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Significant role of the cardio-postural interaction in blood pressure regulation during standing

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Abstract

Cardiovascular and postural control systems have been studied independently despite the increasing evidence showing the importance of cardio-postural interaction in blood pressure regulation. In this study, we aimed to assess the role of cardio-postural 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 years; 8 females) during a sit-to-stand test before and after sub-maximal exercise. The cardio-postural 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 cardio-postural blood pressure control was evident counting for almost half of the interaction time with blood pressure changes that observed in the cardiac baroreflex (36.6-72.5% pre-exercise and 34.7-53.9% post-exercise). Thus, cardio-postural 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 post-exercise 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 cardio-postural interaction could improve our understanding of the autonomic control system and ultimately lead to a more accurate diagnosis of cardio-postural dysfunctions.

Keywords: cardio-postural control, skeletal muscle pump, orthostatic hypotension, mild exercise.

New & Noteworthy

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

Introduction

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 responses (77). In addition, astronauts often experience post-flight 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 following 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 which 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 heart rate 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 heart rate via vagal withdrawal and slower elevation of heart rate 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 (12, 21, 24, 41). It is well recognized that 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. proposed a conceptual model of cardio-locomotor coupling during walking (52). 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 et al. (8, 9) showed the link between postural sway and prevention of syncope in which participants who had poor tilt 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 heart rate 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.

An 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 cardio-postural 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 (cardio-postural

control). In addition, the blood pressure regulation through cardiac baroreflex control of heart rate 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 cardio-postural integration was characterized based on a wavelet-based technique in our previous studies which 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 cardio-postural 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 sub-maximal exercise and signals representing cardiovascular control (heart rate, 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 prior to and after exercise. Mild exercise has been reported to decrease blood pressure during post-exercise standing (31, 33, 40) as a consequence of excessive venous pooling induced by vasodilatation of the leg muscles (22). We hypothesized that: 1) the cardio-postural 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 years; height: 173±8 cm; weight: 67±11 kg; 10 females) with no history of cardiovascular, respiratory, or neurological disease, major musculoskeletal

injuries, or hormone imbalance. The use of prescription medications and naturopathic remedies were reported. Participants taking any substance that could alter cardiovascular regulation or postural stability were excluded. Prior to 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 hours prior to the experiment. The experiment protocol was approved to be of minimal risk by Simon Fraser University's Research Ethics Board complied 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: pre-exercise sit-to-stand test, sub-maximal cycle ergometer exercise, and post-exercise stand test. All tests were conducted in a sensory-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 minutes, after which assistance was provided to transition into upright stance on a force platform for an additional 6 minutes 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-minute sub-maximal exercise protocol. The exercise protocol consisted of a 2-minute warm-up at 25W, followed by 10 minutes at 80W or 100W 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-minute stand test was conducted with eyes closed (forward gaze), and identical pre-test foot placement on the force platform. Approximately 30 seconds elapsed in the transition from the cycle ergometer to the force platform and initiation of data acquisition.

Data Collection

During the pre-exercise sit-to-stand test and post-exercise stand test, electrocardiography (ECG) was acquired with custom equipment from LifePak 8 (Medtronic Inc, MN, USA) in a standard Lead II electrode configuration. Continuous blood pressure was monitored through a non-invasive 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 Inc, MA, USA) 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 antero-posterior sway COPy), were derived from force and moment data obtained with an Accusway Plus force platform (AMTI, MA, USA). The exercise protocol was performed on a digital Jaeger ER 800 cycle ergometer (Wuerzburg, Germany). Data were acquired at a sampling rate of 1000 Hz through a National Instruments PCI-6229 16-bit data acquisition platform and Labview 8.2 software (National Instruments Inc, TX, USA).

Data Analysis

Data analyses were performed in MATLAB (MathWorks, MA, USA). The last five minutes 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 prior to 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 cardio-postural 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, EMG_{imp}) was calculated to represent the muscle contraction strength on a beat-by-beat basis. The concept of impulse was employed because, in a beat-by-beat perspective, the strength of muscle contraction over a heartbeat 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 heartbeat. The resultant COP (COPr) was obtained from COPx and COPy (i.e., $\mathrm{COPr}=\sqrt{\mathrm{COPx}^2+\mathrm{COPy}^2}$) and the change rate of COPr ($COPr_v$) was calculated as the first derivative of COPr and averaged within each beat. The resultant $COPr_v$ 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 prior to the wavelet transform and causality analysis.

Wavelet transform coherence analysis

The wavelet transform coherence (WTC) method was proposed and 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→EMG_{imp} (muscle-pump baroreflex), SBP→$COPr_v$ (baroreflex-mediated postural sway), and $COPr_v$→EMG_{imp} (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 non-linear convergent cross mapping (CCM) method (35, 67). The efficacy of CCM method towards detecting causality between physiological signals and its superior performance over Granger causality with signals of non-linear 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. (supplementary material) (67).

The bidirectional causalities were investigated between the following signal pairs: SBP↔EMG_{imp} (muscle-pump baroreflex vs. blood pressure regulation via mechanical muscle pump effect), $COPr_v$↔EMG_{imp} (posture control vs. muscle contraction induced postural sway) and SBP↔$COPr_v$ (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 heartbeat 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 greater than 0.5 mmHg. Regression slopes (ΔRR/ΔSBP) were calculated for each selected beat sequence and averaged over the entire 5-minute data to obtain the overall BRS.

The time scale 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 post-exercise.

Statistics

Statistical analyses were performed with JMP 12 software (SAS Institute Inc., NC, USA). A two-factor (pre/post exercise and male/female) ANOVA with repeated measures on one factor (pre/post exercise) was used followed by Tukey HSD post hoc test. Residual of the ANOVA model was tested for normality using Shapiro–Wilk test. Data 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. The results are presented as mean ± standard deviation.

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 (8 females; age: 25±2 years (male 26±2 years, female 25±3 years, $p=0.36$); height: 174±9 cm (male 180±4 cm, female 168±7 cm, $p<0.001$); weight: 69±11 kg (male 77±9 kg, female 61±4 kg, $p<0.001$)) were used in the analysis.

Cardiovascular and Postural Variables (Table 1)

HR increased (p=0.002) and SBP decreased (p=0.049) after exercise while DBP and MAP remained unchanged (p=0.42 and 0.17 respectively). EMG and EMG_{imp} were reduced post-exercise (p=0.009 and 0.004 respectively). Male participants tended to have greater COPr (i.e., larger postural sway) than females (p=0.09). No significant interaction effects (exercise × gender) were found in mean values.

Cardio-Postural Coupling and Spontaneous Baroreflex Sensitivity (Table 2)

The averaged percentage time of cardio-postural coupling (SBP→EMG_{imp}, muscle-pump baroreflex) before and after exercise were 21.1% and 18.8% (p=0.52) in HF band, 35.8% and 31.4% (p=0.61) in LF band, and 25.3% and 15.6% (p=0.04) in VLF band. The %SC values for the cardiac baroreflex (SBP→RR) before and after exercise were 56.8% and 54.2% (p=0.38) in HF band, 76.3% and 79.6% (p=0.40) in LF band, and 46.5% and 31.6% (p=0.006) in VLF band. The linear coupling (%SC) between SBP and EMG_{imp} was reduced after exercise in VLF band and the SBP→EMG_{imp} gain values (i.e., the muscle-pump baroreflex sensitivity) decreased across all three frequency bands. The interaction between SBP and RR showed a similar pattern with a reduction of %SC in VLF band and decreased SBP→RR gain values in all frequency bands. In VLF band, the reduction of SBP→RR gain values was only found in females. The %SC and gain values from SBP to $COPr_v$ were not altered by mild exercise but gender difference (male > female) in %SC was observed at LF. Neither exercise nor gender had effects on %SC or gain values from $COPr_v$ to EMG_{imp}.

The spontaneous BRS derived from beat sequence method declined post-exercise 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 are 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 in Figure 3 were from the same participant with low HR (49 bpm pre-exercise and 56 bpm post-exercise). This observation

is consistent with the positive correlation between RR interval and BRS reported previously, 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 (Table 3)

Bidirectional causality between SBP and RR (SBP↔RR) was not affected by either exercise or gender. In terms of cardio-postural control, the causality results revealed significantly stronger causal driving control from EMG_{imp}→SBP, $COPr_v$→SBP, and $COPr_v$→EMG_{imp} compared to causality values in reverse directions ($p<0.05$). This dominant control pattern remained unchanged after exercise with a further reduction of non-dominant causality of SBP→EMG_{imp}, SBP→$COPr_v$, and EMG_{imp}→$COPr_v$ along with decreased $COPr_v$→EMG_{imp} causality.

Discussion

Significant Cardio-Postural 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 also observed that the signs of syncope were eliminated by muscular contraction of lower limbs (46) 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 cardio-postural control of blood pressure in response to orthostatic challenge. The bidirectional cardio-postural interaction (SBP↔EMG_{imp})

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% pre-exercise and 34.7-53.9% post-exercise). This indicates an important cardio-postural component in blood pressure regulation under orthostatic stress in addition to the cardiac baroreflex. Our results revealed strong evidence that integrative cardio-postural 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 has been reported and studied (31, 33, 40). The post-exercise 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 post-exercise 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 post-exercise 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±9.7 mmHg pre-exercise vs. 103±9.4 mmHg post-exercise, p=0.049), post-exercise 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 post-exercise EMG activity (50.0±27.1 μV pre-exercise vs. 39.0±24.4 μV post-exercise, 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 ($\%SC_{SBP\rightarrow EMGimp}$ and $G_{SBP\rightarrow EMGimp}$ in Table 2), which contradicts our hypothesis, could result from the resetting of muscle-pump activity level and the absence of excessive venous pooling post-exercise likely

due to the mild intensity and short duration (12 minutes) 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 ($SBP \rightarrow EMG_{imp}$ and $SBP \rightarrow COPr_v$) compared to that in the non-baroreflex direction ($EMG_{imp} \rightarrow SBP$ and $COPr_v \rightarrow SBP$). After exercise, the strength of causality in baroreflex control direction was further reduced (Fig. 2), which suggests a decoupling in baroreflex-mediated cardio-postural interaction. This is consistent with the aforementioned post-exercise reduction of the muscle-pump baroreflex. Despite the post-exercise reduction of causality strength of muscle-pump baroreflex control, the non-baroreflex causal control was unchanged and the 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 the blood pressure. The CCM causality in $COPr_v \rightarrow EMG_{imp}$ and $EMG_{imp} \rightarrow COPr_v$ declined after exercise with the dominant causal direction ($COPr_v \rightarrow EMG_{imp}$) remaining unchanged, indicating a systemic disassociation of the postural control loop. This could be due to increased contribution to postural sway from sources other than muscle contractions (e.g., respiration (28, 63, 82) and hemodynamics (10, 51)) after exercise.

Gender Effect on Cardio-Postural Control

The cardiac baroreflex sensitivity (i.e., $G_{SBP \rightarrow RR}$) at VLF decreased post-exercise only in females. The distribution of blood volume is known to be different between male and female 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 females may imply greater contribution of splanchnic vasoconstriction in blood pressure regulation after exercise.

Our results revealed gender effects on COPr and cardio-postural control in relation to $COPr_v$. Specifically, male participants presented marginally greater COPr than females ($p=0.09$; Table 1), which likely contributed to the gender differences (male > female) in $\%SC_{SBP\rightarrow COPrv}$ in LF band and $G_{SBP\rightarrow COPrv}$ in 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 gender effect when assessing the feasibility to use COP measurement as a surrogate of EMG in cardio-postural control analysis.

Study Limitation and Future Work

The present study employed a 12-minute 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 post-exercise standing in a healthy, young population. While the current study protocol was able to reveal the existence of significant cardio-postural 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 post-perturbation standing as we hypothesized.

Results of the current study were obtained from 17 healthy, young participants. In terms of the scope of the study to assess the cardio-postural interaction and the effect 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 cardio-postural 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 cardio-postural model. These components will be gradually integrated into the model and the corresponding measurements will be collected in future studies. With 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 infra-red 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 cardio-postural control, as well as the effects of mild exercise on these control mechanisms were studied. Our results revealed a significant component of cardio-postural 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 cardio-postural integration, the current study has clearly revealed the important role of cardio-postural 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 cardio-postural 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 cardio-postural 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 Causal Relationship

Mathematically, the unidirectional causal information flowing from variable X to variable Y (X→Y) can be quantified using the CCM method as:

$X \to Y = |\rho(X, \hat{X}|M_Y)|$ and $Y \to X = 0$.

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

$Y \to X = |\rho(Y, \hat{Y}|M_X)|$ and $X \to Y = 0$.

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:

$X \to Y - Y \to X > 0$ otherwise, it would be negative.

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Disclosures

The authors declare no conflict of interest, financial or otherwise.

Author Contributions

M.B. and A.P.B. conceived and designed research; M.B. and A.G. performed experiments; D.X. and A.K.V. analyzed data and drafted manuscript; D.X., A.K.V., A.G., R.F.R., A.P.B., and K.T. interpreted results of experiments; D.X. prepared figures and created tables; all authors edited the manuscript and approved the final version of the manuscript. *This is a combined effort of the labs of A.P.B. and K.T and both are to be considered senior author.

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Figure Captions

Figure 1. Illustration of the cardio-postural model associated with blood pressure regulation under orthostatic challenge. The cardio-postural integration is hypothesized as baroreflex-mediated skeletal muscle pump activity in response to blood pressure changes (muscle-pump baroreflex). The model also includes the cardiac baroreflex control of heart rate and the limb muscle activation in response to sensory perception of the foot during postural sway through somatosensory control system (i.e., postural control).

Figure 2. Graphic summary of the results for cardiac baroreflex sensitivity, cardio-postural coupling, and bidirectional causality during standing before and after mild exercise (n=17, 8 females). 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; EMG_{imp}: electromyography impulse on a beat-by-beat basis; $COPr_v$: change rate of resultant center of pressure.

N.C.: not changed after exercise; ↓: decreased after exercise.

*: only in females at VLF; †: gender effect (male > female) at LF; ‡: gender effect (male > female).

Figure 3. Linear regression (*left*) and Bland-Altman plot (*right*) between cardiac baroreflex sensitivity (BRS) estimated from the beat sequence method and SBP→RR gain values ($G_{SBP \rightarrow RR}$) in 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 of 0.96 and regression slope of 1.07 ($p<0.0001$) obtained from linear regression indicated a close agreement between the two methods. Bland-Altman plot also showed that the differences between the two methods are within the 95% limits of agreement except for one outlier.

G: gain value; BRS: baroreflex sensitivity; r: correlation coefficient; SD: standard deviation; RR: RR-interval; SBP: systolic blood pressure.

Tables

Table 1. Averaged cardiovascular and postural variables during standing before and after mild exercise (n=17, 8 females). After exercise, heart rate increased while systolic blood pressure and lower limb muscle activity showed reduction. Values are means ± SD.

	Exercise		Gender	
	Pre-	Post-	Male	Female
HR (bpm)	77.1±10.2	88.5±15.4*	79.6±7.0	86.3±18.9
SBP (mmHg)	106±9.7	103±9.4*	104±9.9	105±9.5
DBP (mmHg)	66.7±5.4	65.9±6.5	67.1±6.4	65.3±5.4
MAP (mmHg)	82±6.6	80±6.9	80±6.6	81±7.0
EMG (μV)	50.0±27.1	39.0±24.4*	50.8±34.4	37.4±7.3
EMG_{imp} (μV·s)	40.3±24.3	27.8±19.2*	39.4±28.7	28.0±10.1
COPr (mm)	32.3±13.6	33.5±11.9	37.5±13.1	27.7±10.0‡
$COPr_v$ (mm/s)	9.3±5.3	8.2±3.8	11.0±5.2	6.3±1.6

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; EMG: electromyography; EMG_{imp}: EMG impulse on a beat-by-beat basis; COPr: resultant center of pressure; $COPr_v$: change rate of COPr.

*: Different from pre-exercise, $p<0.05$;

‡: Different from male, $p<0.1$.

Table 2. Spontaneous baroreflex sensitivity and cardio-postural coupling during standing before and after mild exercise (n=17, 8 females). A significant cardio-postural control of blood pressure and a post-exercise reduction of baroreflex-mediated orthostatic regulation were observed. Values are means ± SD.

		Exercise		Gender	
		Pre-	Post-	Male	Female
BRS (ms/mmHg)		12.7±12.6	8.2±7.1*	9.6±3.8	11.3±14.7
$\%SC_{SBP\rightarrow RR}$ (%)	HF	56.8±14.5	54.2±14.5	57.6±13.7	53.1±15.2
	LF	76.3±18.3	79.6±19.2	81.0±16.5	74.5±20.6
	VLF	46.5±21.5	31.6±17.2*	37.7±17.6	40.5±24.1
$G_{SBP\rightarrow RR}$ (ms/mmHg)	HF	14.2±11.8	10.2±11.2*	11.5±4.5	13.0±16.4
	LF	13.7±8.2	9.4±4.3*	11.9±3.8	11.1±9.3
	VLF	11.0±4.5 (*11.4±4.4*)	8.2±4.0† (*6.5±3.4*)	10.2±4.3	8.9±4.6
$\%SC_{SBP\rightarrow EMGimp}$ (%)	HF	21.1±12.0	18.8±11.8	19.7±12.9	20.2±10.7
	LF	35.8±21.0	31.4±19.5	33.0±17.3	34.3±23.4
	VLF	25.3±13.3	15.6±10.7*	22.3±10.5	18.5±15.2
$G_{SBP\rightarrow EMGimp}$ (μV·s/mmHg)	HF	1.76±1.06	1.11±0.84*	1.68±1.06	1.16±0.88
	LF	0.98±0.62	0.58±0.35*	0.86±0.41	0.69±0.65
	VLF	0.86±0.49	0.62±0.40*	0.88±0.53	0.58±0.31
$\%SC_{SBP\rightarrow COPrv}$ (%)	HF	9.9±3.8	11.6±3.1	11.6±3.4	9.8±3.6
	LF	11.4±7.3	11.1±5.6	14.1±5.4	8.1±6.1‡
	VLF	13.6±11.7	11.1±8.6	13.8±10.6	10.8±9.8
$G_{SBP\rightarrow COPrv}$ (mm/mmHg·s)	HF	3.01±3.04	2.04±1.74	3.64±3.00	1.27±0.52§
	LF	1.33±1.15	0.98±0.48	1.50±1.06	0.76±0.36
	VLF	0.98±0.85	1.15±0.87	1.34±1.00	0.69±0.40
$\%SC_{COPrv\rightarrow EMGimp}$ (%)	HF	16.1±7.2	17.9±7.4	18.3±8.6	15.4±5.2
	LF	17.1±8.3	15.6±12.1	18.0±9.3	14.4±11.2
	VLF	14.8±12.7	17.4±17.8	17.3±14.0	14.7±17.0
$G_{COPrv\rightarrow EMGimp}$ (μV·s^2/mm)	HF	1.20±0.66	0.92±0.67	0.87±0.45	1.27±0.82
	LF	1.64±1.52	1.21±1.09	1.07±0.64	1.83±1.74
	VLF	1.74±1.68	0.85±0.56	1.08±0.77	1.52±1.74

BRS: baroreflex sensitivity; %SC: percentage of significant coherence; G: gain value; RR: RR-interval; SBP: systolic blood pressure; EMG_{imp}: electromyography impulse on a beat-by-beat basis; $COPr_v$: change rate of resultant center of pressure.

*: Different from pre-exercise, $p<0.05$;

†: Different from pre-exercise (female only), $p<0.05$ (see *Italic* text for values calculated from female participants only);

‡: Different from male, $p<0.05$;

§: Different from male, $p<0.1$.

Table 3. Bidirectional strength of causality during standing before and after mild exercise (n=17, 8 females). A post-exercise reduction of non-dominant causality (SBP→EMG_{imp}, SBP→$COPr_v$, and EMG_{imp} →$COPr_v$) was observed. Values are means ± SD.

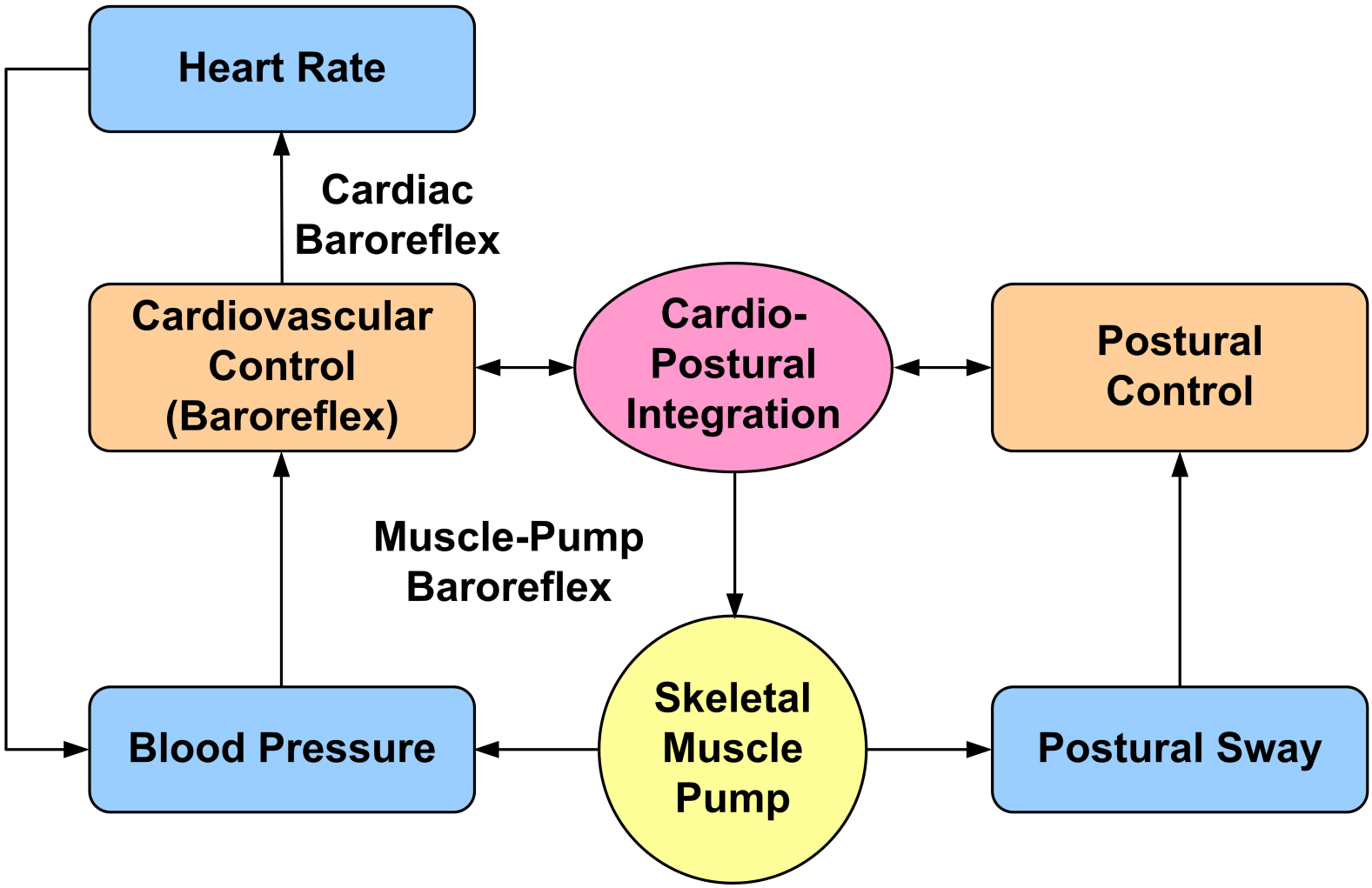
Causal Direction	Exercise		Gender	
	Pre-	Post-	Male	Female
SBP→RR	0.93±0.04	0.95±0.04	0.94±0.04	0.94±0.04
RR→SBP	0.93±0.03	0.94±0.03	0.94±0.03	0.93±0.04
SBP→EMG_{imp}	0.88±0.05	0.82±0.09*	0.86±0.07	0.83±0.09
EMG_{imp}→SBP	0.92±0.04	0.91±0.04	0.92±0.03	0.91±0.04
SBP→$COPr_v$	0.78±0.04	0.73±0.10*	0.78±0.05	0.72±0.09
$COPr_v$→SBP	0.91±0.04	0.90±0.05	0.91±0.04	0.89±0.05
$COPr_v$→EMG_{imp}	0.87±0.06	0.81±0.10*	0.87±0.07	0.81±0.09‡
EMG_{imp}→$COPr_v$	0.81±0.05	0.73±0.12*	0.81±0.06	0.72±0.11†

RR: RR-interval; SBP: systolic blood pressure; EMG_{imp}: electromyography impulse on a beat-by-beat basis; $COPr_v$: change rate of resultant center of pressure.

*: Different from pre-exercise, $p<0.05$;

†: Different from male, $p<0.05$;

‡: Different from male, $p<0.1$.


Heart Rate
Cardiac
Baroreflex
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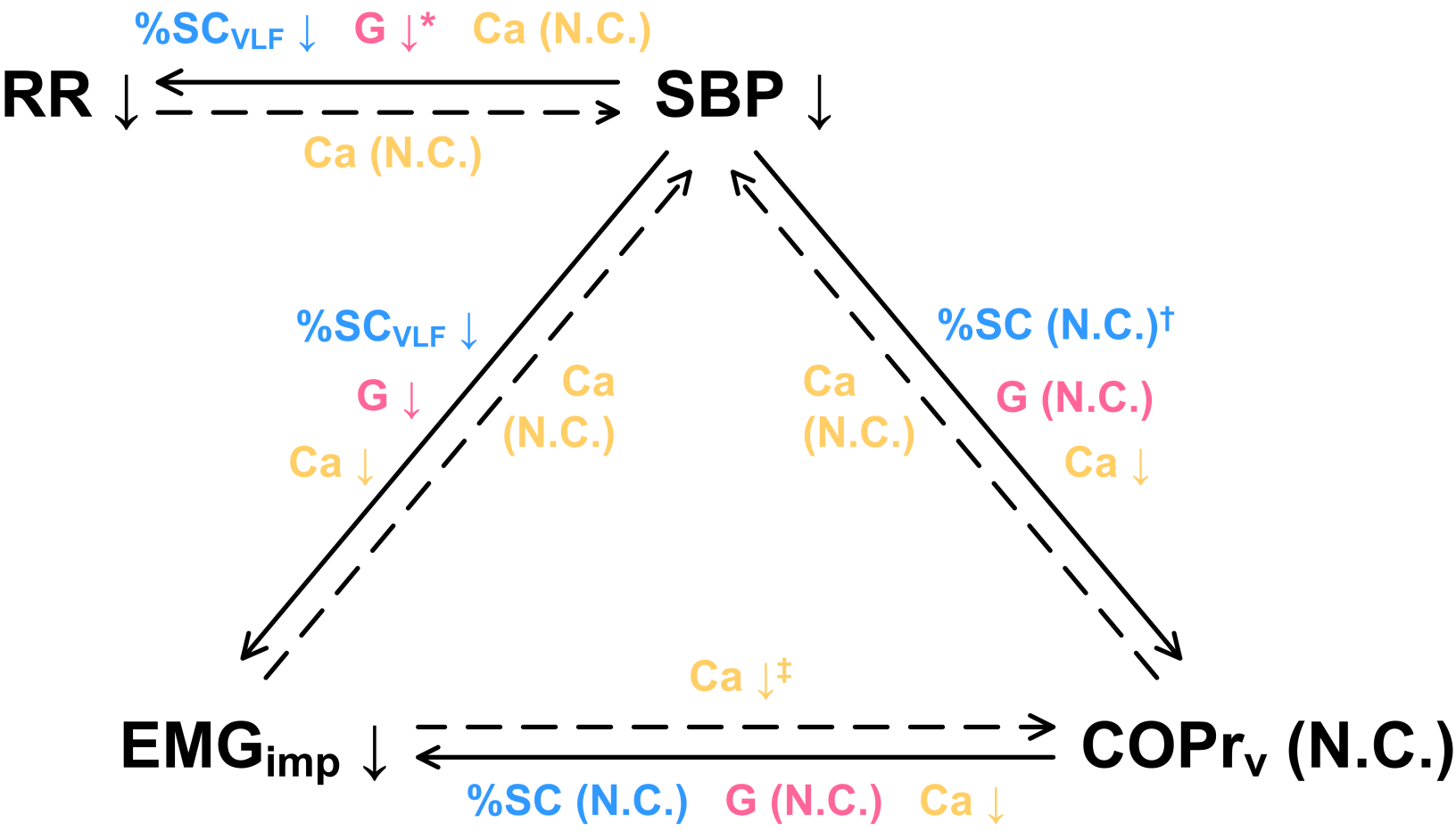
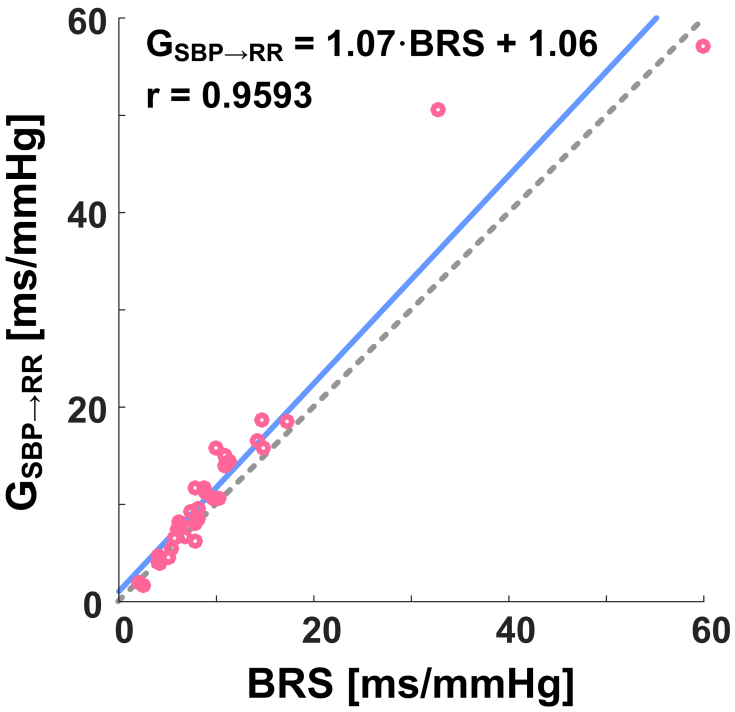
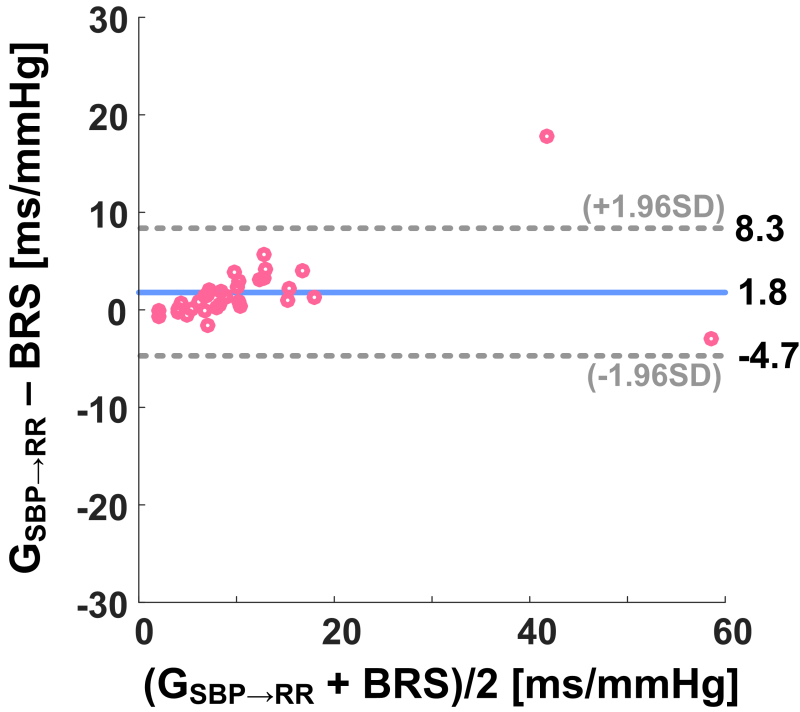
Control
(Baroreflex)
Cardio-
Postural
Integration
Postural
Control
Muscle-Pump
Baroreflex
Blood Pressure
Skeletal
Muscle
Pump
Postural Sway


%SCVLF ↓ G ↓* Ca (N.C.)
RR ↓
SBP ↓
Ca (N.C.)
%SCVLF ↓
G ↓
Ca ↓
Ca (N.C.)
Ca (N.C.)
%SC (N.C.)†
G (N.C.)
Ca ↓
Ca ↓‡
EMGimp ↓
COPrv (N.C.)
%SC (N.C.) G (N.C.) Ca ↓


$G_{SBP→RR}$ = 1.07·BRS + 1.06
r = 0.9593
$G_{SBP→RR}$ [ms/mmHg]
BRS [ms/mmHg]
0
20
40
60


$G_{SBP→RR}$ − BRS [ms/mmHg]
($G_{SBP→RR}$ + BRS)/2 [ms/mmHg]
(+1.96SD)
8.3
1.8
-4.7
(-1.96SD)
30
20
10
0
-10
-20
-30
0
20
40
60