPrv, mm/s</td>
<td>9.3 ± 5.3</td>
<td>8.2 ± 3.8</td>
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</table>

Values are means ± SD; n = 17 participants (9 men and 8 women). After exercise, heart rate (HR) increased while systolic blood pressure (SBP) and lower limb muscle activity showed reductions. DBP, diastolic blood pressure; MAP, mean arterial pressure; EMG, electromyography; EMGimp, EMG impulse on a beat-by-beat basis; COPrv, resultant center of pressure; COPrv, change rate of COPrv. *Different from preexercise, P < 0.05; †different from male participants, P < 0.1.
DISCUSSION

Significant cardiopostural control of blood pressure. Orthostatic intolerance involves factors that modify either cardiac output or peripheral vascular resistance leading to an inability to maintain arterial blood pressure. Extensive research has focused on the interaction of these cardiovascular control factors in relation to orthostatic regulation. However, during prolonged standing, reduced venous return decreases central blood volume and cardiac output, whereas baroreflex-mediated vasoconstriction and elevation of HR become only partially effective in maintaining blood pressure. Decreased intramuscular pressure (i.e., the muscle tonus which maintains the pressure within the tissues and capillaries) was shown to be associated with orthostatic intolerance in otherwise healthy subjects during head-up tilt while the vasomotor and sympathetic tone of the fainters were intensely activated during the period preceding syncope (46). Mayerson and Burch (46) also observed that the signs of syncope were eliminated by muscular contraction of lower limbs indicating the importance of skeletal muscle-pump effect in the prevention of orthostatic hypotension and syncope in addition to arterial baroreflex.

The major finding of this study is the presence of significant cardiopostural control of blood pressure in response to orthostatic challenge. The bidirectional cardiopostural interaction (SBP ↔ EMGimp) revealed by the causality analysis indicates significant feedback baroreflex-mediated muscle-pump activity upon changes in blood pressure other than the well-known feedforward mechanical muscle-pump effect. In terms of the percentage time of interaction with blood pressure changes, the contribution of muscle-pump baroreflex to blood pressure regulation was almost half of that contributed by the cardiac baroreflex (36.6–72.5% preexercise and 34.7–53.9% postexercise). This indicates an important cardiopostural component in blood pressure regulation under orthostatic stress in addition to the cardiac baroreflex. Our results revealed strong evidence that integrative cardiopostural control should be regularly considered as an important factor in research investigating orthostatic intolerance as well as corresponding countermeasures and prevention strategies.

Reduction of baroreflex-mediated orthostatic regulation after mild exercise. Decreased arterial blood pressure after exercise was reported and studied (31, 33, 40). The postexercise hypotension is considered to be the result of combined effects of centrally mediated reduction of sympathetic nerve activity (7, 23), blunted signal transduction from sympathetic outflow into vasoconstriction (22, 23), and local vasodilation...
mechanisms (37, 47). We, therefore, hypothesized that postexercise vasodilation would cause excessive venous pooling leading to a greater involvement of the muscle-pump regulatory mechanism in blood pressure control after exercise.

The results showed that the cardiac baroreflex was blunted postexercise, which could result from a reduction of neural transduction of the baroreflex and the corresponding effects on baroreflex hysteresis (80). While a significant reduction in SBP was observed after exercise (106.2 ± 9.7 mmHg preexercise vs. 102.7 ± 9.4 mmHg postexercise, $P = 0.049$), postexercise hypotension and vasodilation were not evident in the present study inferred from unaltered MAP and DBP (an indicator of peripheral vascular resistance). In addition, decreased postexercise EMG activity (50.0 ± 27.1 μV preexercise vs. 39.0 ± 24.4 μV postexercise, $P = 0.009$) showed even less activation of the muscle pump, suggesting a resetting of the muscle-pump baroreflex after exercise. Therefore, the reduced muscle-pump baroreflex after exercise (%SC,SBP→EMGimp and G,SBP→EMGimp in Table 2), which contradicts our hypothesis, could result from the resetting of muscle-pump activity level and the absence of excessive venous pooling postexercise likely due to the mild intensity and short duration (12 min) of exercise in our protocol. The decline of both cardiac and muscle-pump baroreflexes indicates an overall reduction of baroreflex-mediated orthostatic regulation after mild exercise (Fig. 2). This reduction could also be attributed to the involvement of other local regulatory mechanisms after exercise such as thermoreflex via cutaneous circulation (79).

The results showed weaker ($P < 0.05$) baseline causal relationship in the direction of baroreflex control (SBP → EMGimp and SBP → COPrv) compared with that in the nonbaroreflex direction (EMGimp → SBP and COPrv → SBP). After exercise, the strength of causality in baroreflex control direction was further reduced (Fig. 2), which suggests a decoupling in baroreflex-mediated cardiopostural interaction. This is consistent with the aforementioned postexercise reduction of the muscle-pump baroreflex. Despite the postexercise reduction of causality strength of muscle-pump baroreflex control, the nonbaroreflex causal control was unchanged and blood pressure was well regulated after exercise. Other than the possible involvement of alternative regulatory mechanisms, we speculated that the resetting of muscle-pump baroreflex may lead the system to a more efficient or, in other words, less stressed set point where less baroreflex control of muscle-pump activation is required to maintain blood pressure. The CCM causality in COPrv, → EMGimp and EMGimp, → COPrv declined after exercise with the dominant causal direction (COPrv, → EMGimp) remaining unchanged, indicating a systemic disassociation of the postural control loop. This could be due to

![Graphical summary of the results for cardiac baroreflex sensitivity (BRS), cardiopostural coupling, and bidirectional causality during standing before and after mild exercise.](image1)

**Fig. 2.** Graphic summary of the results for cardiac baroreflex sensitivity (BRS), cardiopostural coupling, and bidirectional causality during standing before and after mild exercise ($n = 17, 9$ men and $8$ women). A reduction of both cardiac and muscle-pump baroreflex controls of blood pressure was observed. %SC, percentage of significant coherence; G, gain value; Ca, causality strength; RR, RR interval; SBP, systolic blood pressure; EMGimp, electromyography impulse on a beat-by-beat basis; COPrv, change rate of resultant center of pressure; N.C., not changed after exercise; ↓, decreased after exercise. "Only in women at very low frequency (VLF); †sex effect (men > women) at low frequency (LF); ‡ sex effect (men > women).

<table>
<thead>
<tr>
<th>Causal Direction</th>
<th>Pre</th>
<th>Post</th>
<th>Male</th>
<th>Female</th>
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<td>SBP → RR</td>
<td>0.93 ± 0.04</td>
<td>0.95 ± 0.04</td>
<td>0.94 ± 0.04</td>
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<td>RR → SBP</td>
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<td>0.94 ± 0.03</td>
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<tr>
<td>SBP → EMGimp</td>
<td>0.88 ± 0.05</td>
<td>0.82 ± 0.09*</td>
<td>0.86 ± 0.07</td>
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<td>0.92 ± 0.04</td>
<td>0.91 ± 0.04</td>
<td>0.92 ± 0.03</td>
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<tr>
<td>COPrv → SBP</td>
<td>0.78 ± 0.04</td>
<td>0.73 ± 0.10*</td>
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<tr>
<td>EMGimp → COPrv</td>
<td>0.81 ± 0.05</td>
<td>0.73 ± 0.12*</td>
<td>0.81 ± 0.06</td>
<td>0.72 ± 0.11†</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 17$ participants ($9$ men and $8$ women). A postexercise reduction of nondominant causality (SBP → EMGimp, SBP → COPrv, and EMGimp, → COPrv) was observed. *Different from preexercise, $P < 0.05$; †different from male participants, $P < 0.05$; ‡ different from male participants, $P < 0.1$.

![Linear regression (left) and Bland-Altman plot (right) between cardiac BRS estimated from the beat sequence method and SBP → RR gain values (G,SBP→RR) in the high-frequency (HF) band from the wavelet transform coherence (WTC) analysis using the pooled data points from all participants before and after mild exercise.](image2)

**Fig. 3.** Linear regression (left) and Bland-Altman plot (right) between cardiac BRS estimated from the beat sequence method and SBP → RR gain values (G,SBP→RR) in the high-frequency (HF) band from the wavelet transform coherence (WTC) analysis using the pooled data points from all participants before and after mild exercise. The correlation coefficient ($r$) of 0.96 and regression slope of 1.07 ($P < 0.0001$) obtained from linear regression indicated a close agreement between the two methods. The Bland-Altman plot also showed that the differences between the two methods were within the 95% limits of agreement except for one outlier.
increased contribution to postural sway from sources other than muscle contractions [e.g., respiration (28, 63, 82) and hemodynamics (10, 51)] after exercise.

Sex effect on cardiopostural control. The cardiac BRS (i.e., $G_{\text{SBP} - \text{RR}}$) at VLF decreased postexercise only in female participants. The distribution of blood volume is known to be different between men and women in that women have greater blood pooling in the splanchnic vascular bed (78), which redistributes blood volume to thoracic compartment during central hypovolemia (1). Therefore, women tend to rely more on slower sympathetic-induced vasoconstriction of the splanchnic vasculature for orthostatic regulation. The reduced baroreflex control of HR in women may imply greater contribution of splanchnic vasconstriction in blood pressure regulation after exercise.

Our results revealed sex effects on COPr and cardiopostural control in relation to COPrc. Specifically, male participants presented marginally greater COPr than female participants ($P = 0.09$; Table 1), which likely contributed to the sex differences (men > women) in %SCSBP in the LF band and $G_{\text{SBP} - \text{COPr}}$ in the HF band (Table 2). While the origin of larger sway in male participants in this study requires further postural investigation, it is important to take into account the sex effect when assessing the feasibility to use COP measurement as a surrogate of EMG in cardiopostural control analysis.

Study limitation and future work. The present study used a 12-min mild exercise protocol as an external perturbation to enhance activation of the muscle-pump baroreflex. However, based on the results, it is possible that short-duration mild exercise was insufficient to evoke excessive venous pooling in the legs during postexercise standing in a healthy, young population. While the current study protocol was able to reveal the existence of significant cardiopostural control in blood pressure regulation, exercise protocols with higher intensity and/or longer duration or protocols specifically designed to increase venous pooling (e.g., passive head-up tilt with inactive muscle pump) may show a greater contribution of muscle-pump baroreflex on orthostatic regulation during postperturbation standing as we hypothesized.

The results of the current study were obtained from 17 healthy, young participants. In terms of the scope of the study to assess the cardiopostural interaction and the effects of mild exercise, only healthy and young participants were included to minimize the confounding effects of age and diseases. However, future investigations on participants of different ages and health conditions (e.g., stroke, concussion, neurodegenerative diseases, and bed rest immobilization) are necessary to evaluate the clinical significance of the cardiopostural model. While the sample size of 17 is reasonable for a controlled experimental exercise study (37, 47, 79, 80), a statistical power analysis should be considered to determine the sample size in the design of future studies.

While our results revealed significant role of the muscle-pump baroreflex in blood pressure regulation, the underlying neural pathways of muscle-pump baroreflex remain unclear and further investigations are warranted. The vestibular system has been shown to have interactions with both postural (11, 14) and cardiovascular (49, 57, 58) control systems. To understand the neural pathways of muscle-pump baroreflex, it would be beneficial to incorporate the vestibular system (through, for example, galvanic vestibular stimulation) in future studies.

Additional factors that may affect the blood pressure regulation such as respiration, temperature, and hormone were not included in the current study to achieve a simplified cardiopostural model. These components will be gradually integrated into the model and the corresponding measurements will be collected in future studies. With an increasing number of variables involved in the model, the bivariate methods used in the study (i.e., WTC and causality analysis) may become insufficient in revealing complex interactions among them and techniques capable of handling more variables (e.g., autoregressive moving average model) should be considered.

The blood volume and vascular resistance in lower limbs were not measured in this study. As a result, the baroreflex control on vascular tone was not studied and information regarding venous pooling and lower limb vascular resistance was inferred from an indirect indicator, DBP. Near-infrared spectroscopy should be considered to quantitatively assess and monitor changes in vascular resistance and venous pooling in the calf.

Conclusions. The present study investigated the interactions between cardiovascular and postural control systems in healthy, young participants during quiet standing before and after mild exercise. The contributions of both cardiac and muscle-pump baroreflexes to blood pressure regulation, the bidirectional causality of cardiopostural control, as well as the effects of mild exercise on these control mechanisms were studied. Our results revealed a significant component of cardiopostural control in relation to the cardiac baroreflex in blood pressure regulation under orthostatic stress. After mild cycling exercise, a reduction of baroreflex-mediated orthostatic regulation of blood pressure was observed in terms of the degree of interaction and causality strength. Although study protocols allowing further increase of venous pooling and hence muscle-pump activity along with further neurological investigations are warranted to improve the understanding of cardiopostural integration, the current study has clearly revealed the important role of cardiopostural control in the orthostatic regulation of blood pressure.

The blood pressure regulation and postural control can be affected by multiple factors including neurodegenerative diseases, aging, and exposure to microgravity. While disorders of cardiovascular and postural control systems are largely diagnosed and treated separately, the existence of significant interactions between the two systems suggests a preferable integrative assessment of cardiopostural systems. For example, postural instability has been shown to be closely related to cognitive function in patients with neurodegenerative diseases (36, 42) and can be identified at the early stage of the diseases (36, 53). The proposed cardiopostural model, therefore, could shed more insight on the central nervous control system and potentially lead to a more accurate diagnosis of cardiovascular and postural dysfunctions.

APPENDIX

Mathematical representation of the causal relationship. Mathematically, the unidirectional causal information flowing from variable X to variable Y ($X \rightarrow Y$) can be quantified using the CCM method as follows:

$$X \rightarrow Y = \left| \rho(X, \hat{X} \mid M_1) \right|$$

and
where $M_Y$ is the shadow manifold of variable $Y$.

Similarly, the unidirectional causal information flowing from $Y$ to $X$ ($Y\rightarrow X$) can be quantified as:

$$Y \rightarrow X = \left| p(Y, \hat{X}|M_Y) \right|$$

and

$$X \rightarrow Y = 0$$

where $M_X$ is the shadow manifold of variable $X$.

In the case of bidirectional causality, the dominant causal interaction can be determined by calculating the difference of two causal events, for example, if there is a dominant causal information flowing from $X$ to $Y$, then:

$$X \rightarrow Y - Y \rightarrow X > 0$$

otherwise, it would be negative.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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