Effect of muscle metaboreflex activation on carotid-cardiac baroreflex function in humans

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Submitted 19 December 2007; accepted in final form 5 March 2008

Fisher JP, Young CN, Fadel PJ. Effect of muscle metaboreflex activation on carotid-cardiac baroreflex function in humans. Am J Physiol Heart Circ Physiol 294: H2296–H2304, 2008. First published March 7, 2008; doi:10.1152/ajpheart.91497.2007.—Whether the activation of metabolically sensitive skeletal muscle afferents (i.e., muscle metaboreflex) influences cardiac baroreflex responsiveness remains incompletely understood. A potential explanation for contrasting findings of previous reports may be related to differences in the magnitude of muscle metaboreflex activation utilized. Therefore, the present study was designed to investigate the influence of graded intensities of muscle metaboreflex activation on carotid baroreflex function. In eight healthy subjects (24 ± 1 yr), the graded isolation of the muscle metaboreflex was achieved by post-exercise ischemia (PEI) following moderate- (PEI-M) and high- (PEI-H) intensity isometric handgrip performed at 35% and 45% maximum voluntary contraction, respectively. Beat-to-beat heart rate (HR) and blood pressure were measured continuously. Rapid pulse trains of neck pressure and neck suction (+40 to −80 Torr) were applied to derive carotid baroreflex stimulus-response curves. Mean blood pressure increased significantly from rest during PEI-M (+13 ± 3 mmHg) and was further augmented during PEI-H (+26 ± 4 mmHg), indicating graded metaboreflex activation. However, the operating point gain and maximal gain (−0.51 ± 0.09, −0.48 ± 0.13, and −0.49 ± 0.12 beats·min⁻¹·mmHg⁻¹ for rest; PEI-M and PEI-H) of the carotid-cardiac baroreflex function curve were unchanged from rest during PEI-M and PEI-H (P > 0.05 vs. rest). Furthermore, the carotid-cardiac baroreflex function curve was progressively reset rightward from rest to PEI-M to PEI-H, with no upward resetting. These findings suggest that the muscle metaboreflex contributes to the resetting of the carotid baroreflex control of HR; however, it would appear not to influence carotid-cardiac baroreflex responsiveness in humans, even with high-intensity activation during PEI.

heart rate; carotid baroreceptors; skeletal muscle afferents

DURING BOTH STATIC and dynamic exercise, the arterial baroreflex is reset to operate around the prevailing blood pressure in an exercise intensity-dependent manner (35, 37, 39, 43). This exercise-induced modulation of baroreflex function is mediated by central signals from the higher brain (i.e., central command) (18, 22, 32, 38) and by afferent signals arising from working skeletal muscle (i.e., exercise pressor reflex) (17, 32, 44, 50) that are composed of mechanically and metabolically sensitive afferents (6, 27, 30). With the use of the variable pressure neck collar and the fitting of response data to a logistic function curve, the resetting of the carotid baroreflex control of heart rate (HR), blood pressure, and sympathetic nerve activity during exercise has been shown to occur with a maintained maximal gain (i.e., sensitivity). However, for HR control, the point around which HR is regulated (i.e., the operating point) moves away from the position of maximal gain at the center of the baroreflex function curve (i.e., centering point) and toward the threshold of the reflex to a location of lesser gain. Although the activation of central command has been associated with this relocation of the operating point (18), selective augmentation (17) or attenuation (50) of the exercise pressor reflex during exercise does not appear to influence the operating point gain of the baroreflex.

More recent work in consciously exercising dogs has suggested that the graded activation of metabolically sensitive skeletal muscle afferents (i.e., muscle metaboreflex) leads to a progressive decrease in spontaneous indexes of arterial cardiac baroreflex sensitivity (47), which is representative of the gain around the operating point of the full baroreflex function curve (37, 40). In contrast, previous studies in humans examining the influence of the muscle metaboreflex on either arterial- or carotid-cardiac baroreflex sensitivity have found equivocal results reporting increases (5), decreases (20), or no change (8, 22–24, 52) in sensitivity. One possible explanation for these contrasting reports may be related to the differences in the magnitude of muscle metaboreflex activation utilized. Indeed, it has been proposed that robust muscle metaboreflex activation and the coincident sympathoexcitation are capable of reducing cardiac baroreflex sensitivity (20). However, this proposition remains to be rigorously tested in humans since the majority of studies have only used one modest intensity of muscle metaboreflex activation (5, 8, 21–24, 52).

Another possibility that may have also contributed to the contrasting reports surrounding whether the muscle metaboreflex influences cardiac baroreflex responsiveness (5, 8, 21–24, 52) may be related to the use of different techniques for the determination of baroreflex control. In this regard, the majority of previous studies have relied solely on the spontaneous indexes of arterial cardiac baroreflex sensitivity (e.g., sequence technique). Because these spontaneous indexes only provide an estimate of baroreflex sensitivity around the operating point (37, 40), it is plausible that reports of decreases in baroreflex sensitivity elicited by the muscle metaboreflex are due to a shift of the operating point to a location of lesser gain. Alternatively, a muscle metaboreflex-mediated reduction in maximal baroreflex gain may also occur with robust metaboreflex activation. However, these possibilities remain to be carefully delineated and require the concomitant determination of the operating point gain and maximal gain of the full baroreflex function curve.

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With this background in mind, the present investigation was designed to investigate the influence of graded intensities of muscle metaboreflex activation on cardiac baroreflex function. To accomplish this, the activation of the muscle metaboreflex was isolated during a period of post-exercise ischemia (PEI) following both moderate- and high-intensity isometric hand-grip (HG) while full carotid baroreflex function curves were derived. The aim of this study was to determine whether robust increases in muscle metaboreflex activation can lead to either 1) a movement of the operating point toward the threshold of the carotid-cardiac baroreflex function curve and a consequent decrease in operating point gain or 2) a reduction in maximal baroreflex gain.

METHODS

We studied eight young healthy individuals (7 men and 1 woman) with an age of 24 ± 1 yr, weight of 75 ± 4 kg, and height of 181 ± 3 cm. The subjects were asymptomatic for cardiovascular or respiratory disease and were not taking any medications. The subjects were recreationally active, typically engaging in low- (e.g., walking) and moderate- (e.g., jogging, stationary bike) intensity aerobic activities (2 to 3 days/wk), but importantly, none were training competitively. All moderate- (e.g., jogging, stationary bike) intensity aerobic activities (2 to 3 days/wk) were performed last to determine whether satisfactory carotid-cardiac baroreflex function curves could be obtained during PEI and thus to assess the protocol feasibility before performing the higher-intensity exercise bout. Each exercise bout was separated by at least 20 min to ensure the return of cardiovascular variables to resting baseline values. Satisfactory carotid baroreflex function curves were obtained in all subjects during PEI-M and PEI-H. However, preliminary studies employing isometric exercise at >45% MVC in an attempt to further increase muscle metaboreflex activation during PEI were found to elicit significant subject discomfort, which impeded the determination of carotid-cardiac baroreflex function curves (as described in Derivation of Carotid Baroreflex Function Curves).

Carotid baroreflex control. Full carotid-cardiac and carotid-vasomotor (i.e., mean blood pressure) baroreflex function curves were derived at rest, during isometric HG, and during PEI in each subject, as previously described (12, 15, 17). A malleable lead neck collar that encircled the anterior two-thirds of the neck was fitted for the application of neck pressure (NP) and neck suction (NS). Appropriate neck chamber placement was ensured by first fitting the subjects based on observed neck size and then performing resting trials of NP and NS to determine directionally appropriate and consistent HR responses. Carotid baroreflex function was determined using the rapid NP and NS protocol administered during a 10–15-s breath hold at end expiration. Twelve consecutive pulses of 500-ms duration ranging from +40 to −80 mmHg (in the order of 40, 40, 40, 40, 20, 10, 0, −10, −20, −40, −60, and −80) were delivered to the carotid sinus precisely 50 ms after the R-wave of the ECG (10). After the delivery of each pressure pulse, the neck chamber was vented to atmospheric pressure. The generated pressure within the neck collar was measured by a transducer (model DP45; Validyne Engineering, Northridge, CA). Five to six trains of the rapid NP and NS protocol were performed at rest, whereas due to time constraints, two to three trains were delivered during HG and three to four trains were delivered during PEI. We were unable to obtain baroreflex function curves in a small number of subjects at the end of HG due to the inability to perform the breath hold without an inadvertent Valsalva maneuver (2 subjects during 35% MVC and 4 subjects during the 45% MVC trial). In these individuals, the curves obtained earlier in HG (at ~75 s) were corrected to account for the blood pressure and HR responses obtained at end exercise. In other words, the absolute values of the baroreflex curve were adjusted to account for any further increases in blood pressure and HR that occurred during HG to better reflect the resetting of the baroreflex with exercise. A minimum of 30 to 45 s of recovery was allotted between NP and NS trials to allow all physiological variables to return to prestimulus values.

Derivation of Carotid Baroreflex Function Curves

Carotid-cardiac and carotid-vasomotor stimulus-response curves were determined by plotting the changes in HR and mean blood pressure, respectively, elicited by NP and NS against the estimated
carotid sinus pressure (ECSP), which was calculated as mean blood pressure minus neck chamber pressure. Carotid baroreflex stimulus-response data were individually fit for each subject to the logistic function model described by Kent et al. (28), which incorporates the following equation:

\[
\text{Dependent variable} = A_1 \left[1 + \exp \left(A_2 \left(\text{ECSP} - A_3\right)\right)\right]^{-1} + A_4 \ (1)
\]

where the dependent variable is HR or mean blood pressure, \(A_1\) is the range of response of the dependent variable (maximum − minimum), \(A_2\) is the gain coefficient (i.e., slope), \(A_3\) is the centering point or carotid sinus pressure required to elicit equal pressor and depressor responses, and \(A_4\) is the minimum response. Individual data were applied to this model by a nonlinear least-squares regression that minimizes the sum of squares error and predicts a curve of best fit for the data.

The carotid baroreflex operating point gain and maximal gain were calculated using the following equations:

\[
G_{op} = A_1 A_2 \exp \left[A_2 \left(\text{ECSP}_{op} - A_3\right)\right] / \left\{1 + \exp \left[A_2 \left(\text{ECSP}_{op} - A_3\right)\right]\right\} \ (2)
\]

\[
G_{\text{max}} = -A_1 A_3 / 4 \ (3)
\]

where \(G_{op}\) is the gain of the carotid baroreflex function curve at the operating point, \(G_{\text{max}}\) is the maximal gain of the carotid baroreflex function curve, and ECSP_{op} is the ECSP at the operating point (i.e., prestimulus mean blood pressure). The \(G_{op}\) was calculated as the gain at the operating point and used to provide a measure of responsiveness at the operating point of the carotid baroreflex function curve, whereas the \(G_{\text{max}}\) was calculated as the gain at the centering point and used as an index of overall carotid baroreflex responsiveness. The threshold and saturation, described as the minimum and maximum ECSP, respectively, that elicit a reflex change in HR or mean blood pressure, were calculated using the following equation:

\[
\text{Threshold} = -2.944 / A_2 + A_3 \quad \text{and} \quad \text{Saturation} = -2.944 / A_2 + A_3 \ (4)
\]

These calculations have been found to be the ECSP at which HR and mean blood pressure were within 5% of the maximal or minimal response (31). The parameters for all subjects within an experimental condition were averaged to provide group mean responses.

Statistical Analysis

The statistical comparisons of physiological variables were made using ANOVA with repeated-measures, and a Student-Newman-Keuls test was employed post hoc. Statistical significance was set at \(P < 0.05\). Results are presented as means ± SE. Of note, carotid baroreflex responses of the one woman in the present study were similar to those of the men during both HG and PEI, and removal of this data did not influence the main conclusions of the study. The analyses were conducted using SigmaStat (Jandel Scientific Software; SPSS, Chicago, IL) for Windows.

RESULTS

HG Exercise

The cardiovascular variables measured at rest and during graded HG exercise (35% and 45% HG) are shown in Table 1. There were no statistically significant differences between baseline parameters obtained before any of the HG trials, thus to improve the clarity of the presentation only, data from the first rest period have been presented.

RPE values were significantly increased from 35% to 45% HG, indicating the grading of the two exercise intensities. As expected, blood pressure and HR increased significantly from rest during isometric HG at 35% MVC and were additionally augmented during 45% MVC HG (Table 1 and Fig. 1). This was accompanied by an upward and rightward resetting of the carotid-cardiac baroreflex curve from rest, as indicated by progressive increases in the minimum response and centering point and significant elevations in the threshold and saturation from rest (Table 2 and Fig. 2). The maximal gain and operating point gain of the cardiac baroreflex function curve were unchanged during HG. A similar upward and rightward resetting without a change in gain was found for the carotid-vasomotor baroreflex function curve during 35% and 45% HG (Table 3).

PEI

Blood pressure was significantly elevated from rest during PEI-M and was further augmented during PEI-H, whereas HR returned to baseline values (Table 1 and Fig. 1). Importantly, the graded isolation of the muscle metaboreflex achieved during PEI-M and PEI-H did not result in a significant change in the operating point gain \((P > 0.05\) vs. rest) or maximal gain \((P > 0.05\) vs. rest) of the carotid-cardiac baroreflex function curve (Table 2 and Fig. 2). Furthermore, muscle metaboreflex activation was not associated with a movement of the operating point of the carotid baroreflex function curve away from the centering point \((-1 ± 1, 1 ± 1,\) and \(1 ± 1\) beats/min during rest; PEI-M and PEI-H, respectively; \(P > 0.05\) vs. rest). However, during PEI-M and PEI-H, there was a rightward resetting of the carotid-cardiac baroreflex function curve (Fig. 2) as indicated by a progressive increase in the centering point and an elevation in the threshold and saturation from rest (Table 2 and Fig. 3). In contrast, the minimum response was unchanged from rest \((P > 0.05\) vs. rest), demonstrating that the graded activation of the muscle metaboreflex did not elicit any upward resetting of the carotid-cardiac baroreflex function curve. For the carotid-vasomotor curve, both an upward and rightward resetting were present during PEI-M and PEI-H compared with rest without any changes in gain (Table 3).

Changes from HG to PEI

When compared with 35% and 45% HG, the minimum HR response \((A_4)\) and centering point \((A_3)\) were significantly reduced during PEI-M and PEI-H, indicative of a downward and leftward resetting of the carotid-cardiac baroreflex function curve (Table 2 and Fig. 2). However, the decreases in the threshold and saturation of the carotid-cardiac curve from HG to PEI did not reach statistical significance \((P > 0.05)\), although both remained significantly greater than those of the

Table 1. Selected physiological variables at rest, during graded HG and isolated activation of the muscle metaboreflex with PEI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>35% HG</th>
<th>PEI-M</th>
<th>45% HG</th>
<th>PEI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mmHg</td>
<td>87±2</td>
<td>107±3*</td>
<td>100±3*</td>
<td>117±3†</td>
<td>113±4‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65±2</td>
<td>78±2*</td>
<td>63±2§</td>
<td>91±3†</td>
<td>64±2§</td>
</tr>
<tr>
<td>RPE</td>
<td>6±0.0</td>
<td>13±0.4*</td>
<td>—</td>
<td>16±1†</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SE. PEI, post-exercise ischemia; BP, blood pressure; RPE, rating of perceived exertion; HG, isometric handgrip; PEI-M, PEI following 35% HG; PEI-H, PEI following 45% HG. *P < 0.05, different from rest; †P < 0.05, different from 35% HG; ‡P < 0.05, different from PEI-M; §P < 0.05, different from HG of corresponding trial.
rest group. A tendency for a downward and leftward resetting of the carotid-vasomotor baroreflex curve was present from HG to PEI although the centering point, minimum response, threshold, and saturation were not different between PEI-M and 35% HG or between PEI-H and 45% HG (Table 3). However, these parameters of the carotid-vasomotor curve remained significantly increased from rest during both PEI-M and PEI-H.

**DISCUSSION**

The novel finding of the present study is that graded and robust muscle metaboreflex activation did not affect carotid-cardiac baroreflex responsiveness. Despite a progressive rightward resetting of the carotid-cardiac baroreflex stimulus-response relationship, the operating point gain and the maximal gain of the carotid baroreflex function curve remained unchanged. These findings suggest that although the muscle metaboreflex contributes to the resetting of the carotid baroreflex control of HR, it would appear not to influence carotid-cardiac baroreflex responsiveness in humans, even with high-intensity activation during PEI.

Recent findings have indicated that graded and robust muscle metaboreflex activation, induced by a reduction of hindlimb blood flow in consciously exercising dogs at a moderate and high intensity, progressively decreased spontaneous measures of arterial cardiac baroreflex sensitivity (47). This prompted us to investigate whether previous results in humans demonstrating that cardiac baroreflex responsiveness was unaffected by the muscle metaboreflex were due to the intensity of muscle metaboreflex activation (8, 22–24, 52). Indeed, in contrast to the work in animals, the majority of human studies have generally used only one relatively low intensity of muscle metaboreflex stimulation (5, 8, 22–24, 52). In addition, Iellamo et al. (20) recently reported that an augmented metaboreflex response during PEI following dynamic exercise in spaceflight compared with preflight was associated with a reduction in arterial cardiac baroreflex sensitivity, suggesting that the magnitude of the metaboreflex activation may indeed be important to alter the baroreflex control of HR. However, despite the robust muscle metaboreflex activation observed in the present study during PEI following isometric exercise, we found a clear preservation of cardiac baroreflex responsiveness when assessed using either the operating point gain or the maximal gain of the carotid-cardiac baroreflex function curve.

Aside from differences in the magnitude of metaboreflex stimulation, we also considered whether the use of different techniques for the determination of baroreflex control may have contributed to prior contrasting reports surrounding whether the muscle metaboreflex influences cardiac baroreflex responsiveness (5, 8, 20–24, 47, 52). In this regard, the majority of the previous animal and human investigations in this area have employed spontaneous techniques such as the sequence technique to estimate arterial cardiac baroreflex sen-

**Table 2. Logistic model parameters and derived variables describing carotid baroreflex control of heart rate at rest, during graded HG and isolated activation of the muscle metaboreflex with PEI**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>35% HG</th>
<th>PEI-M</th>
<th>45% HG</th>
<th>PEI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1, beats/min</td>
<td>14±1</td>
<td>14±2</td>
<td>12±1</td>
<td>16±2</td>
<td>11±1§</td>
</tr>
<tr>
<td>A2, au</td>
<td>0.15±0.03</td>
<td>0.15±0.03</td>
<td>0.16±0.02</td>
<td>0.15±0.03</td>
<td>0.19±0.04</td>
</tr>
<tr>
<td>A3, mmHg</td>
<td>95±2</td>
<td>117±5*</td>
<td>106±2*§</td>
<td>130±2*‡</td>
<td>118±3*§‡</td>
</tr>
<tr>
<td>A4, beats/min</td>
<td>57±2</td>
<td>70±3*</td>
<td>58±28</td>
<td>82±2‡</td>
<td>59±2‡</td>
</tr>
<tr>
<td>Threshold, mmHg</td>
<td>72±2</td>
<td>95±6*</td>
<td>85±3*</td>
<td>106±5*</td>
<td>97±5*</td>
</tr>
<tr>
<td>Saturation, mmHg</td>
<td>118±5</td>
<td>140±5*</td>
<td>128±5</td>
<td>153±5*</td>
<td>140±5*</td>
</tr>
<tr>
<td>Gmax, beats·min⁻¹·mmHg⁻¹</td>
<td>−0.51±0.09</td>
<td>−0.52±0.12</td>
<td>−0.48±0.13</td>
<td>−0.56±0.10</td>
<td>−0.49±0.12</td>
</tr>
<tr>
<td>Gop, beats·min⁻¹·mmHg⁻¹</td>
<td>−0.35±0.05</td>
<td>−0.24±0.06</td>
<td>−0.29±0.03</td>
<td>−0.24±0.06</td>
<td>−0.27±0.06</td>
</tr>
</tbody>
</table>

Values are means ± SE. A1, response range; A2, gain coefficient; A3, centering point; A4, minimum response; Gmax, maximal gain; Gop, operating point gain, au, arbitrary units. * P < 0.05, different from rest; † P < 0.05, different from 35% HG; ‡ P < 0.05, different from PEI-M; § P < 0.05, different from HG of corresponding trial.
Of note, this methodology only provides an estimate of the baroreflex gain around the operating point of the full baroreflex stimulus-response curve (37, 40). This is an important consideration given that during dynamic exercise the operating point shifts closer to the threshold of the baroreflex function curve and to a location of lesser gain as exercise intensity increases, even though the maximal gain of the baroreflex function curve is well maintained (35, 37, 43).

Thus we rationalized that perhaps the decrease in arterial cardiac baroreflex sensitivity recently reported during metaboreflex activation was due to a movement of the operating point. Although studies have clearly indicated a role for central command and its influence on the parasympathetic control of HR in mediating this shift in the operating point and associated decrease in the operating point gain of the cardiac baroreflex (18, 35, 37, 43), the potential for the robust activation of the metaboreflex to also contribute to the movement of the operating point had not been previously tested in humans. However, in the present study, we did not observe a muscle metaboreflex-mediated movement of the operating point or a reduction in operating point gain. Furthermore, we did not observe any metaboreflex-induced changes in the maximal gain of the cardiac baroreflex function curve. These findings are in agreement with previous studies that have selectively augmented or attenuated exercise.

![Carotid-cardiac baroreflex function curves during graded HG and subsequent isolated activation of the muscle metaboreflex with PEI.](image)

### Table 3. Logistic model parameters and derived variables describing carotid baroreflex control of blood pressure, i.e., carotid-vasomotor curve, at rest, during graded HG and isolated activation of the muscle metaboreflex with PEI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>35% HG</th>
<th>PEI-M</th>
<th>45% HG</th>
<th>PEI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$, mmHg</td>
<td>13±1</td>
<td>12±1</td>
<td>11±1</td>
<td>11±1</td>
<td>10±1</td>
</tr>
<tr>
<td>$A_2$, au</td>
<td>0.09±0.01</td>
<td>0.09±0.03</td>
<td>0.10±0.01</td>
<td>0.10±0.01</td>
<td>0.09±0.01</td>
</tr>
<tr>
<td>$A_3$, mmHg</td>
<td>91±2</td>
<td>114±5*</td>
<td>108±4*</td>
<td>129±6*†</td>
<td>123±5*†</td>
</tr>
<tr>
<td>$A_4$, mmHg</td>
<td>79±1</td>
<td>102±4*</td>
<td>97±4*</td>
<td>116±8*†</td>
<td>109±4*†</td>
</tr>
<tr>
<td>Threshold, mmHg</td>
<td>54±5</td>
<td>71±7*</td>
<td>75±6*</td>
<td>95±6*†</td>
<td>91±5*†</td>
</tr>
<tr>
<td>Saturation, mmHg</td>
<td>129±6</td>
<td>156±9*</td>
<td>141±4</td>
<td>163±9*</td>
<td>154±5*</td>
</tr>
<tr>
<td>$G_{max}$, mmHg/mmHg</td>
<td>−0.25±0.02</td>
<td>−0.25±0.06</td>
<td>−0.24±0.01</td>
<td>−0.26±0.06</td>
<td>−0.23±0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05, different from rest; †P < 0.05, different from 35% HG; ‡P < 0.05, different from PEI-M.
pressor reflex activation (i.e., mechano- and metaboreceptors) by using medical antishock trousers (17) or epidural anesthesia (50), respectively. More importantly, our results extend these observations by isolating the influence of the muscle metaboreceptors and accomplishing a much more robust activation of this reflex.

Although we rationalized that the intensity of metaboreflex activation may influence either the operating point gain or maximal gain of the carotid-cardiac baroreflex function curve, the results indicated preserved cardiac baroreflex responsiveness even during the robust activation of the muscle metaboreflex. In contrast, a clear influence of the muscle metaboreflex on baroreflex resetting was observed since during graded PEI the carotid-cardiac baroreflex function curve was progressively reset to the right. In addition, the modest leftward resetting from HG to PEI also emphasizes the importance of the muscle metaboreflex to baroreflex resetting during isometric exercise (see Fig. 2). Indeed, if the muscle metaboreflex was not involved with exercise resetting, one would expect the baroreflex function curve to reset back to resting levels during PEI; however, this was clearly not the case. Although the specific reason(s) for an effect of metaboreflex activation on cardiac baroreflex resetting but not on its sensitivity is unclear, this finding warrants discussion.

Neuroanatomical evidence indicates that the arterial baroreflex, central command, and skeletal muscle afferents share common central neural pathways including the nucleus tractus solitarius (NTS) and rostral ventral lateral medulla (9, 41). Indeed, the resetting of the baroreflex function curve during exercise without a change in responsiveness has been proposed to represent alterations in inhibitory inputs to the NTS from central command and/or skeletal muscle afferents (41, 42, 46). According to the model proposed by Potts (41), the expected increase in the excitability of barosensitive NTS neurons, caused by the exercise-induced elevation in blood pressure, is offset by the activation of an inhibitory neural circuit within the NTS by feedback from skeletal muscle afferents. Based on this model, in the current study, we would speculate that the influence of graded muscle metaboreflex-mediated increases in blood pressure on barosensitive NTS neurons is counteracted by a progressive metaboreceptor-activated inhibitory neural circuit within the NTS. This would explain the progressive rightward resetting of the carotid-cardiac baroreflex function curve with changes in operating point gain or maximal gain observed during graded PEI.

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![Graphs](http://ajpheart.physiology.org/)

**Fig. 3.** Selected logistic model parameters and derived variables describing carotid baroreflex control of heart rate at rest and during graded activation of the muscle metaboreflex with PEI. Summary data for the logistic model parameters of response range (A1; A), gain coefficient (A2; B), centering point (A3; C), minimum response (A4; D), and the derived variables of threshold (E) and saturation (F) for the carotid-cardiac baroreflex function curves at rest and during PEI-M and PEI-H are shown. Graded muscle metaboreflex activation elicited an increase from rest in centering point, threshold, and saturation, whereas the minimum response was not significantly changed, indicating a progressive rightward resetting of the carotid-cardiac baroreflex function curve with no upward resetting. *P < 0.05, different from rest; #P < 0.05, different from PEI-M. au, Arbitrary units.
The lack of a muscle metaboreflex-mediated modulation of cardiac baroreflex sensitivity may also be related to an absence of an interaction between muscle metaboreceptors and the control of parasympathetic activity (8). Although there is some indication that skeletal muscle afferents may converge directly on cardiac vagal neurons in the brain stem to alter cardiac baroreflex responsiveness (26), this may be selective for muscle mechanoreceptors (19) contributing to HR control at the onset of exercise. However, the influence of the muscle mechanoreflex on the control of HR appears to be modest (7, 14, 19). In contrast, central command has been shown to have a clear and robust influence on vagally mediated alterations in HR (34). In this regard, numerous studies have indicated a role for central command in the modulation of cardiac baroreflex responsiveness as well as baroreflex resetting during exercise (18, 32, 35, 38). Collectively, the available data suggest that any exercise-induced alterations in cardiac baroreflex responsiveness (35, 37, 43) more likely result from centrally mediated reductions in vagal tone rather than via the activation of the muscle metaboreflex.

Interestingly, in the present study, we also found that the graded and robust muscle metaboreflex activation had no effect on the sensitivity of the carotid baroreflex control of blood pressure, although a clear influence on resetting was present. Indeed, during PEI, an upward and rightward resetting of the carotid-vasomotor baroreflex function curve from rest was observed with no change in gain (see Table 3). Therefore, similar to the baroreflex control of HR, the muscle metaboreflex is involved in the resetting of the baroreflex control of blood pressure without influencing its sensitivity.

In this study, graded muscle metaboreflex activation was accomplished during a period of PEI following moderate- and high-intensity isometric HG (1). The advantage of this well-established experimental approach is that the isolated influence of the muscle metaboreflex on baroreflex control could be easily graded without the confounding effects of neural inputs from central command and mechanically sensitive skeletal muscle afferents (13, 29, 48). However, an alternative strategy may have been to use bilateral thigh cuffs to partially restrict blood flow to the exercising muscle (16), similar to the partial terminal aortic occlusion model used in recent animal experiments (47). In this regard, there are distinct differences in cardiovascular neural control when metaboreflex activation is achieved during PEI compared with when reductions in exercising muscle blood flow are utilized. Notably, both HR and blood pressure increase when muscle metaboreflex is activated during exercise (2, 47), whereas when muscle metaboreflex is activated in the recovery period after exercise using PEI, only blood pressure and sympathetic nerve activity remain elevated while HR declines toward resting values. Indeed, during PEI, although sympathetic nerve activity to the heart is maintained at high levels, parasympathetic outflow increases with the cessation of exercise (24, 36). Thus, despite elevated sympathetic outflow, bradycardia occurs during PEI, which appears to be the result of an overwhelming effect of parasympathetic activation due to baroreflex mechanisms and/or the loss of central command (36). These differences in sympathovagal balance, resulting from variations in the methods used to elicit muscle metaboreflex activation, may explain the conflicting results of the present study and those of previous animal work using ischemic exercise to stimulate the metaboreflex (47).

Indeed, our findings apply to the isolation of the muscle metaboreflex during PEI and not the actual exercise period.

Several other factors that may influence the muscle metaboreflex contribution to cardiovascular responses and baroreflex control during exercise as well as during PEI should be mentioned. Indeed, the type of exercise (i.e., isometric vs. dynamic), the size of the exercising muscle mass, and the exercise intensity all can be modulating factors (33). In this regard, in contrast to the findings of the present study in which PEI followed isometric HG, recent work has demonstrated reductions in spontaneous arterial cardiac baroreflex sensitivity during PEI following dynamic leg cycling (20). Although differences in methods employed to examine baroreflex sensitivity cannot be discounted, it is also presently unclear whether differences in metaboreflex activation are present during PEI following isometric versus dynamic exercise. Thus the results of the present study following small muscle mass static exercise cannot be generalized to large muscle dynamic exercise. Indeed, future studies are needed to address these important issues.

A potential limitation in the design of the present investigation is that the rapid trains of NP and NS were performed during a short end-expiratory breath holding during HG. Although necessary to prevent respiratory-mediated fluctuations in cardiac vagal tone from influencing the determination of cardiac baroreflex function (11), a potential caveat is that a short apnea performed during isometric exercise may have cardiovascular effects in itself (53). However, these effects appear modest and much less profound than those produced during an apnea performed during dynamic exercise (53). In addition, all subjects were familiarized with the protocol and procedures in a preliminary session, and care was taken to habituate the subjects to the breath-hold maneuver. The use of a breath hold during rapid trains of NP and NS has also been used in several previous studies investigating baroreflex resetting during isometric exercise (15, 17, 18, 38, 50). In regard to the interpretation of the current findings, it should be noted that we solely described carotid baroreflex function without any measure of arterial or aortic baroreflex control. However, because of the parallel activity of the aortic and carotid baroreceptors (45, 51), the assumption is made that a selective modeling of the carotid baroreflex would be characteristic of the arterial baroreflex, particularly at the operating point (37).

In summary, graded and robust muscle metaboreflex activation had no effect on the operating point gain or the maximal gain of the carotid-cardiac baroreflex stimulus-response relationship but did elicit a progressive rightward resetting of the baroreflex function curve. These findings suggest that although the muscle metaboreflex contributes to the resetting of the carotid baroreflex control of HR during exercise, it would appear not to influence carotid-cardiac baroreflex responsiveness in humans, even with high-intensity activation during PEI.
MO, and by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-076636. J. P. Fisher was supported by an American Heart Association Heartland Affiliate Postdoctoral Fellowship (0720064Z).

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