Muscle chemoreflex alters carotid sinus baroreflex response in humans

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Papelier, Y., P. Escourrou, F. Helloco, and L. B. Rowell. Muscle chemoreflex alters carotid sinus baroreflex response in humans. J. Appl. Physiol. 82(2): 577–583, 1997.—The arterial baroreflex opposes pressor responses to muscle ischemia (muscle chemoreflex). Our experiments sought to quantify the unknown effects of muscle chemoreflex on carotid sinus baroreflex (CSB) sensitivity. We generated CSB stimulus-response (S-R) curves by pulsatile application (triggered by each electrocardiogram R wave) of positive and negative neck pressure (from 60 to −80 mmHg in 20-mmHg steps of 20 s each) in seven normal young men. S-R curves were obtained at rest (upright), during the last 3 min of upright cycle ergometer exercise (150 W), and at the first minute of postexercise recovery with leg circulation free (control). A second study repeated the same procedures, except that leg circulation was occluded 20 s before the end of exercise to elicit muscle chemoreflex, and occlusion was maintained during recovery measurements (3- to 4-min duration). S-R curves for CSB were shifted upward and rightward (25 mmHg) to higher arterial blood pressure (BP) by exercise and less so (10 mmHg) in recovery (free leg flow). Postexercise occlusion (muscle chemoreflex) raised BP and shifted S-R curves above exercise curves. CSB gain rose from −0.26 ± 0.06 (control) to −0.44 ± 0.08 (occlusion) during positive neck pressure application and was reduced from −0.14 ± 0.04 to zero (−0.04 ± 0.03) during negative neck pressure. Heart rate responses during postexercise muscle chemoreflex were not significantly different from control. Results reveal a nonlinear summation of CSB and muscle chemoreflex effects on BP. BP-raising capability of muscle chemoreflex enhances CSB responses to hypotension but overpowers baroreflex opposition to hypertension.

arterial pressure; reflex sensitivity; autonomic nervous system; resetting; exercise

THE CAROTID SINUS BAROREFLEX response curve appears to be reset or shifted to a higher operating pressure in response to dynamic exercise in intact dogs (19, 36), rabbits (7), and humans (24, 26, 32), but sensitivity of the response is unaffected (34). The term “resetting” refers to a shift in the baroreflex stimulus-response (S-R) curve that relates carotid sinus transmural pressure to systemic blood pressure (BP). The S-R curve is shifted rightward to a higher carotid sinus pressure (CSP; 7, 26, 24). Such shifts are presumably caused by a stimulus that alters the activity of central neurons of the baroreflex arc (16, 20, 29, 30).

Rowell and O’Leary (29) proposed that the signal that resets the arterial baroreflex during exercise is central command. An intact baroreflex is necessary to raise BP at the onset of exercise (5, 19, 36). Central command appears to cause the initial rise in BP and cardiac output by rapid vagal withdrawal (7, 12, 13), whereas any contribution of sympathetic nervous activity (SNA) is delayed at least 10–15 s (37). Conversely, in moderate to severe exercise, the rise in SNA contributes to the rise in BP and cardiac output. This contribution becomes dominant after vagal withdrawal [e.g., above a heart rate (HR) of ~100 beats/min in humans].

In addition to the arterial baroreflex, a muscle chemoreflex can also raise HR (21), cardiac output (5, 39), and SNA (20). We do not know whether or at what exercise intensity the muscle chemoreflex becomes tonically active in humans (27). Sherif et al. (33) showed that during exercise the arterial baroreflex reduced the sensitivity of the muscle chemoreflex, but the effect of the chemoreflex on the baroreflex has not been defined. A possible effect of the muscle chemoreflex on the arterial baroreflex could be a marked change in baroreflex sensitivity or gain. Depending on whether baroreceptors are stimulated or inhibited, the two reflexes could have opposing or additive effects on systemic BP and SNA. If such were the case, then the previous findings of constant slopes (sensitivity) for the carotid sinus baroreflex at rest and across various work rates (19, 24, 26, 36) are not consistent with a tonically active muscle chemoreflex during mild to heavy exercise with unrestricted muscle perfusion.

The evidence for an action of a muscle chemoreflex in humans originates from experiments on subjects in whom the limb circulation was occluded (with thigh cuffs) during both exercise and postexercise recovery (2). Systemic BP is then raised by a sympathetic-mediated rise in cardiac output and by vasconstriction. The goal of these experiments was to test the hypothesis that the baroreflex and chemoreflex act in summation on the control of BP. Our aim was to establish S-R curves for the human carotid sinus baroreflex during seated rest, exercise, and exercise recovery with normal free flow recovery and to compare these curves with those obtained during exercise recovery with severe muscle ischemia. The ischemia-induced muscle chemoreflex was generated by total circulatory occlusion of the legs.

METHODS

Subjects. Seven normal physically active men (age 22 ± 2.1 yr, height 81 ± 3.7 cm, weight 77 ± 5.6 kg) gave their written informed consent to the institutionally approved protocol. None was taking any medication, and all of them had normal findings in a physical examination. They refrained from having coffee and smoking on the day of experiment.
Arterial BP. A Finapres 2300 E (Ohmeda, Boulder, CO) was used to record BP from a cuff placed on the middle finger of the left hand. Each subject was instructed to keep his finger relaxed on a special handlebar (Scott, Sun Valley, ID) that supported the elbows and forearms during rest and exercise. Mean BP was derived from a filter network with a time constant of 2 s. Systolic and diastolic BP values obtained by the Finapres 2300 E have been previously validated during bicycle exercise against invasive BP measurement (14, 15, 25). Ieda et al. (14) showed that mean arterial pressure (MAP) computed noninvasively from finger plethysmographic measurements was 6 mmHg lower than intrabrachial arterial pressure at rest. This difference (6 ± 5 mmHg) remained unchanged during exercise (6 ± 3 mmHg) up to 280 ± 40 W and during postexercise recovery. In addition, from measurements recorded with the Finapres 2300 E during exercise, Papelier et al. (24) found S-R curves similar to those found by Potts et al. (26), who used invasive radial artery measurements. HR was obtained from the electrocardiogram (ECG) by a Biotach amplifier (Gould). All variables were recorded on a Gould ES 1000 recorder.

A lead neck chamber enclosed the front two-thirds of the neck, extending from the mandible and the ear lobes to the sternum and clavicle (8). One part of the chamber was connected by a solenoid valve to a vacuum that could apply either pressure or suction. Chamber pressure was measured by a Statham P23 ID transducer mounted on the chamber. The ECG was monitored continuously (Siemens Mingograph) and fed into a computer from which a routine detected the R wave and triggered the opening of the valve with a 40-ms delay; the stimulus duration was 400 ms at rest and during recovery and 200 ms at exercise. Chamber pressure during the opening of the valve was changed from 60 to −80 mmHg by decrements of 20 mmHg. Each decrement of this staircase of neck pressure stimulus was applied over a 20-s duration, and measurements were achieved during steady-state response, that is, in the interval of 15–20 s after start of the stimulus. This delay permitted the completion of both rapid vagal and slow sympathetic responses.

Exercise protocol. On the day of the experiment, the subject came to the laboratory in the morning after a light breakfast. The experimental protocol is illustrated in Fig. 1. Subjects exercised on an electrically braked cycle ergometer (Siemens Mingograph) and fed into a computer from which a routine computing the linear regression (31) by the least squares method was performed to compare the slopes of the two entire curves are significantly different from zero. Moreover, the slopes of the two entire curves are significantly different from zero, and the shape of the S-R curve is broadly altered. The slope of the positive neck pressures side (left side) of the S-R curve appears to be significantly steeper. In contrast, with negative neck pressures, the slope of the right side of the S-R curve was significantly reduced to become not significantly different from zero. Moreover, the slopes of the two entire curves are significantly different from zero.

RESULTS

At the onset of pulsatile neck suction, mean BP and, to a smaller extent, HR decreased. Both reached a steady state 10–15 s after the onset of stimulus (Fig. 2).

Figure 3 shows the relationship between MAP and CSP during the control period (A) and test period with leg occlusion (B). During the control period, the S-R curve was shifted upward and rightward by 27 mmHg during exercise and returned back close to the resting curve and values during recovery. There was no significant effect of the exercise bout on the slope of the S-R curve. For the test period (Fig. 3B), resting and exercise curves were similar to control. Muscle chemoreflex stimulation by postexercise leg occlusion induced an upward shift of the prevailing pressure compared with the free flow recovery. This shift is even greater than the shift previously elicited by exercise bout. In addition, the shape of the S-R curve is broadly altered. The slope of the positive neck pressures side (left side) of the S-R curve appears to be significantly steeper. In contrast, with negative neck pressures, the slope of the right side of the S-R curve was significantly reduced to become not significantly different from zero.
The recovery S-R curve is flatter with leg occlusion than during free-flow recovery.

Table 1 shows the changes in prevailing BP and HR, and the values of slopes (± SD) of linear regressions for mean BP and HR, during recovery without and with thigh cuffs inflated. Figure 4 represents these significant changes in the curve for MAP.

Figure 5 shows the relationship between HR and CSP during control period (A) and test period with leg occlusion (B). During exercise, changing CSP had little effect on the slope of the response curve, which was not significantly different from the resting curve. During recovery of control period, the baroreflex response curve returned back to the values observed at rest. For the test period, muscle chemoreflex stimulation by leg occlusion does not induce a significant upward shift of recovery curve compared with control recovery (91 ± 18 vs. 84 ± 16.7 beats/min), and the slope remained unchanged (−0.18 ± 0.025 vs. −0.16 ± 0.021 beats·min⁻¹·mmHg⁻¹).

DISCUSSION

The primary finding from this study is that the activation of the muscle chemoreflex, by producing severe muscle ischemia, markedly changed the shape of the carotid sinus S-R curve. Figure 3 reveals a nonlinear summation of the effects of arterial baroreflex and muscle chemoreflex on arterial pressure and thus presumably on SNA as well. When carotid sinus transmural pressure was lowered below the prevailing BP (that is below its presumed operating point), each rise in systemic BP with each increment in positive neck pressure was progressively more pronounced. The
slope (or sensitivity) of the function curve was significantly increased (Table 1). This upward shift of the function curve could be attributed to the additive effects of the vasoconstriction caused by reduced carotid sinus transmural pressure (i.e., similar to carotid sinus hypotension) and to the vasoconstriction caused by muscle ischemia. When carotid sinus transmural pressure was raised above prevailing BP by application of negative pressure to the neck, the reduction in systemic BP previously seen during both rest and exercise was virtually abolished. The slope of the function curve over a range of CSP above the operating point for the reflex was not significantly different from zero. This upward shift of the function curve could be attributed to two opposing effects on SNA. The reductions in SNA and in systemic BP normally induced by carotid sinus hypertension were overcome here by the augmentation in SNA caused by muscle ischemia (i.e., the muscle chemoreflex).

Potential limitations of the study. It was not possible to superpose the two reflexes during exercise because the 3–4 min of total occlusion needed to complete the S-R curve would cause severe discomfort. Alternatively, partial occlusion to reduce rather than arrest blood flow would cause severe venous congestion and probable damage to venous valves. Investigating the muscle chemoreflex during recovery allows one to isolate it from any effects of muscle mechanoreflex or central command, although the interaction of the two reflexes during exercise cannot be evaluated. However, as much as the chemoreflex per se markedly altered the baroreflex slope, whereas neither exercise nor recovery per se did so, interaction of these two reflexes during exercise would probably reveal the same effects on baroreflex slope (i.e., sensitivity).

<table>
<thead>
<tr>
<th>Recovery: Free Flow vs. Leg Occlusion</th>
<th>Test 1, control</th>
<th>Test 2, postexercise ischemia</th>
<th>DF</th>
<th>Comparison, test 1 vs. test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Prevailing MAP, mmHg</td>
<td>-17 ± 7.3</td>
<td>6 ± 6.9</td>
<td>6</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Slope, mmHg</td>
<td>-0.2060 ± 0.0289</td>
<td>-0.1293 ± 0.0215</td>
<td>54</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Entire</td>
<td>-0.1425 ± 0.0407</td>
<td>-0.0465 ± 0.0323</td>
<td>33</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Right</td>
<td>-0.2662 ± 0.0663</td>
<td>-0.4450 ± 0.0804</td>
<td>19</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Left</td>
<td>-0.1647 ± 0.0206</td>
<td>-0.1838 ± 0.0247</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Prevailing HR, beats/min</td>
<td>-49 ± 7.4</td>
<td>-44 ± 10.3</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Slope, beats·min⁻¹·mmHg⁻¹</td>
<td>-0.1300 ± 0.0366</td>
<td>-0.1098 ± 0.0472</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Entire</td>
<td>-0.3533 ± 0.0970</td>
<td>-0.3898 ± 0.0874</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Right</td>
<td>-0.1647 ± 0.0206</td>
<td>-0.1838 ± 0.0247</td>
<td>54</td>
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<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD. Prevailing mean arterial pressure (MAP) and prevailing heart rate (HR) recovery – exercise. CSP, carotid sinus pressure; Δ, change; DF, degrees of freedom; NS, not significant.

Fig. 4. Changes in baroreflex sensitivity (slope of MAP vs. CSP) during leg occlusion recovery vs. free-flow recovery, for entire, right (negative neck pressure), and left (positive neck pressure) parts of S-R curve. During recovery, leg occlusion significantly decreased baroreflex sensitivity to negative neck pressure and increased sensitivity to positive neck pressure.

Fig. 5. S-R for heart rate (HR) vs. CSP. A: curves obtained from rest (○), exercise (●), and recovery (▲) without leg occlusion (control). B: curves obtained from test period (with leg occlusion). HR responses to carotid sinus stimulation were not significantly different between recovery without or with leg occlusion. Dashed lines, movement of prevailing heart rate point.
Pain. The issue of pain as a possible contribution to pressor responses to ischemia has been dealt with repeatedly (1, 11, 28). Alam and Smirk (1) showed that pain was not involved in the BP reflex ischemic response in man. Furthermore, Freund et al. (11) showed that BP response remained similar after withdrawal of painful sensations by gradual sensory nerve blockade in humans. In the present study, we eliminated or greatly minimized discomfort by proper packing and securing of cuff placement, as described previously (28).

Competition between aortic and carotid sinus baroreceptors is always a concern as discussed previously (24, 34). If the superimposability of the S-R curves for these two baroreflexes [found in dogs by Angel1-James and de Burgh Daly (4)] applies to humans, then the aortic reflex should reduce carotid sinus reflex sensitivity to the same degree across conditions. Thus comparisons would be valid.

Transmission of neck chamber pressure was reviewed by Eckberg and Sleight (9). Some have found complete transmission in both dogs and humans, whereas one group observed transmission of positive and negative pressure to be reduced by 14 and 36%, respectively, at the sinus (18). Whichever findings apply, comparisons of curves are valid because transmission defects should be the same across conditions (24).

Hemodynamic effect of the occlusion. Mechanical effects of occlusion on BP observed at rest are commonly <10 mmHg (6, 28, 38). Bonde-Petersen et al. (6) showed an increase of 6 mmHg MAP at rest, after 1-min leg occlusion, and 9 mmHg after 3 min. William-son et al. (38), using a similar design, found an increase of ~3 mmHg MAP (from ~83 to 86 mmHg) with only thigh cuff inflation and no significant alteration of total peripheral resistance. Therefore, in the present study, the rise in BP cannot be explained by the reduction in vascular conductance due to the occlusion of the circulation of the both legs. Again, Wyss et al. (39) showed in dogs that the rise in BP is attributable to a rise in cardiac output and to a fall in vascular conductance resulting mostly from active vasoconstriction and only partly from passive mechanical effect of leg circulation occlusion. Conversely, during exercise and recovery, purely mechanical effects per se would be large (without a baroreflex) and could easily reach 250–300 mmHg, depending on leg blood flow (6, 27). However BP is maintained during postexercise occlusion at a particular level by combined responses of chemoreflex and baroreflex (i.e., by variable combination of elevated cardiac output and/or vasoconstriction outflow) (27).

The purely mechanical effect of occlusion during recovery subsequent to mild exercise with sensory blockade (no chemoreflex) was very small relative to the unblocked reflex pressor response [see Figs. 1–4 in Freund et al. (11)].

Perhaps the most serious limitation would be applications of neck pressure during a non-steady-state response to the muscle chemoreflex. The protocol for producing the chemoreflex was the same as used in several previous studies (6, 10, 11, 28) during which BP also remained virtually constant during 3 min of postexercise occlusion.

Interaction between baroreflex and chemoreflex on BP. The effects of muscle chemoreflex activation on the carotid S-R curve have not been described previously. The only direct evidence concerning the interaction between these two reflexes was obtained from dogs in which sinoaortic denervation eliminated baroreflex opposition to the rise in systemic BP generated by the chemoreflex (33). The slope or sensitivity of the muscle chemoreflex increased by a factor of 2.25 after denervation of the arterial baroreceptors. Thus the baroreflex could reduce the pressor response to muscle ischemia by 60%. However, these results provided no evidence concerning how the muscle chemoreflex might affect the strength of the baroreflex.

The sensitivity of the carotid sinus reflex during exercise, as found previously (19, 24, 26, 36), was not significantly different from the sensitivity at rest. The same was true during recovery without occlusion. Because occlusion during exercise raised BP by increasing SNA and altering cardiac output and vasoconstric-tion outflow (39), it would be expected to have the same effects on the carotid sinus S-R curve during exercise as it does during postexercise occlusion. That is, in both conditions, the reductions in SNA and in systemic BP caused by carotid sinus hypertension (neck suction) would be opposed by the augmentation of SNA and BP caused by muscle ischemia. If this is so, then the constancy of baroreflex slope from rest to heavy exercise [up to 70–75% of maximal O2 uptake (24)] suggests that the sympathetic responses to carotid sinus hypertension and hypotension are not being opposed by an active muscle chemoreflex. It is particularly unlikely that the muscle chemoreflex would exert such an effect during mild to moderate exercise, because the gain of the muscle chemoreflex [effect of a change in femoral BP on systemic BP corrected for the mechanical effects of occlusion (39)] is two times greater than the gain of the carotid sinus reflex (the effect of a change in CSP on systemic BP) when the latter is nonoperative (33). Thus, the muscle chemoreflex could readily reduce baroreflex gain to zero when their effects on BP are opposed. Similarly, it could double carotid sinus effects of BP when both reflexes function to raise BP. We saw carotid sinus gain rise from 0.26 to 0.44 during occlusion. The implication is that the muscle chemoreflex is not tonically active. If this is correct, then we might expect small reductions in muscle perfusion during heavy exercise to alter baroreflex sensitivity.

Chemoreflex and baroreflex effects on HR. HR was less affected than systemic BP by the manipulation of CSP during exercise. During recovery from exercise with or without ischemia, the slopes of the function curves were the same. The apparent lack of a significant effect of the muscle chemoreflex on HR is a consistent finding (20, 21) that is attributed to a differential effect of the muscle chemoreflex on sympathetic activation of the heart vs. the blood vessels. However, with parasympathetic blockade (atropine), both systemic BP and HR remained elevated during
postexercise ischemia in dogs, whereas β-blockade reduced this tachycardia (21). Thus, during postexercise ischemia, the muscle chemoreflex-induced rise in SNA to the heart is maintained. But the sudden restoration of vagal activity at the cessation of exercise obscures the effects of the sustained cardiac sympathetic activation (21). Sympathetic activation of sinus node activity is normally overpowered by the dominance of vagal control (17). This lack of effect of muscle chemoreflex stimulation on the slope of S-R curve for HR is consistent with the fact that, at the end of exercise, central command acting on cardiovascular system rapidly decreases because of the suspension of somatomotor activation.

Importance of muscle chemoreflex in exercise. Any suggestion that the muscle chemoreflex does not alter the baroreflex sensitivity during exercise (i.e., under free-flow conditions) warrants caution, even if the slope of the S-R curve remains constant across multiple work rates. The muscle chemoreflex is a flow-sensitive pressure-raising reflex that can also partially restore blood flow to muscle when its flow is reduced below a critical threshold at which oxygen transport to muscle becomes inadequate (22, 39). The reflex does not appear to be tonically active under free-flow conditions. This partial restoration of muscle blood flow requires an increase in cardiac output (6, 39). Otherwise, if exercise is severe and the ability to raise cardiac output is limited, the muscle chemoreflex simply overpowers the baroreflex and drives up BP by vasoconstricting active muscle mass, which in these conditions represents ~80% or more of total vascular conductance. Because cardiac output cannot increase and because vasoconstriction to other major vascular beds is close to maximum, the muscle chemoreflex cannot raise total blood flow in this setting. Possibly the recently discovered differences in α-adrenoreceptor sensitivity to norepinephrine and metabolites of oxidative and glycolytic muscle fibers (3, 23, 35) optimize the intramuscular distribution of blood flow when the chemoreflex is activated. On the other hand, whenever the total mass of active muscle and the rise in total vascular conductance overwhelm cardiac pumping capacity, any decline in BP could be more easily reversed by the additive actions of the muscle chemoreflex and the arterial baroreflex.

In conclusion, our results show that muscle chemoreflex reduced the sensitivity of the carotid sinus S-R curve to zero with carotid sinus hypertension and raised this sensitivity with carotid sinus hypotension. These results do not allow us to draw a conclusion on the effect of muscle chemoreflex on carotid sinus baroreflex during exercise, but they put forward a hypothesis that can be easily tested in nonhuman species.

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