WISE 2005: stroke volume changes contribute to the pressor response during ischemic handgrip exercise in women

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Shoemaker JK, Mattar L, Kerbeci P, Trotter S, Arbeille P, Hughson RL. WISE 2005: stroke volume changes contribute to the pressor response during ischemic handgrip exercise in women. J Appl Physiol 103: 228–233, 2007. First published April 5, 2007; doi:10.1152/japplphysiol.01334.2006.—The mechanism of the pressor response to small muscle mass (e.g., forearm) exercise and during metaboreflex activation may include elevations in cardiac output (Q) or total peripheral resistance (TPR). Increases in Q must be supported by reductions in visceral venous volume to sustain venous return as heart rate (HR) increases. Therefore, this study tested the hypothesis that increases in Q, supported by reductions in splanchnic volume (portal vein constriction), explain the pressor response during handgrip exercise and metaboreflex activation. Seventeen healthy women performed 2 min of static ischemic handgrip exercise and 2 min of postexercise circulatory occlusion (PECO) while HR, stroke volume and superficial femoral artery flow (Doppler), blood pressure (Finometer), portal vein diameter (ultrasound imaging), and muscle sympathetic nerve activity (MSNA; microneurography) were measured followed by the calculation of Q, TPR, and leg vascular resistance (LVR). Compared with baseline, mean arterial blood pressure (MAP) (P < 0.001) and Q (P < 0.001) both increased in each minute of exercise accompanied by a ∼5% reduction in portal vein diameter (P < 0.05). MAP remained elevated during PECO, whereas Q decreased below exercise levels. MSNA was elevated above baseline during the second minute of exercise and through the PECO period (P < 0.05). Neither TPR nor LVR was changed from baseline during exercise and PECO. The data indicate that the majority of the blood pressure response to ischemic handgrip exercise in women was due to mobilization of central blood volume and elevated stroke volume and Q rather than elevations in TVR or LVR resistance.

Cardiac output; microneurography; muscle sympathetic nerve activity; metaboreflex

In 2006, a point-counterpoint debate was published that addressed whether the exercise pressor response does or does not restore blood flow to skeletal muscle (25). A fundamental basis of this debate is whether the rise in blood pressure during exercise is due to elevations in cardiac output (Q) or to neurally induced increases in peripheral vascular resistance (TPR).

Based on measures of limb hemodynamics and muscle sympathetic nerve activity (MSNA) in humans, it has been concluded that an elevated total TPR must mechanistically determine the pressor response to fatiguing exercise (18, 30, 32, 38). However, it has also been observed that the leg vascular resistance (LVR) response to static handgrip exercise was more closely associated with arterial pressure than with MSNA (34). These latter data raise the possibility that the change in LVR was a myogenic development in response to the rise in mean arterial pressure (MAP) that was caused by some other mechanism. Such a concern is consistent with earlier data (6, 11, 12, 17, 36) where static handgrip exercise that increased MAP also resulted in elevated Q with little change in systemic vascular resistance.

Similarly, instrumented canine models using graded reductions in muscle perfusion as the animals ran on a treadmill have provided considerable information on the important role of flow during exercise with metaboreflex activation (3, 23, 26). It is possible that the conclusions from these canine studies are limited to dynamic exercise using large muscle mass activation with additional concern that they may be impacted by the physical occlusion of the descending aorta, which will affect cardiac afterload and systemic conductance. Furthermore, these studies that support a primary role of Q in the human exercise pressure response (11, 12, 23, 36) were based on observations made during volitional effort in the exercise and were not designed to isolate a role of peripheral muscle metabolic afferent signals. In contrast, Crisafulli et al. (6) observed an increase in stroke volume (SV) during a period of postexercise ischemia but not during the preceding period of volitional moderate-intensity exercise.

An important element in the Q response is whether it is driven entirely by the rise in heart rate (HR) or whether SV also increases. To date, the role of HR vs. SV in the Q response to handgrip exercise is equivocal with some reporting an increase in SV (23, 33), whereas others emphasize the HR component (8). It may be that the role of SV varies with the ability to elevate HR, as shown previously in a paced heart model (23). For SV to rise, a maintenance or even increase in right atrial pressure (33) or cardiac contractility (23) would be expected to occur. In turn, an increase in right atrial pressure may require a redistribution of blood volume from the visceral organs. To our knowledge, the impact of fatiguing exercise on the portal circulation has not been reported. However, results of increased impedance in the abdominal region during exercise (36) would suggest such a reduction in blood volume.

To date, there is little understanding of how SV and HR combine to affect Q during static exercise vs. metaboreflex activation per se. Therefore, the primary purpose of this study was to test the hypothesis that Q is the primary determinant of
the pressor response during static handgrip exercise in humans and that this response requires an increase in SV. In turn, this elevated venous return would be associated with a mobilization of visceral blood volume toward the heart. A secondary hypothesis was that the mechanism(s) affecting MAP may be different during exercise, where central and peripheral activation features occur, vs. during postexercise circulatory occlusion (PECO), where the peripheral metaboreflex is emphasized.

To address these hypotheses, MSNA, HR, MAP, Q, TPR, LVR, and portal vein diameter were measured before and during ischemic fatiguing handgrip exercise, during 2 min of PECO, and then again in recovery. The results indicated that during the forearm contraction, Q was sole determinant of increases in MAP due to elevations in HR and SV despite large increases in MSNA. Reduced portal vein diameter during the contraction suggested a reduction in splanchnic blood volume. During isolated metaboreflex activation, the role of Q was less dominant and portal vein diameter returned to normal.

**METHODS**

**Participants.** Eighteen healthy normotensive women participated in this study. These participants were 32 ± 4 yr of age (range = 25–40 yr), 165 ± 7 cm in height (range = 155–181 cm), and 59 ± 6 kg in weight (range = 49–66 kg) (values are means ± SD). They were informed of all testing procedures and any risks associated with testing before providing signed consent to participate. All experimental procedures were approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Midi-Pyrénées (France), Committee for the Protection of Human Subjects at Johnson Space Center, and local ethics committees, including Office of Research Ethics, University of Waterloo. No nicotine, alcoholic beverages or caffeine were permitted, and no physical exercise was performed for a minimum of 24 h before the commencement of testing.

This study was part of a larger set of experiments performed on the participants in preparation for the Women International Space Simulation for Exploration (WISE) 2005 bed rest study in women. Because of the complex scheduling efforts, it was not possible to coordinate testing according to menstrual phase. As such, one of the 18 volunteers was tested during the menstrual phase. A review of her results indicated that they all fell close to the mean of the overall group response.

**Experimental design.** All testing was performed while subjects were in the supine position. The volunteers performed two maximal voluntary handgrip contractions (MVCs), the largest of which was used to determine the relative intensity of the exercise sessions. Immediately before the 2-min baseline period, forearm ischemia was induced by inflating a blood pressure cuff placed around the upper portion of the exercising arm to suprasystolic levels. Thus the forearm was ischemic throughout the entire protocol to eliminate potential variations in forearm perfusion during exercise or PECO phases from affecting the results. After 2 min of baseline rest, subjects performed 2 min of static handgrip contraction at 40% MVC with the target force displayed on an oscilloscope. Subsequently, 2 min of PECO occurred before the cuff was deflated and the recovery process was initiated. The PECO period allowed isolation of the peripheral metaboreflex and determination of how it affected cardiovascular function in contrast to the central and peripheral components at play during the volitional exercise (1). Subjects were requested to evaluate their relative effort at the end of the exercise on the 20-point Borg scale and report it at the end of all data collection.

**Measurements.** MAP was measured continuously by finger-cuff plethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) on the middle finger of the nonexercising hand that was maintained at heart level. HR was measured from the electrocardiogram. SV velocity (SVV) in the ascending aorta was obtained from the suprasternal notch with a handheld 2.0-MHz pulsed-wave probe (model 500, Multigon). Femoral artery diameter (Acuson 128XP) and flow velocity (Cardiolab, European Space Agency) were measured from the superficial femoral artery to quantify lower leg blood flow. All analog signals were sampled in real time at 100 Hz with an online acquisition and analysis system (PowerLab, ADInstruments; Castle Hill, New South Wales, Australia) and stored on a computer for subsequent analysis.

**Data analysis.** For each protocol the beat-by-beat MAP, HR, and SVV data were determined. Beat-by-beat SV was then calculated as the product of SVV and the vessel cross-sectional area (πr²; where r is vessel radius), and it was corrected for variations in R-R interval. Q was then calculated as the product of SV and HR. TPR was calculated as TPR = MAP/Q. Superficial femoral vascular resistance was also calculated as the quotient of pressure and flow. For steady-state levels, beat-by-beat data were averaged over the last 30 s of each minute of baseline, each level of exercise, and recovery.

**Statistical analysis.** The effect of the exercise period on each variable was assessed using a repeated-measures one-way ANOVA [Statistical Analysis System (SAS) V. 8.0.2, SAS Institute Cary, NC]. Significant main effects were further assessed using Tukey’s post hoc analysis. Statistical probability level was set at 0.05. Data values are presented as mean ± standard deviation.

**RESULTS**

The Borg scale rating at end exercise was 15 ± 1 units, indicating a moderately fatigued forearm.

**Hemodynamic variables.** Figure 1 displays the hemodynamic responses. Compared with baseline, MAP was increased during the exercise and PECO periods (P < 0.001). HR was elevated during the exercise period only (P < 0.001), recovering to baseline values during the first minute of PECO. Compared with baseline, SV was increased during exercise alone (P < 0.05). Consequently, Q was elevated during the 2 min of exercise (P < 0.05) but not during PECO. TPR was unchanged from baseline in both the exercise and PECO periods (Fig. 1). The increase in superficial femoral artery blood flow above baseline [change in leg blood flow (ΔLBF)] was strongly and directly correlated with the change in Q (ΔQ) through the protocol [ΔLBF = 20.6 + (ΔQ) − 6.8; r = 0.6; P < 0.001]. However, there was notable intersubject variability so that the rise in LBF during handgrip exercise, although following the pattern of change in Q, was not statistically different from baseline (Fig. 2). As with systemic TPR, vascular resistance in the superficial femoral artery distribution was unchanged between baseline, static handgrip, and PECO periods. (Fig. 2).
MSNA. Compared with baseline (13 ± 6 bursts/min), MSNA burst rate was increased to 28 ± 14 bursts/min by the second minute of exercise (Fig. 3; \( P < 0.05 \)) and remained elevated during the PECO periods. Burst height was not changed from baseline levels during either the exercise or PECO periods. Thus total MSNA was elevated above baseline levels (3 ± 3 units) due to the burst rate response (Fig. 3; \( P < 0.05 \)).

Portal vein. Compared with baseline (10.3 ± 0.9 mm), portal vein diameter was reduced by ∼5% to 9.7 ± 0.8 mm \( (P < 0.05) \) during the second minute of exercise (Fig. 4). However, this response was confined to the exercise period with portal vein diameter returning to baseline levels during the second minute of PECO.

DISCUSSION

The results indicate that stroke volume rises during volitional isometric small muscle mass exercise along with HR so that the MAP response to this handgrip exercise task was accounted for by the ∼1 l/min rise in \( \dot{Q} \). Consistent with a rise in SV during the exercise was the reduction in portal vein diameter, which suggests splanchnic vasoconstriction (2) and a mobilization of visceral blood volume towards the heart. In contrast, there was no apparent change in LVR or TPR in either the handgrip or PECO phases despite the rise in MSNA. The study observations also indicate that the role of \( \dot{Q} \) and visceral blood volume mobilization was most evident during the exercise component of the protocol, returning toward baseline levels during PECO. Together, the data point to a concerted response whereby central blood volume decreased during the forearm exercise to elevate SV and blood pressure through increased \( \dot{Q} \) at levels that were proportionately high for the level of systemic conductance. The data further emphasize the importance of changes in the control features between the volitional exercise and the PECO phases where dominance switches from central command and muscle reflex contributions during the contraction to the metaboreflex component during PECO.

The present data address a key issue regarding the role of the metaboreflex to elevate flow and/or vascular resistance. In this...
context, the metaboreflex is defined as the response elicited by metaboreceptors in skeletal muscle rather than the more generalized pressor response that occurs during exercise. The overall pressor response that occurs during volitional exercise is more complex in its control. During muscular contractions, a large cortical component withdraws vagal constraint of heart rate (18, 37). Also, ascending metaboreceptor inputs contribute to the sympathetic response during exercise. Conversely, cortical contributions associated with muscle contractions are removed during the PECO phase when the sympathetic responses are governed primarily by metaboreceptor inputs, and when vagal outflow increases and dominates adrenergic cardiac stimulation, reducing HR to baseline levels (22, 24). The postexercise ischemia phase emphasizes the important role of cortical elements in the control of $Q$ during exercise that are not present, or are present to a much smaller degree, when afferent information from fatigued muscle is the primary signal.

The observation of concurrent MSNA and MAP responses in human-based studies of fatiguing exercise have led to the speculation that the neurogenic vasoconstriction is the driving determinant of the pressor response during metaboreflex activation (18, 32). However, these studies did not measure $Q$. Consequently, the present results are in agreement with a growing number of studies that indicate that vascular resistance plays a minor role in the pressor response to fatiguing exercise (27, 40). For example, using a flow-limited exercise model, O’Leary et al. (27), and others (40), have demonstrated that the pressor response that develops during dynamic treadmill running exercise, under conditions that activate the muscle metaboreflex, is due primarily to elevated cardiac output. Similarly, an elevated $Q$ has been reported in humans but the measures were limited to the volitional component of static leg (5, 39) or handgrip (36) exercise.

An important feature about the $Q$ response, however, is whether it is facilitated by SV and/or HR. In this regard, conclusions may vary depending on experimental designs that favor volitional exercise vs. metaboreflex inputs alone. The canine treadmill model obtains results during the volitional exercise period and does not isolate the metaboreflex component from central command. Other studies have focused attention on the postexercise metaboreflex phase and report little change in $Q$ if the previous exercise was of moderate intensity (e.g., 30–40% MVC) (5, 22). Heavier contractions of 70% MVC may elicit a sustained $Q$ response during the PECO phase (5). The present data have examined both phases in the same individuals providing confirmation that influences on $Q$ appear to be regulated independently from, or at least in an interactive manner with, metaboreflex inputs from fatiguing skeletal muscle.

Determinants of whether a $Q$ response is mediated by SV or HR may also be affected by factors that affect atrial filling. For example, Friedman et al. (8) observed that the pressor response to static leg exercise was driven primarily by $Q$, which, in turn, was due to HR and not SV. In that study, the subjects were in the upright posture, in contrast to the supine position of the present participants. It is likely that the impact of posture to reduce venous return and concurrently constrict the portal circulation (2) would make it difficult to produce further reductions in splanchnic blood volume during handgrip. Thus,

![Fig. 3. Muscle sympathetic nerve activity (MSNA) as measured in the peroneal nerve during the handgrip protocol. Values are means ± SD. MSNATOT, sum of all MSNA burst heights during each respective minute; au, arbitrary units. *Significantly different from Base, $P < 0.05$.](image)

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![Fig. 4. Relative change in portal vein diameter from baseline during the handgrip (Grip) and PECO phases of the exercise protocol. Values are means ± SD. See text for absolute values and statistics. *Significantly different from preexercise baseline and from PECO, $P < 0.05$.](image)

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HR is the only option available to elevate Q in the upright position. The idea that the contributions of SV to the exercise pressor response depend on the HR is supported by a paced heart model where handgrip resulted in an increase to atrial filling when HR was paced at a slow rate (23). Thus it appears that either HR or SV can be used as needed to accomplish the task of elevating Q during static exercise. In the supine subject, SV appears to be an important feature.

Closer examination of the neurogenic and hemodynamic time course of the pressor response provides the additional suggestion that sympathetic activation is not the sole determinant of the pressor response during volitional static exercise in this human model. For example, arterial pressure begins its ascent at the immediate onset of exercise along with HR, whereas the sympathetic response (as measured by MSNA) is delayed by 15–30 s, depending on the exercise intensity. Furthermore, earlier results had indicated that the rise in MAP during static exercise was not affected by α- or β-adrenergic blockade, either independently or in combination with atropine (19).

Therefore the important observation of this study was the elevation in SV during static exercise. The elevated SV indicates that the rise in Q is not solely dependent on the tachycardia that occurs during handgrip. While enhanced cardiac contractility may be contributing to this response, it was also examined whether a redistribution of visceral blood volume developed during this form of exercise. The reduction in portal vein diameter late in exercise supports that hypothesis pointing to a complex regulatory system during volitional static exercise.

In view of these data, and considering the context of the debate regarding pressor responses to exercise (25), it must be asked how the sympathetic nervous system fits into the integrated response where TPR does not change late in exercise, but constriction in the renal, mesenteric, and/or splanchnic beds must have occurred. The full MAP response was not apparent until both Q and MSNA had peaked, emphasizing the combined impact of these two contributors. Although spatial and temporal variations in the distribution of sympathetic outflow must occur (3, 20), it may be argued that increasing limb vasoconstriction does not appear to be the goal of elevated sympathetic outflow (29). Our observations would suggest that the elevated MSNA, coincident with baroreflex resetting (28), central command, and metaboreflex activation (18, 38), has a primary role in 1) preventing vasoconstriction in the face of rising Q and 2) modifying (or affecting) venous return through targeting the central vasculature and perhaps veins. Furthermore, recent observations relating renal artery flow patterns at the onset of handgrip exercise (20) support the hypothesis of an early and coordinated pattern of neurogenic activation to renal beds that may precede MSNA measures made in the limb. We did not measure the change in portal vein diameter during the first minute of exercise, but the rapid MAP and SV responses suggest that this pattern of coordinated cardiovascular control may be occurring. Because this early response has been related to mechanoreceptors (20), it will be of interest to investigate further the regional sympathetic responses in this exercise model and how these may be differentially affected by mechanoreceptors vs. metaboreceptors.

Methodological considerations. The experimental model used here incorporated ischemic exercise so that individual differences in the pressure-induced changes in blood flow to the active muscle that affect the metaboreflex activation were eliminated. Therefore, these data cannot address the issue of whether this reflex elicits increased flow in the working muscle. Also, the use of an ischemic model may augment the metabolic stimulus for muscle chemoreflex activation and, thereby, alter the normal interrelationship between cortical and muscle neurogenic contributions. However, similar results have been observed in dynamic, nonischemic static leg exercise (23). Also, impedance plethysmographic measures of regional blood volume suggest that cardiac preload and SV were also augmented in a nonischemic static handgrip task (36). Furthermore, the evidence that SV was only augmented during the first minute of volitional exercise, but not during the PECO phase, suggests that signals coming from the skeletal muscle are not the dominant determinant of SV during static exercise.

Although it is assumed that the PECO protocol isolates the sympathoexcitatory muscle metaboreflex, the full situation is likely to be more complex. For example, the large increase in vagal output during PECO occurs with, but overwhelms, the ongoing sympathetic activation of the heart (22). Also, baroreflex resetting is a notable feature of isometric exercise (10, 31), and this will influence cardiovascular control. However, the details of the impact of altered sympathovagal balance and baroreflex resetting on cardiac function during these manoeuvres have not been determined, to our knowledge.

One study limitation is that the portal vein response is only an indirect indicator of reductions in splanchnic blood volume towards the heart and would be enhanced by direct measures of mesenteric resistance. Such measures would assist in determining whether portal vein changes were induced actively or passively. However, these latter measures are difficult to achieve in humans during exercise. Nonetheless, the diminished portal vein diameter is consistent with the elevated venous return and SV.

An important feature of this study was that the participants were young healthy women. Therefore, the results may be delimited by the population studied because there are several reports of sex-dependent differences in autonomic cardiovascular control (4, 35). Previously, Ettinger et al. (7) observed that the pressor and HR responses to a handgrip exercise protocol was smaller in the female vs. male counterparts. These differences were observed when the exercise component of the protocol was nonischemic. However, when the exercise and PECO period were both performed with total ischemia, these sex differences were minimized. Nonetheless, the MAP response remained suppressed in the women compared with men. Also, increases in LVR have been reported during this type of protocol in male populations (32, 34). Although neural responses to this type of exercise may not be different between men and women (7), the varied pressor responses between men and women may be related to greater end organ α-adrenergic receptor sensitivity in men vs. women (16). In this regard, the present results are consistent with previous reports suggesting that women demonstrate greater emphasis on cardiac function (heart rate) during cardiovascular reflex activation than men, who rely more on vascular resistance (4, 21, 35). Comprehensive experimental designs with a range of data outcomes are still required to address the sex-dependent variations in cardiovascular control during static contractions.
In summary, in this study, measures of Q, MSNA and vascular resistance both during fatiguing handgrip exercise and the period of PECO revealed that changes in Q were the primary determinant of the exercise pressor response in these healthy women. In addition, a role of central blood volume mobilization to support the rise in SV was observed. An important result was that the elevation of Q was most apparent during contractions. Thus a speculative scenario is developed whereby sympathetic activation during fatiguing exercise is needed to direct blood toward the heart so that total flow increases. However, the role of Q was not evident during the isolated metaboreflex period, emphasizing that Q is dominated by factors that are independent from, or that interact with, metaboreflex inputs from fatiguing skeletal muscle.

REFERENCES