Exercise intensity influences cardiac baroreflex function at the onset of isometric exercise in humans

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1Department of Medical Pharmacology and Physiology, and 2Dalton Cardiovascular Research Center, University of Missouri, Columbia; 3Harry S. Truman Memorial Veterans Hospital, Department of Veterans Affairs Medical Center, Columbia, Missouri; 4Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth; and 5Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

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Fisher JP, Ogoh S, Young CN, Keller DM, Fadel PJ. Exercise intensity influences cardiac baroreflex function at the onset of isometric exercise in humans. J Appl Physiol 103: 941–947, 2007. First published June 21, 2007; doi:10.1152/japplphysiol.00412.2007.—We sought to examine the influence of exercise intensity on carotid baroreflex (CBR) control of heart rate (HR) and mean arterial pressure (MAP) at the onset of exercise in humans. To accomplish this, eight subjects performed multiple 1-min bouts of isometric handgrip (HG) exercise at 15, 30, 45 and 60% maximal voluntary contraction (MVC), while breathing at a metronome set at eupneic frequency. Neck suction (NS) of −60 Torr was applied for 5 s at endexpiration to stimulate the CBR at rest, at the onset of HG (<1 s), and after ~40 s of HG. Beat-to-beat measurements of HR and MAP were recorded throughout. Cardiac responses to NS at onset of 15% (~12 ± 2 beats/min) and 30% (~10 ± 2 beats/min) MVC HG were similar to rest (~10 ± 1 beats/min). However, HR responses to NS were reduced at the onset of 45% and 60% MVC HG (~6 ± 2 and ~4 ± 1 beats/min, respectively; P < 0.001). In contrast to HR, MAP responses to NS were not different from rest at exercise onset. Furthermore, both HR and MAP responses to NS applied at ~40 s of HG were similar to rest. In summary, CBR control of HR was transiently blunted at the immediate onset of high-intensity HG, whereas MAP responses were preserved demonstrating differential baroreflex control of HR and blood pressure at exercise onset. Collectively, these results suggest that carotid-cardiac baroreflex control is dynamically modulated throughout isometric exercise in humans, whereas carotid baroreflex regulation of blood pressure is wellmaintained.

arterial baroreflex; blood pressure; heart rate

The arterial baroreflex buffers moment-to-moment fluctuations in arterial blood pressure via modulation of autonomic neural activity to the heart and vasculature. Numerous studies in animals and humans have identified that the arterial baroreflex is reset to operate around the prevailing blood pressure established by static and dynamic exercise with no change in maximal gain (1, 4, 8, 13, 31, 38). This exercise-induced arterial baroreflex resetting is mediated by central signals arising from higher brain centers (i.e., central command) (17, 21, 29, 35) and by peripheral feedback arising from exercising skeletal muscle (i.e., the exercise pressor reflex) (3, 16, 21, 29, 45) that is composed of mechanically and metabolically sensitive afferents (5, 23, 28). Collectively, these neural inputs contribute to the resetting of the baroreflex in direct relation to the intensity of exercise (11, 39).

Notably, the majority of human studies examining baroreflex function during exercise have done so after steady-state exercise conditions had been established. However, it remains unclear whether arterial baroreflex characteristics derived during steady-state exercise are representative of the entire exercise period. Indeed, there is evidence from animal studies to suggest that baroreflex-mediated responses are transiently attenuated at the immediate onset of exercise and restored during the latter, or steady-state, period of exercise (24, 26, 30, 32). A blunting of cardiac baroreflex responsiveness at the onset of static exercise was initially identified by McWilliam and colleagues (30) in a decerebrate cat model indicating a rapid modulation of the baroreflex by skeletal muscle afferents. In contrast, more recent work by Matsukawa and colleagues (24, 26, 32) reporting a similar attenuation of baroreflex cardiac responses at the onset of voluntary isometric exercise using trained conscious cats indicated that this immediate blunting was mediated via central command, whereas experimental maneuvers to selectively activate the exercise pressor reflex had no effect. In addition to heart rate (HR), these latter studies reported no change in baroreflex control of arterial blood pressure at exercise onset, indicating a differential modulation of baroreflex control of HR and blood pressure at the onset of exercise. Taken together, these findings suggest that the cardiac component of the baroreflex is attenuated at the onset of exercise via inputs from skeletal muscle afferents and/or central command, whereas the blood pressure, or vasomotor, component of the baroreflex is preserved. Despite the extensive studies in animals, whether arterial baroreflex function is similarly modulated at the onset of exercise in humans is unclear.

This remains a significant question considering the importance of the arterial baroreflex for maintaining appropriate neural cardiovascular adjustments to exercise, particularly during the transition from rest to exercise (41). Studies in both animals and humans have consistently demonstrated that interruption of arterial baroreflex input leads to altered cardiac and pressor responses to exercise (7, 42, 43, 47). Indeed, it has been concluded that a functional arterial baroreflex is requisite for a normal cardiac, pressor, and sympathetic response to exercise, most notably at exercise onset (7). However, how arterial baroreflex function is being modulated at the onset and

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throughout a bout of exercise to allow for appropriate cardiovascular adjustments remains to be determined in humans.

Therefore, the present study was designed to investigate carotid baroreflex (CBR) responsiveness in the transition from rest to exercise in humans. This was accomplished by assessing HR and blood pressure responses to CBR stimulation via neck suction (NS) at rest, at the immediate onset of (<1 s) and ~40 s into isometric handgrip (HG) exercise. Furthermore, because the initial cardiovascular responses to exercise are intimately linked to exercise intensity due to graded activation of central command and skeletal muscle afferents (23, 44), we examined the influence of exercise intensity on CBR control by having subjects perform HG at 15, 30, 45, and 60% of maximal voluntary contraction (MVC). We hypothesized that as exercise intensity increased, cardiac responses to NS would be progressively attenuated at the immediate onset of exercise whereas CBR-mediated blood pressure responses would be well maintained.

METHODS

Eight young healthy individuals (7 men) with a mean age of 25 ± 1 yr, weight of 75 ± 3 kg, and height of 177 ± 2 cm were recruited for this study. All subjects were free of any cardiovascular and pulmonary disorders and were not using prescribed or over-the-counter medications. All procedures and protocols conformed to the Declaration of Helsinki and were approved by the Institutional Review Board at the University of Missouri and the Research and Development committee at the Harry S. Truman Memorial Veterans Hospital. Following a detailed verbal explanation of the intended experimental measures and procedures, each subject gave informed consent before participation. Before any experimental sessions were conducted, all subjects were familiarized with the testing protocols. Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for 24 h before testing. On the experimental day, the subjects arrived at the laboratory a minimum of 2 h following a light meal. All studies were performed at a constant room temperature between 23 and 24°C with external stimuli minimized.

Experimental Measurements

HR was continuously monitored using a lead II electrocardiogram (model Q710, Quinton Instrument, Bothell, WA). Arterial blood pressure was measured on a continuous basis using finger photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). The Finometer was placed on the middle finger of the left hand while supported on an adjustable bedside table positioned at heart level. Before recordings were started, diastolic blood pressure (DBP) of the Finometer was matched with DBP measurements obtained from the brachial artery using an automated sphygmomanometer (Tango +., SunTech Medical Instruments, Raleigh, NC). Respiratory movements were monitored using a strain gauge pneumograph placed in a stable position over the abdomen (Pneumotrace, UFI, Morro Bay, CA). Ratings of perceived exertion (RPE) were obtained using the standard 6–20 Borg scale (2). All cardiovascular variables were sampled at 1,000 Hz and stored for offline analysis (Powerlab, AD Instruments, Bella Vista, NSW, Australia).

Experimental Procedures

HG. During the experimental session, subjects were seated in a semirecumbent position on a medical examination table with a HG dynamometer (model 78010, Lafayette Instrument, Lafayette, IN) held in the right hand while the limb was supported on an adjustable bedside table. MVC was determined as the highest force produced during three to five maximal efforts, each separated by 1 min. For the experimental protocol, the force exerted by the subject, expressed as a percentage of maximum, was continuously recorded and displayed on a computer screen positioned in front of the subject at eye level.

CBR stimulation. A malleable lead collar was fitted around the neck for the application of 5-s pulses of NS at ~60 Torr (38). Before the experimental session, appropriate neck chamber placement was ensured by first fitting the subjects based on observed neck size, and then performing resting trials of NS to determine directionally appropriate and consistent HR and mean arterial pressure (MAP) responses. Changes in neck collar pressure were generated by a variable pressure source and delivered to the neck collar through large-bore two-way solenoid valves (model 8215B, Asco, Florham Park, NJ). A pressure transducer (model DP45, Validyne Engineering, Northridge, CA) was connected to a port on the collar to accurately quantify the stimulus applied.

Control of breathing. Our pilot work suggested that asking subjects to perform an end-expiratory breath hold during NS at exercise onset precipitated the performance of a Valsalva maneuver, particularly during high-intensity HG. Thus, to avoid the confounding effects of straining maneuvers on the HR and MAP responses to NS and to control for the effects of respiratory phase on CBR-mediated responses (9, 10), NS was applied at the end of a normal expiration. This was accomplished by having subjects breathe to a metronome set at their eupneic frequency throughout the experimental protocols. Breathing rate was determined during a 10-min baseline period. This strategy allowed an investigator to manually trigger the application of NS to coincide with end expiration determined by continually monitoring the subjects’ respiratory phase displayed on a computer screen. Subjects were instructed to maintain metronome breathing throughout the application of NS.

Experimental Protocol

Graded isometric HG exercise. Subjects performed isometric HG exercise at 15, 30, 45, and 60% MVC. Following a 3-min rest period, subjects were instructed to start the HG exercise and maintain the desired force for 1 min, after which a 3-min recovery period was performed. A 5-s pulse of NS at ~60 Torr was applied during the first and second minutes of exercise, at the immediate onset of exercise (<1 s), and after ~40 s of each exercise bout. To allow for the timing of NS with end expiration at the onset of exercise, subjects were instructed to start exercise by an investigator monitoring their respiratory pattern. Exercise trials were performed in random order and separated by at least 15 min to ensure reestablishment of baseline HR and MAP before commencing the subsequent trial. Subjects performed two trials at each exercise intensity.

Data and Statistical Analysis

Cardiovascular variables were calculated at rest and during the last 10 s of isometric HG exercise. Responses to both exercise trials performed at each intensity (15, 30, 45, and 60% MVC) were averaged for individual subjects and then combined to provide a group mean. The responses to NS were calculated as the difference between the prestimulus HR and MAP and the nadir (1 cardiac cycle) elicited by CBR stimulation. Because no statistical differences were found between CBR responses in the repeat NS trials performed at rest, all resting trials were averaged together for each subject to provide a resting mean. Similarly, NS responses during the repeat exercise trials at each intensity were averaged. Statistical comparisons of physiological variables were made using a one-way repeated-measures ANOVA test, and a Student-Newman-Keuls test was employed post hoc to investigate significant main effects. Statistical significance was set at P < 0.05. Results are presented as means ± SE. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL) for Windows.
both the HR and MAP responses to NS applied at 60% MVC trials, respectively, Figs. 1 and 3). Furthermore, were not different from rest in any trial (Fig. 4). However, HR responses to NS were significantly reduced from rest at the start of 45% and 60% MVC HG (1 beats/min, respectively; *P < 0.001). As expected, RPE was significantly and progressively increased from rest as exercise intensity increased (Table 1).

**CBR Function During Graded Isometric HG Exercise**

As shown in Figs. 1 and 2, the bradycardic responses to NS at the immediate onset of isometric HG exercise performed at 15% (~12 ± 2 beats/min) and 30% (~10 ± 2 beats/min) MVC were not different from rest (~10 ± 1 beats/min). However, HR responses to NS were significantly reduced from rest at the start of 45% and 60% MVC HG (~6 ± 2 and ~4 ± 1 beats/min, respectively; *P < 0.05). In contrast to HR, the MAP responses to NS were not different from rest (~7 ± 1 mmHg) at the immediate onset of exercise in any trial (~8 ± 1, ~7 ± 1, ~8 ± 1, and ~7 ± 2 mmHg, for the 15, 30, 45, and 60% MVC trials, respectively, Figs. 1 and 3). Furthermore, both the HR and MAP responses to NS applied at ~40 s of HG were not different from rest in any trial (Fig. 4).

**DISCUSSION**

The major finding of the present study is the transient blunting of CBR-mediated control of HR at the onset of high-intensity isometric exercise in humans. Notably, these attenuated cardiac responses were restored during the latter period of exercise (~40 s), indicating dynamic modulation of the CBR throughout exercise. In contrast to the observed alteration in cardiac responses, CBR control of blood pressure appeared to be well maintained at all time points studied, demonstrating differential baroreflex control of HR and blood pressure at exercise onset. Collectively, these data indicate a dynamic modulation of CBR control of HR throughout exercise in humans, whereas CBR regulation of blood pressure is well maintained.

The majority of studies that have investigated CBR function during exercise in humans have reported that the CBR was reset to the prevailing level of systemic pressure and was able to respond to transient changes in carotid sinus pressure as effectively as at rest (1, 8, 12, 13, 16, 17, 38). However, these studies have focused on the latter, steady-state portion of exercise without specific consideration of the immediate onset of exercise. In the present study, by comparing CBR responses at the onset of exercise with those obtained at a later time point, we provide the first experimental evidence in humans that CBR control of HR dynamically changes throughout a given bout of exercise. These data are in general agreement with previous work performed in consciously exercising cats (24, 26, 32). To date, the only previous study to examine CBR responsiveness at various time points during isometric exercise in humans indicated a consistent blunting in baroreflex cardiac responses throughout HG (25). Although the reason for the differential findings of the present study (i.e., restored CBR control of HR during the latter portion of HG) are not readily apparent, the differences might be attributable to the use of R-R interval to assess baroreflex-mediated cardiac responses in the prior study (25) as opposed to assessment of HR. This analytic discrep-

**RESULTS**

The cardiovascular variables measured at rest and in response to the 1-min bouts of isometric HG exercise are presented in Table 1. The changes in HR and blood pressure evoked by 15 and 30% MVC HG did not reach statistical significance. However, during the 45 and 60% MVC HG trials, HR, systolic blood pressure, DBP, and MAP were all significantly increased from rest (*P < 0.001). As expected, RPE was significantly and progressively increased from rest as exercise intensity increased (Table 1).

**Table 1. Selected physiological variables at rest and during the last 10 s of handgrip exercise.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>15% HG</th>
<th>30% HG</th>
<th>45% HG</th>
<th>60% HG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>62 ± 4</td>
<td>61 ± 4</td>
<td>66 ± 4</td>
<td>78 ± 4*</td>
<td>89 ± 4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125 ± 4</td>
<td>129 ± 3</td>
<td>134 ± 5</td>
<td>149 ± 8*</td>
<td>161 ± 8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72 ± 2</td>
<td>75 ± 2</td>
<td>78 ± 5</td>
<td>88 ± 6*</td>
<td>96 ± 5*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91 ± 4</td>
<td>94 ± 2</td>
<td>99 ± 5</td>
<td>112 ± 6*</td>
<td>122 ± 5*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RPE</td>
<td>6 ± 0.6*</td>
<td>9 ± 0.6*</td>
<td>12 ± 0.4*</td>
<td>14 ± 0.4*</td>
<td>17 ± 0.3*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values ± SEM. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RPE, rating of perceived exertion; HG, handgrip. *Different from rest, *P < 0.05. HR and RPE, n = 8. Blood pressure, n = 7.
Carotid baroreflex function at exercise onset

ancy has been previously discussed (11, 33, 39). Nonetheless, the findings of the present work support the concept that the functional characteristics of the arterial baroreflex dynamically change during exercise in humans. This concept is further substantiated by recent work examining the sympathetic arm of the baroreflex during isometric HG (20). Importantly, we demonstrate that CBR modulation during exercise may be occurring on a faster time scale than that reported for sympathetic nerve activity and may reflect the dominance of vagal activity in mediating baroreflex-mediated HR responses (14, 34). Overall, we suggest that the dynamic modulation of the baroreflex throughout exercise may be important to allow for the continuous autonomic and cardiovascular adjustments necessary to sustain exercise.

Despite cardiac baroreflex responsiveness being blunted at the onset of higher exercise intensities, CBR control of blood pressure was maintained at all time points studied. These findings demonstrate differential regulation of baroreflex-mediated HR and blood pressure responses and are in agreement with previous studies (16, 24, 39). The reasons for this divergent baroreflex responsiveness at exercise onset are unclear. However, it is plausible that the blunting of baroreflex-mediated HR responses at the onset of exercise provides a mechanism by which HR is rapidly increased at the start of voluntary exercise. This concept has been suggested by Matsukawa and coworkers (24, 26, 27, 32) from studies performed in conscious cats, and we now provide support for this mechanism of cardioacceleration at exercise onset in humans. In contrast, the preservation of blood pressure control via the baroreflex, particularly at the onset of exercise, may serve to prevent excessive exercise-induced pressor responses (22).

In agreement with our findings, several animal studies have also reported an inhibition of the cardiac component of the baroreflex at the onset of static exercise (24, 26, 30, 32). These studies have indicated that inputs from both skeletal muscle afferents and central command are capable of modulating the cardiac component of the baroreflex at exercise onset. Because skeletal muscle mechanoreceptors (the mechanical component of the exercise pressor reflex) and central command are simultaneously activated at the onset of volitional exercise, partitioning the contribution of each during exercise is challenging. In the present study, an increase in the level of perceived effort (i.e., RPE) was aligned with the increases in exercise intensity, suggestive of a progressive augmentation of central command activation. However, a role for the muscle mechanoreflex, which would also be activated at the start of exercise in relation to the intensity of

Fig. 2. HR responses from 1 subject during the application of neck suction (NS) at rest and at the immediate onset of 15% and 60% maximal voluntary contraction isometric HG. Expiration is denoted by the downward deflection in the respiratory tracing. au, Arbitrary units.

Fig. 3. MAP responses from 1 subject during the application of NS at rest and at the immediate onset of 15% and 60% maximal voluntary contraction isometric HG. Expiration is denoted by the downward deflection in the respiratory tracing.
contraction, cannot be ruled out (19, 30). Indeed, recent findings indicate that activation of mechanically sensitive skeletal muscle afferents by stretching a resting muscle is capable of attenuating cardiac function to NS in humans (19). Thus it is likely that, similar to animal studies (24, 26, 30, 32), both feedback from skeletal muscle afferents and higher brain centers can potentially attenuate cardiac baroreflex responsiveness at the onset of static exercise in humans. However, it should be noted that both animal (27) and human (44) studies have identified that the initial changes in HR at the onset of exercise are more related to voluntary effort rather than contractile force, demonstrating the dominance of central command at this time. Nevertheless, given that inputs from skeletal muscle afferents and central command have been shown to interact in the modulation of arterial baroreflex function during exercise (6, 15, 29), we suggest that these two neural inputs are likely working in concert to modulate baroreflex function at exercise onset in humans.

The blunting of the baroreflex-mediated HR responses at the onset of high-intensity exercise may be explained by a reduction in the sensitivity of the baroreflex function curve (i.e., reduced maximal gain) (26, 30) or a rapid resetting of the curve toward a higher blood pressure (36, 37). Based on animal studies, these potential changes in baroreflex function have been proposed to represent alterations in inhibitory inputs to the nucleus tractus solitarius (NTS) from central command and/or skeletal muscle afferents (36, 40, 46). In fact, recent findings have demonstrated that barosensory cells in the NTS receive convergent inputs from both skeletal muscle afferents and central command (6). Alternatively, these neural inputs may be converging directly on cardiac vagal neurons in the brain stem to alter cardiac baroreflex responsiveness (19, 46) potentially explaining the preservation of blood pressure control. Indeed, the differential control of HR and blood pressure at exercise onset suggests that discreet inputs are selectively modifying the cardiac component of the baroreflex at this time.

Adding to the complexity in understanding underlying mechanisms is the observation that cardiac responses to NS were only blunted at the onset of higher exercise intensities. These findings suggest that a robust activation of central command and/or skeletal muscle afferents is required to inhibit the cardiac baroreflex and that this is not achieved at lower exercise intensities. Moreover, the restoration of cardiac baroreflex responses after ~40 s of exercise suggests that inputs from central command and skeletal muscle afferents to neural sites of central baroreflex integration are likely different at this time compared with exercise onset. Indeed, there is likely a continually changing balance between the excitatory input to central cardiovascular centers arising from the activation of the arterial baroreflex and the opposing inhibitory influences from central command and skeletal muscle afferents throughout a bout of isometric exercise. In this regard, according to the conceptual framework for baroreflex resetting during exercise recently outlined by Potts (36), the increase in excitatory baroreflex input elicited by the exercise-induced elevation in blood pressure is offset via activation of inhibitory neural circuits by skeletal muscle afferents. Recent work suggests that similar inhibitory inputs may arise from central command (6). Within this scheme a potential explanation for the observed blunting of the cardiac baroreflex at the onset of exercise may be due to the lack of an immediate rise in blood pressure, and thus inhibitory inputs from skeletal muscle afferents and/or central command are minimally opposed by excitatory inputs from the baroreflex. These alterations would appear to be selective for the modulation of cardiac vagal tone potentially via baroreflex and nucleus ambiguous pathways (36). Furthermore, as exercise continues, the progressive increase in blood pressure would now be expected to increase excitatory baroreflex inputs and offset inhibitory inputs of skeletal muscle afferents and central command, leading to the restoration of cardiac baroreflex responses.

An alternative explanation for the differences in cardiac baroreflex responses at the onset compared with later during exercise may relate to differences in activation patterns of central command and skeletal muscle afferents. Indeed, the majority of mechanically sensitive muscle afferents typically respond vigorously at the onset of muscle contraction but adapt rapidly and decrease their firing rate as contraction continues (23). Similarly, central command activation patterns may also dynamically change throughout exercise, particularly during high-intensity isometric contractions when inhibitory spinal reflexes cause a decline in motoneuron firing rates (i.e., “the wisdom of the nervous system”) (18). Nevertheless, further studies in both humans and animals are needed to better understand the complex interactions contributing to the time-dependent and divergent modification of the baroreflex throughout exercise.
In summary, our findings indicate that CBR-mediated HR responses were attenuated at the immediate onset of high-intensity isometric exercise when mechanically sensitive skeletal muscle afferents and central command were activated together. Importantly, these cardiac responses were restored during the latter period of HG, indicating a dynamic modulation of the CBR throughout exercise. This alteration in CBR function appeared to be selective for cardiac control because CBR-mediated blood pressure responses were preserved at all time points studied. Collectively, these data indicate a dynamic modulation of carotid baroreflex control of HR throughout exercise in humans, whereas carotid baroreflex regulation of blood pressure is well maintained.

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