Cardiopulmonary baroreflex is reset during dynamic exercise

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Ogoh, Shigehiko, R. Matthew Brothers, Quinton Barnes, Wendy L. Eubank, Megan N. Hawkins, Sushmita Purkayastha, Albert O-Yurvati, and Peter B. Raven. Cardiopulmonary baroreflex is reset during dynamic exercise. J Appl Physiol 100: 51–59, 2006.—The purpose of this study was to examine the hypothesis that the operating point of the cardiopulmonary baroreflex resets to the higher cardiac filling pressure of exercise associated with the increased cardiac filling volumes. Eight men (age 26 ± 1 yr; height 180 ± 3 cm; weight 86 ± 6 kg; means ± SE) participated in the present study. Lower body negative pressure (LBNP) was applied at 8 and 16 Torr to decrease central venous pressure (25% human serum albumin solution were administered until CVP was induced change in cardiac filling volume. These data indicate that the cardiopulmonary baroreflex had been reset during exercise, whether acute resetting of the carotid baroreflex was classically reset to regulate the cardiac filling volume. In-}

MECHANORECEPTORS DIFFUSELY located within the walls of the cardiac atria and ventricles, coronary and pulmonary arteries, and the great veins have been reported to alter systemic vascular conductance via a sympathetically mediated reflex (1). Animal and human experiments indicate that the reflex arc consists of mechanosensitive baroreceptors, which when deformed provide afferent neural information to the medullary cardiovascular centers via the vagus, resulting in increases or decreases in the outflow of efferent sympathetic nerve traffic to the peripheral vasculature (14, 17, 21, 22, 37, 43). The anatomical location of these mechanoreceptors and their physiological role in monitoring cardiac filling has resulted in them being identified as a population of cardiopulmonary baroreceptors. More recently the mechanoreceptors located within the vascular walls of the coronary arteries appear to function as coronary baroreceptors with modulatory reflex control of the systemic vasculature (7, 8, 23, 24). However, the cardiopulmonary baroreceptors of the heart and great veins were previously identified to function as volume receptors (10, 11). Therefore, we suggest that at supine rest the established euvo-
tion, they found during exercise an upward shift of the stimulus-response curve of both heart rate and arterial pressure to changes in the carotid sinus pressure. When the experiments were repeated after acute bilateral vagotomy during exercise, the blood pressure was lower and the stimulus response curve of the carotid baroreflex was shifted to a lower operating range of arterial pressures, suggesting that reflex responses to changes in cardiopulmonary baroreceptor loads are involved in establishing the blood pressure to be regulated (45). Moreover, when cardiac vagal afferent nerve traffic in conscious trained rabbits was interrupted by local anesthetics, renal sympathetic nerve activity was significantly increased (6). Similar to investigations (17) performed at rest in which unloading of the cardiopulmonary baroreceptors was performed during exercise, the sensitivity of cardiopulmonary baroreflex control of FVR was not different from that at rest (20), suggesting an acute resetting of the cardiopulmonary baroreflex’s operating point. However, the lack of evidence regarding the loading of the cardiopulmonary baroreceptors and their reflex control of FVR during exercise makes it unclear whether the cardiopulmonary baroreflex has been reset to operate at the increased CVP associated with the exercise. The purpose of the present investigation was to test the hypothesis that exercise resets the cardiopulmonary baroreflex to operate at the exercise induced increase in CBV. This was accomplished by decreasing CBV using LBNP and increasing CBV using acute volume expansion via infusions of human serum albumin during rest and exercise and measuring the changes in FVR.

METHODS

Eight men (age 26 ± 1 yr; height 180 ± 3 cm; weight 86 ± 6 kg; means ± SE) were recruited for voluntary participation in the present study. All subjects were free of any known cardiovascular and pulmonary disorders and were not using prescribed or over-the-counter medications. Each subject provided written, informed consent for the study, which was approved by the University of North Texas Health Science Center Institutional Review Board. Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol intake for at least a day before testing. Before any experiments were performed, each subject visited the laboratory for familiarization with the techniques and procedures of protocol. All experiments were conducted at a constant room temperature (25.2 ± 0.3°C).

Maximal exercise stress test. On experimental day 1, each subject performed a maximal incremental load test to volitional fatigue in a 70° back-supported semirecumbent position by cycling on an electronically braked cycle ergometer placed within the LBNP box. This test served as the initial screening test and provided evidence of suitability for the study. Before the exercise test, the subject’s resting blood pressure and 12-lead electrocardiogram were recorded at seated and standing positions. The cycle workload was set at 50 W for initial 2 min and was increased 30 W each minute. Criteria for attainment of peak oxygen uptake (VO₂ peak) included the inability to maintain a cycling cadence of 60 rpm accompanied by a respiratory quotient that exceeds 1.10 or a documented plateau of oxygen uptake. Subjects breathed through a mouthpiece attached to a low-resistance turbine volume transducer (model VMM E-2A, Sensor Medics, Anaheim, CA) and mass spectrometry (model MGA1100B, Perkin-Elmer, St. Louis, MO) for determination of oxygen uptake. The actual experimental protocol was scheduled on a separate day at least 3 days after the day of the maximal exercise stress test.

Experimental protocol. On experimental day 2, after instrumentation, the subjects were positioned in the 70° back-supported semirecumbent position with the lower body in the LBNP box. In addition, a mercury-in-Silastic strain gauge was placed over the largest part of the subject’s forearm for the measurement of forearm blood flow (FFB) using venous occlusion plethysmography. Occlusion cuffs were placed at the subject’s wrist and upper arm. The subject was sealed in the LNB box at the level of the iliac crest with a flexible rubber dam. The electrically braked cycle ergometer placed in the LBNP box was adjusted to each subject’s leg length. During exercise full extension of the leg was >20° above the horizontal plane of hip.

After subjects rested for 30 min in the 70° back-supported semirecumbent position while beat-to-beat hemodynamic recordings of heart rate (HR), CVP, and arterial blood pressure (ABP) were made, LBNP of 8 Torr (LB8) was applied for 2 min before another 6 min of HR, CVP, and ABP recordings and measures of cardiac output (Q) and FBF were obtained. Similar measures of HR, CVP, ABP, Q, and FBF were made after 2 min of LBNP at 16 Torr (LB16), which was applied immediately after completion of the 8 min of LB8 (Fig. 1, protocol 1). After completion of the resting LBNP protocols and a further 5 min of rest, the subject began cycling at 50 W for 2 min, after which the workload was increased 20 W each minute until each subject achieved his VO₂ peak (104% ± 38% of VO₂ peak) was attained. After ∼6–8 min of attaining the 50% VO₂ peak workload, the same dynamic and steady-state hemodynamic measurements were made. Subsequently, 40 min after the control exercise bout, the subjects repeated the 50% VO₂ peak exercise workload. Additionally, 2 min before the beginning of the exercise LB8 was applied. After 6 min of exercise in the LB8 condition the same dynamic and steady-state hemodynamic measurements were obtained. The exercise during LB8 condition was performed for ∼15 min and was followed by another 40-min rest before the LB16 exercise conditions and hemodynamic measurements were performed (Fig. 1, protocol 2). After another 40 min of rest 50 ml of human serum albumin was infused via the antecubital vein catheter. After waiting for a period of 15 min and assessing the subject’s reaction to the human serum albumin (none of the subjects reported any discomfort associated with an allergic reaction), we infused a further 50 ml of human serum albumin until at least a 1 mmHg increase in CVP occurred (INF1). After the completion of INF1, both the resting and exercise protocols, described above, were repeated, along with the same measurement protocol. Subsequently, after another 40-min rest, the rest and exercise protocols, along with the same measurements, were repeated after an additional 150-ml infusion of human serum albumin to a minimum increase in CVP of 2 mmHg (INF2). During the course of the experiments the subjects were constantly questioned about their comfort (Fig. 1, protocol 3). One subject did not complete the entire experiment because of the physical discomfort associated with the 70° back-supported semirecumbent position, especially during the exercise infusion experiments. The infusion volume of 25% albumin was 1.20 ± 0.06 ml/kg (INF1), and the additional volume was 1.60 ± 0.06 ml/kg for INF2. During the resting and exercise experiments, HR, ABP, and CBF were recorded continuously. At each stage of LBNP, or albumin infusion, FBF and Q were measured.

Measurements. HR was monitored with a standard lead II electrocardiogram (model 78342A, Hewlett-Packard). ABP and CVP were measured directly. A cannula (1.1 mm ID, 20 gauge) was placed in the brachial artery for measurement of the ABP. Another cannula (17-gauge, 65-cm radiopaque catheter) was introduced into the superior vena cava via the basilica vein for measurement CVP. Each pressure was recorded with a disposable pressure transducer (Maximum Medical, Athens, TX) positioned at the level of the right atrium in the midaxillary line. In addition, the catheters had extension tubes connected to a slow drip of heparinized normal saline (2 U/ml). A venous catheter (1.2 mm ID, 18 gauge) was inserted into the median antece- 

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measures of Q, mean arterial pressure (MAP), and CVP (Q/MAP – CVP). The FBF was determined by venous occlusion plethysmography employing a dual-loop mercury-in-Silastic strain gauge to determine changes in venous volume (46). Forearm vascular conductance (FVC) was calculated from the ratio FBF/MAP and expressed in conductance units. The venous occlusion cuff pressure was set at 40 mmHg, and an arterial occlusion cuff (inflated to 250 mmHg) was used to prevent arterial inflow into the hand during each blood flow measurement.

**Cardiopulmonary baroreflex.** By using 8 and 16 Torr LBNP and two discrete infusions of 25% human serum albumin solution at rest and during the performance of constant workload (50% \( \dot{V}O_2 \) peak) exercise and quantifying the resultant responses of CVP, SV, FVC, and TSVC, we describe a linear model of the cardiopulmonary-mediated reflex response of FVC or TSVC to changes in CVP or SV.

**Coherence analysis.** To estimate the dynamic regulation of the cardiopulmonary baroreflex, the relationship between MAP and CVP was evaluated. The correlation between the beat-to-beat changes in CVP and MAP was evaluated by the magnitude-squared coherence function, defined previously (27, 29). Beat-to-beat values of MAP and CVP were obtained by integrating analog signals within each cardiac cycle. Subsequent linear interpolating and resampling at 2 Hz for spectral analysis was performed. The coherence function was calculated in the very low- (VLF, 0.02–0.07 Hz), low- (LF, 0.07–0.20 Hz), and high- (HF, 0.20–0.30 Hz) frequency ranges (27, 29).

**Statistics.** Statistical comparisons of physiological variables were made by utilizing a repeated-measures two-way ANOVA with a 5 × 2 design (condition × exercise). A Student-Newman-Keuls test was employed post hoc when interactions were significant. The relationships between FVC or TSVC and changes in CVP or SV were described by using simple linear regression analysis of group averaged data. However, a paired t-test comparison of the slopes of the linear regression equations between rest and exercise were made using individual data points. Statistical significance was set at \( P < 0.05 \) and results are presented as means ± SE. Analyses were conducted by using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL).

**RESULTS**

This study involved two protocols that manipulated the loading status of the cardiopulmonary baroreceptors. One protocol used LBNP to unload the cardiopulmonary baroreflex, and the second protocol used human serum albumin infusions to load the cardiopulmonary baroreflex. In response to LB8 and LB16, the reduction in CVP was 1.5 ± 0.3 and 2.6 ± 0.5 mmHg at rest and 1.1 ± 0.4 and 3.0 ± 0.4 mmHg during exercise, respectively. In response to INF1 and INF2, the increase in CVP was 1.8 ± 0.6 and 2.4 ± 0.4 mmHg at rest and 2.9 ± 0.9 and 4.6 ± 0.9 mmHg during exercise, respectively.
The LB8 and LB16 conditions did not affect MAP at rest or during exercise (Table 1). An increase in HR was observed during LBNP at rest (LB8 and LB16; +4 ± 1 and +7 ± 2 beats/min, respectively, P < 0.05) and during exercise (+8 ± 3 and +14 ± 4 beats/min, respectively, P < 0.05). However, Q decreased because of a larger reduction in SV compared with the increase in HR during LB16 (Fig. 2). In addition, a decrease in FVC and TSVC occurred to maintain MAP during a reduction in CBV caused by LBNP at rest and during exercise (Fig. 3). Interestingly, HR gradually increased during the infusion of albumin at rest (INF1 and INF2; +16 ± 3 and +16 ± 4 beats/min, respectively, P < 0.05) and during exercise (+14 ± 4 and +17 ± 4 beats/min, respectively, P < 0.05). In contrast to the response to central hypovolemia, Q, SV, TSVC, and FVC increased both at rest and during exercise. The Q increased because of the increases in HR and SV that occurred during the infusion. Pulse pressure (PP) significantly increased from rest to exercise (P < 0.001). However, both LBNP and the infusion of albumin did not affect PP at rest or during exercise (P < 0.05).

Vascular responses to hypovolemia and hypervolemia (cardiopulmonary baroreflex control of the peripheral vasculature) are shown in Fig. 4. Although both FVC and TSVC increased from rest to exercise by 17 ± 7 and 89 ± 11%, respectively, the vascular responses to the changes in CVP at LB8, LB16, INF1, and INF2 were the same during exercise. The linear relationships between CVP, %CVP, or SV and FVC or TSVC were statistically significant (P < 0.001) at rest and during exercise (Figs. 4 and 5). There was no significant difference in the average slope of the linear regression between FVC and CVP (P = 0.96), FVC and %CVP (P = 0.226), and FVC and SV (P = 0.291) for all subjects between rest and exercise (Fig. 6).

In the examination of the dynamic relationship between beat-to-beat changes in CVP and MAP we used frequency domain dynamic linear analysis (Fig. 7). The coherence between CVP and MAP in the LF range was not altered from rest to exercise, indicating that the changes in CBV did not affect...
MAP variability. In contrast, the HF coherence between CVP and MAP was above 0.5 both at rest and during exercise, suggesting that dynamic variations in cardiac filling affected MAP variability.

DISCUSSION

The data of the present investigation indicate that, in the transition from rest to dynamic exercise, the operating point of the cardiopulmonary baroreflex is reset to the increased cardiac filling volume associated with the exercise. Furthermore, because the coherence of the variability of CVP and MAP in the LF range was not changed from rest to exercise and the coherence value was <0.5, we conclude that the dynamic changes in CBV were not related to the fluctuations in the MAP, suggesting that beat-to-beat dynamic changes in CBV were buffered by the cardiopulmonary baroreflex control of the peripheral vasculature. However, because the coherence between the variability of CVP and MAP was >0.5 in the HF range in both rest and exercise, we conclude that the dynamic changes in CBV were related to the fluctuations in MAP, probably as a result of respiratory-induced fluctuations in intrathoracic pressures and venous return, which were not buffered by the cardiopulmonary baroreflex. Because of the similarity of the coherence between CVP variability and MAP variability between rest and exercise, we conclude that the cardiopulmonary baroreflex had been reset.

The interaction between mechanoreceptors, diffusely located within the walls of the heart and the walls of the pulmonary arteries and great veins, and the medullary cardiovascular center nuclei has been shown to provide tonic restraint on sympathetic outflow to the peripheral vasculature (1). For example, when cardiac vagal afferent nerve traffic from the cardiac mechanoreceptors in conscious trained rabbits was interrupted by an infusion of anesthetic into the pericardial sac, renal sympathetic nerve activity was markedly increased (6). By using LBNP in humans at rest and thereby decreasing CBV,
limb vascular resistances and muscle sympathetic nerve activity and norepinephrine spillover were immediately increased (2, 3, 21, 37, 43). These findings suggest a threshold of CBV below which cardiopulmonary-mediated reflex responses are disengaged to protect against decreases in cardiac filling. Subsequently, when CBV was increased by using leg raising combined with lower body positive pressure with subjects in the supine position (37), a CVP was identified above which the FVC was increased, indicating a suppression of central outflow of sympathetic activity when the cardiopulmonary baroreceptors were engaged. Furthermore, the ΔCVP responses obtained in response to the ΔCVP were modeled to the logistic function curve identifying a threshold, saturation, operating range, and pressure (CVP), response range and G max of the cardiopulmonary baroreflex (34).

During exercise the presence of an operational point of CBV was first identified in the classical animal experiments of Donald and coworkers (25, 39, 45), in which cardiopulmonary afferent information was interrupted by use of bilateral vagotomy in exercising dogs. Resting and exercising blood pressures were higher and the carotid baroreflex operating range of the vagotomized animals was increased compared with nonvagotomized animals when aortic baroreceptors were intact (25). In similar experiments when both aortic denervation and bilateral vagotomy were used, exercising blood pressures were lower and the stimulus-response curve was shifted to a lower operating range of arterial pressures. In human studies, it has been reported that the sensitivity of the cardiopulmonary baroreflex control of FVR using responses to LBNP of less than −20 Torr was the same at rest and during exercise (20). Similarly, carotid baroreflex control of MAP, an index of vasomotor response (28), was unchanged from rest to exercise (28, 33). The data of the present investigation expand the findings of the previous work by using human serum albumin infusions to raise CBV and load the cardiopulmonary receptors. Although the responses to the increases and decreases in CBV were unable to fit a logistic function model of a reflex function curve, the linear responses of FVC and TSVC to the changes in CBV were exactly the same between rest and exercise, confirming the presence of cardiopulmonary baroreflex resetting due to exercise (see Figs. 4–6). Furthermore, the data support the concept of an operational point of CVP or CBV of the cardiopulmonary baroreflex.

During static handgrip exercise it was found that the cardiopulmonary baroreflex did not inhibit the increased sympathetic outflow associated with the activation of the exercise pressor reflex (36). However, recent work using the exercising dog model indicates that it is the arterial baroreflex that buffers the increased sympathetic outflow that occurs with the activation of the exercise pressor reflex (18). The idea that the cardiopul-

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Fig. 5. Summary of the linear relationships between SV and FVC (top) or TSVC (bottom) at rest (●) and during exercise (○). Symbols denote actual group data for all subjects (means ± SE). Lines represent the regression line calculated from the group average data.

Fig. 6. Group averaged (n = 8) sensitivity of cardiopulmonary baroreflex at rest and during exercise. Bars represent the average slope of linear regression line between CVP and FVC (left), between %CVP and FVC (middle), and between SV and FVC (right) for all subjects (means ± SE) at rest and during exercise.
The lack of coherence between the variations in CVP and MAP at rest and during exercise in the LF range indicates that beat-to-beat dynamic changes in CBV are buffered by the cardiopulmonary baroreflex control of the peripheral vasculature (Fig. 7). However, the significant coherence between CVP variability and MAP variability in the HF range (Fig. 7) suggests that the dynamic changes in CBV induced by respiratory fluctuations in intrathoracic pressures are transferred directly to the arterial vasculature without cardiopulmonary baroreflex modulation.

Potential limitations to our interpretation of the data of the present investigation are related to 1) measures of CVP during exercise and its use as an index of changes in CBV; 2) thermal stress; and 3) involvement of the arterial baroreflexes in the vascular responses to changes in CBV.

The use of the measurement of CVP as a relative indicator of the status of the CBV requires that the cardiac and pulmonary compliances need to remain fixed and unvaried (32). During the experimental manipulations of the present investigation, especially during exercise, we were unable to confirm that these criteria were consistently maintained for each subject. We therefore normalized for these individual differences by identifying group average changes in CVP at rest for both LB8 and LB16 and for INF1 and INF2 in absolute values, and we compared the reflex responses to the change in absolute CVP and as a percentage (%CVP). Furthermore, we confirmed that these changes in absolute CVP and in %CVP reflected changes in CBV by expressing the reflex responses in relation to the measured changes in SV (Fig. 5), a well-established index of ΔCBV (26, 35). Despite the uncertainty in the absolute value of CVP for each individual during exercise, it was unlikely that the dynamic measure of CVP variability was affected. Hence, our interpretations of the lack of coherence between CVP variability and MAP variability in the LF range and the significant coherence of the same variables in the HF range remain valid.

The increase in blood flow to the inactive forearm during leg exercise is exclusively directed to the skin (16). In addition, heat stress significantly reduces the sensitivity of the cutaneous vessels to constrict in response to norepinephrine (47). Thus during leg exercise when the thermal load is increased the major changes in FVC occur in the cutaneous circulation and may compromise cardiopulmonary baroreflex responses. Furthermore, the slope of the relationship between decreases in FVC and decreases in SV during LBNP was lower in 32°C than in 25°C ambient conditions. However, when the exercise is mild (<50% \( \text{Vo}_{2\text{peak}} \)), esophageal temperature was unchanged until minute 15. In the present investigation exercise bouts were performed for <20 min in an ambient environment of 25 ± 1°C with a cooling fan’s airflow focused on the subject’s thorax, thereby negating any buildup of heat in the subject and compromising the measures of cardiopulmonary baroreflex responses.

In unanesthetized humans and animals the selective stimulation of the cardiopulmonary baroreceptors has proven to be difficult to achieve without some suspected stimulation of the arterial baroreceptors (34). For example, imaging data of the aortic arch’s surface area during LBNP (40) or diameter determinations of the carotid artery during LBNP or head-up tilt (19) have identified reductions in surface area or diameter length, respectively. However, below LBNP 20 Torr or
head-up tilt of 60°, no efferent reflex responses in HR were observed (19, 40), suggesting that arterial baroreflex involvement was minimal. In contrast, during the onset of LBNP or head-up tilt the reflex increase in FVR to the decrease in CBV was immediate. Furthermore, this immediate reflex increase in FVR occurs without alterations in MAP or arterial PP (14, 17, 30), further confirming the minimal involvement of the arterial baroreflexes in the increases in sympathetic activity.

In summary, FVC and TSVC increased from rest to exercise. However, there was no significant difference in the responses of both FVC and TSVC to LBNP and the infusion of albumin between rest and exercise. These data indicate that the cardiopulmonary baroreflex had been reset during exercise to a new operating point related to the exercise-induced change in CBV.

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