Muscle chemoreflex-induced increases in right atrial pressure

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Sheriff, Don D., Robert A. Augustyniak, and Donal S. O'Leary. Muscle chemoreflex-induced increases in right atrial pressure. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H767–H775, 1998.—When oxygen delivery to active muscle is too low for the ongoing rate of metabolism, metabolites accumulate and stimulate sensory nerves within the muscle leading to sympathetic activation (muscle chemoreflex). To study the effects of this reflex on RAP, we focused on its ability to increase arterial pressure or the activity of the nerves that mediate this response. Clearly, a rise in cardiac output (CO) constitutes an important adjustment, because it increases the total blood flow available to be distributed among organs competing for flow. However, increments in heart rate and contractility provide limited means of raising CO because of the inverse relationship that exists between CO and right atrial pressure (RAP) in the intact circulation. Our goal was to test whether muscle chemoreflex activation, achieved via graded reductions in hindlimb blood flow by partial vascular occlusion, elicits peripheral vascular adjustments that raise RAP. In four conscious dogs exercising on a treadmill at 3.2 km/h 0% grade, RAP was well maintained during reflex activation despite increases in CO and arterial pressure that are expected to reduce RAP. Thus peripheral vascular adjustments elicited by the reflex successfully defend RAP in a setting where it would otherwise fall. To isolate the effects of the reflex on RAP, CO was maintained constant by ventricular pacing in conjunction with β1-adrenergic blockade with atenolol. When the reflex was activated by reducing hindlimb blood flow from 0.6 to 0.31/min, RAP rose from 5.1 ± 0.8 to 7.4 ± 0.4 mmHg (P < 0.05) despite continued large (40 mmHg) increases in arterial pressure. During heavier exercise (6.4 km/h 10% grade) in five dogs with normal ventricular function, the reflex raised RAP from 5.7 ± 0.9 to 6.6 ± 0.8 mmHg (P < 0.05) despite increases in CO and arterial pressure. We conclude that the muscle chemoreflex is capable of eliciting substantial increases in RAP.

Dynamic exercise; muscle blood flow; central venous pressure; cardiac filling pressure; venous physiology; venous return; cardiac output; autonomic nervous system; sympathetic nervous system; vasoconstriction; venoconstriction; atrioventricular block; ventricular pacing; vascular occlusion; muscle metaboreflex; dog

WHEN OXYGEN DELIVERY to active muscle is too low for the ongoing rate of metabolism, metabolites accumulate and stimulate sensory nerves within the muscle. Activation of these nerves elicits a muscle chemoreflex that increases sympathetic nerve activity. During mild exercise, pressor responses are elicited when partial vascular occlusion reduces oxygen delivery below a critical threshold value (30). Total or complete vascular occlusion of arteries supplying active muscle activates this reflex after a short latency (25) and, depending on the extent of the ischemia, large (50 mmHg) increases in arterial pressure can result despite buffering by arterial baroreflexes (27) and cardiac afferents (3). Importantly, the rise in arterial pressure acts successfully to restore blood flow to the hypoperfused muscles, at least in dogs when blood flow is reduced by partial vascular occlusion (19). Whether blood flow restoration occurs during reflex activation in humans is a matter of controversy. (9, 23). The reflex pressor responses to muscle ischemia are attributable to increases in cardiac output (17, 36) and regional vasoconstriction (14, 15, 34). In dogs, the strategy employed to increase arterial pressure appears to depend on exercise intensity; the animals rely primarily on cardiac output during mild exercise, whereas peripheral vasoconstriction becomes more important as exercise intensity rises (36).

Clearly, an increase in cardiac output constitutes an important adjustment to muscle ischemia, because it increases the total blood flow available to be distributed among organs competing for flow. Several studies have shown that activation of the muscle chemoreflex elicits increases in heart rate (10, 16, 36) and myocardial contractility (13, 17). However, increments in heart rate or contractility, either alone or together, cannot elicit substantial increases in cardiac output in the intact circulation (4), because the distribution of blood volume in the peripheral circulation is dependent on blood flow (11). A rise in cardiac output produced by an improvement in cardiac pump performance increases pressures in the peripheral circulation because blood vessels offer resistance to flow, and blood volume accumulates in the periphery because blood vessels are distensible (particularly those located in the splanchnic and cutaneous circulations). The accumulation of blood volume in the periphery that occurs when cardiac output rises causes cardiac output to transiently exceed venous return and central venous volume and right atrial pressure decrease accordingly. As a consequence of these features, an inverse relationship between cardiac output and right atrial pressure is produced (32). The functional significance of this inverse relationship is that the fall in right atrial pressure limits any rise in cardiac output through its effect on stroke volume via the length-tension relationship. At the onset of dynamic exercise, this inverse relationship is transiently overcome because the skeletal muscle pump...
(28, 29) and local metabolic vasodilation direct the increase in cardiac output to noncompliant skeletal muscle. During steady-state exercise, the inverse relationship between cardiac output and right atrial pressure is reestablished, and once again changes in cardiac output produced by changes in cardiac pump performance are accompanied by proportionally opposite changes in right atrial pressure (32). Thus peripheral vascular adjustments that act to maintain or increase right atrial pressure must accompany increments in heart rate and contractility if cardiac output is to rise substantially.

The goal of the present study was to test whether the muscle chemoreflex elicits peripheral vascular adjustments that raise right atrial pressure. Right atrial pressure was measured while the muscle chemoreflex was activated by graded, partial compression of the terminal aorta of dogs performing mild (3.2 km/h 0% grade) and moderate (6.4 km/h 10% grade) treadmill exercise. To isolate the effects of the chemoreflex on right atrial pressure during mild exercise, experiments were repeated during mild exercise, while cardiac output was maintained constant by ventricular pacing in conjunction with \(\beta_1\)-adrenergic blockade with atenolol. We found that the muscle chemoreflex is capable of preventing a fall in right atrial pressure when cardiac output rises during reflex activation in mild exercise and is capable of eliciting substantial increases in right atrial pressure when the normal rise in cardiac output is prevented during mild exercise. Finally, we found that the muscle chemoreflex is capable of eliciting a significant rise in right atrial pressure when the reflex is activated during moderate exercise despite increases in cardiac output and arterial pressure.

METHODOLOGIES

Eight mongrel dogs of either gender were selected for their willingness to run on a motor-driven treadmill. All procedures were reviewed and approved by the Institutional Animal Use and Care Committee of either Wayne State University School of Medicine or the University of Washington School of Medicine and were in conformance with the Guide for the Care and Use of Laboratory Animals (DHEW (DHSS) Publication No. (NIH) 85–23, Revised 1985, Office of Scientific and Health Reports, DRR/NIH, Bethesda, MD 20892). The dogs were familiarized with treadmill running in a series of training sessions before the following aseptic surgical procedures were performed.

Surgical Preparation

Six animals were prepared in the following series of aseptic surgical procedures. First, a right thoracotomy was performed, an ultrasonic transit-time blood flow transducer (Transonic) was placed on the ascending aorta, and pacing leads were sutured to the apex of the left ventricle. In a second procedure, a blood flow transducer was placed on the terminal aorta just proximal to the iliac arteries via a retroperitoneal or midline venous approach. A vascular occlusion cuff was implanted just distal to the flow probe, and a catheter was inserted into the aorta via a side branch and directed above the flow probe. Finally, a flow probe was placed on a renal artery. In a final procedure, 1) a catheter was inserted into a side branch of the femoral artery and advanced into the abdominal aorta, where it was positioned distal to the flow probe; 2) a catheter was inserted into a side branch of the femoral vein and advanced into the abdominal vena cava; and 3) a catheter was inserted into the right jugular vein and advanced to the caval-right atrial junction.

After each procedure, buprenorphine (0.015 mg/kg iv) and acepromazine (0.1 mg/kg im) were administered for analgesia and sedation, respectively. The animals were treated with cephalolin (500 mg iv) immediately pre- and postoperatively and with cephapax (30 mg/kg po, tid) for 1 wk postoperatively. The animals were allowed to recover for at least 1 wk after each procedure. All experiments were performed after the animals had recovered from the surgery and were afebrile, active, and of good appetite.

Experimental Protocols

The animal was brought to the laboratory and placed on the treadmill. The abdominal aortic, femoral arterial, and central venous catheters were connected to pressure transducers (Spectromed 10 EZ), and the flow probes were connected to flowmeters (Transonic). Heart rate was determined by a cardiometer triggered by the signal from the flow probe on the ascending aorta. All variables were recorded on a physiograph (Gould 3800), and beat-by-beat mean values were calculated and stored on a microcomputer.

Mild exercise with normal cardiac function. The animal stood quietly on the treadmill until the measured variables achieved steady values. The treadmill was then started at 3.2 km/h 0% grade. Once a steady state was achieved, hindlimb blood flow was decreased by partially inflating the vascular occlusion cuff. The partial occlusion was sustained until the measured variables achieved steady values (3–5 min). A further reduction in hindlimb perfusion was then imposed, and these procedures were repeated until a large increase in systemic arterial pressure was elicited. Figure 1 provides an example of these procedures. The aim here was to examine the response of right atrial pressure in a setting where the muscle chemoreflex normally increases arterial pressure by raising cardiac output.

Mild exercise with constant cardiac output. On another day, the animals were administered atenolol (2 mg/kg iv), and pacing of the heart at 225 beats/min was instigated in order to achieve constant cardiac output. A large rise in right atrial pressure was achieved by doubling the blood flow measured in a single renal artery and dividing the result by the difference between the systemic arterial and right atrial pressures. Hindlimb vascular conductance was calculated as terminal aortic flow divided by the difference between the systemic arterial and right atrial pressures. Hindlimb vascular conductance was calculated as terminal aortic flow divided by the difference between the systemic arterial and right atrial pressures. Hindlimb vascular conductance was calculated as terminal aortic flow divided by the difference between the systemic arterial and right atrial pressures.
arterial and right atrial pressures. The vascular conductance of the nonischemic regions excluding the kidneys was calculated as total vascular conductance minus the renal and hindlimb conductances.

**Mild exercise with normal cardiac function.** Two regression lines were fit to the nonlinear responses observed in the four dogs studied during mild exercise as described previously (16, 19, 27, 30, 36).

We predicted the fall in right atrial pressure that would be expected if the reflex-induced rise in cardiac output was produced entirely by increments in cardiac pump performance (increased rate and contractility). This was achieved by multiplying the measured change in cardiac output by 2.1 mmHg l⁻¹ min and subtracting the result from the control level of right atrial pressure. The coefficient 2.1 mmHg l⁻¹ min is the average of the previously reported slopes of the inverse relationship between cardiac output and right atrial pressure generated at rest and during exercise by ventricular pacing in atrioventricular-blocked dogs (31, 32). The difference between the predicted pressure and the pressure measured during reflex activation was taken to reflect the extent to which peripheral vascular adjustments evoked by the muscle chemoreflex altered right atrial pressure.

**RESULTS**

**Mild Exercise With Normal Cardiac Function**

Figure 2, left panels, illustrates the group mean responses of four animals during control experiments (normal reflex control of heart rate and cardiac output). Reflex activation raised arterial pressure from ~100 to 160 mmHg. The reflex contribution to this pressor response (i.e., the rise in arterial pressure above that which would be produced by the passive effects of occlusion alone) was attributable primarily to a rise in cardiac output elicited by the reflex inasmuch as there was little net vasoconstriction in the nonischemic regions. Renal blood flow (twice the blood flow measured in a single renal artery) was reduced from 198 ± 33 ml/min during control exercise (unrestricted hindlimb perfusion) to 168 ± 24 ml/min during the severest...
ischemia (P < 0.05). Renal vascular conductance was reduced from 2.08 ± 0.34 to 1.08 ± 0.15 ml·min⁻¹·mmHg⁻¹ at these two time points (P < 0.05). Right atrial pressure was well maintained (Fig. 2, solid line at top). The dashed line in the top panel of Fig. 2 predicts that right atrial pressure would have fallen by 3 mmHg if the reflex had only increased heart rate and contractility.

Mild Exercise With Constant Cardiac Output

The right panels of Fig. 2 illustrate the group mean responses of the same four animals during experiments in which cardiac output was maintained constant by ventricular pacing and blockade of β₁-adrenergic receptors. Compared with the control responses depicted on the left of Fig. 2, maintaining cardiac output constant caused only a small reduction in the magnitude of the rise in arterial pressure elicited by the chemoreflex. Thus the reflex contribution to this pressor response is attributable to vasoconstriction in the nonischemic regions, which caused the vascular conductance of these regions to fall from 28.5 ± 4.0 to 24.7 ± 4.6 ml·min⁻¹·mmHg⁻¹ (P < 0.01), and vasoconstriction in the renal vasculature. Renal blood flow fell from 150 ± 27 to 123 ± 19 ml/min (P = 0.08), and renal vascular conductance fell from 1.51 ± 0.28 to 0.85 ± 0.12 ml·min⁻¹·mmHg⁻¹ (P < 0.05). In these experiments, right atrial pressure rose from 5.1 ± 0.8 to 7.4 ± 0.4 mmHg (P < 0.05).

Moderate Exercise With Normal Cardiac Function

The hemodynamic responses to graded reductions in hindlimb blood flow from an experiment in a single animal performing moderate exercise are shown in Fig. 1. Graded reductions in hindlimb perfusion elicited chemoreflex-induced increases in arterial pressure, cardiac output, and right atrial pressure, which rose by ~2 mmHg in this example.
Group mean responses of the five dogs studied during moderate exercise are shown in Fig. 3. Reflex control of cardiac function was intact during these experiments. Renal blood flow was reduced from 176 ± 34 ml/min during exercise with unrestricted hindlimb perfusion to 151 ± 30 ml/min (P = 0.09) during the largest decrement in hindlimb perfusion. For the same two time points, renal vascular conductance was significantly reduced from 1.71 ± 0.28 to 0.95 ± 0.17 ml·min⁻¹·mmHg⁻¹ (P < 0.01). The rise in cardiac output elicited by the reflex was predicted to reduce right atrial pressure to ~1 mmHg (dashed line in top panel of Fig. 3). In contrast, right atrial pressure rose from 5.7 ± 0.9 to 6.6 ± 0.8 mmHg (P < 0.05) despite the statistically significant increases in cardiac output (P < 0.05) and arterial pressure (P < 0.001).

DISCUSSION

The principal new findings of this study reveal that the muscle chemoreflex exerts a marked influence on cardiac filling pressure. When activated by partial vascular occlusion during mild exercise, the reflex successfully defends right atrial pressure in the face of increases in cardiac output and arterial pressure that are expected to reduce atrial pressure. When the rise in cardiac output normally evoked by the reflex during mild exercise is blocked, the muscle chemoreflex is capable of eliciting a substantial increase in right atrial pressure. Finally, during moderate exercise the reflex is capable of eliciting a significant increase in right atrial pressure even though cardiac output and arterial pressure both rise. The influence of the muscle chemoreflex on venous function is likely an important component of the reflex with respect to its ability to regulate muscle blood flow.

The hemodynamic responses we observed during graded partial occlusion of the terminal aorta of dogs exercising on a treadmill were in most respects similar to previous reports (14–17, 19, 27, 30, 36). During mild exercise with normal cardiac function, graded reductions in terminal aortic flow below a threshold resulted in graded increases in arterial pressure, heart rate, and cardiac output, and the rise in cardiac output elicited by the chemoreflex accounted for a substantial fraction of the reflex-induced rise in arterial pressure. That is, there was no change in the calculated vascular conductance of the nonischemic regions, and the 1.0 ml·min⁻¹·mmHg⁻¹ fall in renal conductance is expected to raise arterial pressure by only ~2 mmHg. Blockade of the normal reflex-induced rise in cardiac output by rapid pacing and β₁-blockade caused only a small (6%) reduction in the rise in arterial pressure generated by the reflex, which meant that the dogs now relied on peripheral vasoconstriction as the sole mechanism for raising pressure. This reduction is less than the 40% reduction caused by β₁-blockade alone (16) but is similar to the effects of pacing alone (17). During moderate exercise with normal cardiac function there was no apparent threshold for muscle chemoreflex responses. Compared with the responses during moderate exercise reported by Wyss and co-workers (36), the animals in the present study did not rely as strongly on peripheral vasoconstriction to raise pressure. Importantly, the reflex behaved differently at the two workloads in the present study in that it consistently raised right atrial pressure during moderate exercise, whereas right atrial pressure responses were less consistent during mild exercise with normal cardiac function.

Fig. 3. Group mean responses of 5 dogs to graded terminal aortic occlusion during treadmill exercise at 6.4 km/h 10% grade with reflex control of HR and contractility intact. RAP rose (solid line in top panel) despite large increases in MAP and CO, which are expected to reduce RAP. Dashed line in top panel depicts the fall in RAP that is predicted to occur owing to the rise in CO. Traces depicting VC in the bottom panel are, from top down, TVC, NIVC, and HLVC.
The passive, hydraulic (nonreflex) effects of mechanical occlusion of the terminal aorta are expected to have competing effects on right atrial pressure. The observation that right atrial pressure was unaltered during the initial reductions in hindlimb flow imposed during mild exercise before the muscle chemoreflex was activated indicates that these competing factors likely offset one another.

Rationale

The traditional approach to study muscle chemoreflex function has been to measure the rise in arterial pressure induced by partial or complete vascular occlusion of an exercising limb, and the magnitude of the rise in arterial pressure has been interpreted as a measure of the extent to which the reflex operates to restore blood flow to the hypoperfused skeletal muscles. When partial occlusions are imposed, the rise in arterial pressure is functionally important, because it constitutes an effective means of increasing blood flow across the high resistance imposed by the occluding device. Several investigators have examined the mechanisms by which the muscle chemoreflex can potentially raise arterial pressure, including peripheral vasconstriction (14, 15, 34), tachycardia (10, 16, 36), and increased myocardial contractility (13, 17). Vasconstriction within vascular beds remote from the ischemic muscles will tend to raise arterial pressure and can possibly redistribute a portion of the prevailing cardiac output to the ischemic muscles. Increments in heart rate and contractility on the other hand will tend to raise pressure by increasing cardiac output. In addition to experimentally or pathologically imposed restriction of muscle blood flow, there are physiological conditions in which active muscle may be hypoperfused. Examples are the competing demands for blood flow between groups of active muscles (5, 24) and the competing demands between active muscle and the cutaneous circulation during exercise in a hot environment (22). In settings such as these, the muscle chemoreflex could function effectively without raising arterial pressure if it were to increase cardiac output and make more blood flow available to be distributed among the organs competing for flow, thereby lessening the need for the vasconstriction that such competition might otherwise engender (5, 8).

Previous studies on the effects of the muscle chemoreflex on cardiac function have focussed on the influence of this reflex on heart rate and myocardial contractility. Increments in heart rate and contractility, however, represent limited means of raising cardiac output. Raising heart rate alone via cardiac pacing has little influence on cardiac output in the intact circulation (32, 35), because stroke volume falls in proportion to the increase in rate owing to decreased ventricular filling. This is particularly true when heart rate is already elevated such as during exercise (32). When heart rate is raised by activation of sympathetic nerves to the heart, the resulting enhancement of the speed of ventricular relaxation is likely important in helping to preserve ventricular end-diastolic volume in the face of the reduced diastolic filling time. Inasmuch as ejection fraction is already quite high during exercise in healthy subjects, there is little additional end-systolic volume that can be expelled to augment stroke volume through an increase in myocardial contractility. Finally, any rise in cardiac output that can be achieved through an improvement in cardiac pump performance is self-limiting owing to the inverse relationship between cardiac output and right atrial pressure (32). Because raising heart rate and contractility provides limited means of raising cardiac output, the ability to maintain or increase cardiac filling pressure is important if the muscle chemoreflex is to function effectively.

Mild Exercise With Normal Cardiac Function

Overall, we found that cardiac filling pressure was well maintained when the muscle chemoreflex was activated by partial vascular occlusion of the terminal aorta in dogs performing mild exercise. In two dogs right atrial pressure fell, and it rose in two other dogs. Thus the muscle chemoreflex elicits peripheral vascular adjustments that successfully defend cardiac filling pressure despite substantial increments in arterial pressure and cardiac output, which would otherwise lower filling pressure. Although there was a lack of a measurable net decrease in the lumped vascular conductance of the nonischemic regions during reflex activation, this should not be taken as evidence that the reflex does not elicit important peripheral vascular adjustments in this setting. Some organs have been demonstrated to vasoconstrict (14, 15), as did the kidneys in the present study, whereas others are expected to dilate in this setting (see Distribution of Cardiac Output). Thus the hemodynamic adjustments that accompany muscle chemoreflex activation during mild exercise ensure the maintenance of an adequate filling pressure. This in turn permits the reflex-induced increases in heart rate and contractility to raise cardiac output to a greater extent than it could have been raised if filling pressure had been permitted to fall.

Mild Exercise With Constant Cardiac Output

Because changes in cardiac pump performance cause proportionally opposite changes in central venous volume and pressure, it is crucial that cardiac output be maintained constant when estimates are made of the extent to which reflex mechanisms alter central venous volume or pressure (7). We employed $\beta_1$-adrenergic receptor blockade and rapid ventricular pacing to hold cardiac output constant. These procedures caused cardiac output to be lower on average than during control experiments and, as expected, this was associated with higher right atrial pressures.

We found that right atrial pressure rose by over 2 mmHg when the muscle chemoreflex was activated while cardiac output was held constant. This finding demonstrates that the muscle chemoreflex can elicit a sizable increase in right atrial pressure despite the continued large rise in arterial pressure, which would otherwise reduce right atrial pressure.
Moderate Exercise With Normal Cardiac Function

Importantly, our results during moderate exercise demonstrate that the muscle chemoreflex can successfully raise right atrial pressure even when cardiac output and arterial pressure rise substantially. The rise in right atrial pressure in this setting indicates that the reflex evokes splanchnic constriction, causing blood volume to be transferred to central veins; i.e., constriction of the relatively noncompliant forelimb (12) and renal vasculatures is not expected to influence right atrial pressure directly. In this setting, the alterations in venous function induced by the muscle chemoreflex take an active role in raising cardiac output by raising cardiac filling pressure. The rise in cardiac filling pressure works in concert with the reflex-induced increases in heart rate and contractility in raising the total amount of blood flow available to be distributed among the organs competing for flow.

Mechanisms That Alter Right Atrial Pressure

Multiple factors that influence right atrial pressure are associated with reductions in hindlimb flow that activate the chemoreflex, some of which are competing. Several factors are expected to reduce right atrial pressure during reflex activation. The reflex-induced increase in arterial pressure is expected to reduce right atrial pressure owing to the transfer of blood volume from the venous to the arterial system. Also, the rise in cardiac output is expected to reduce right atrial pressure by ~2 mmHg for each 1 l/min increase in cardiac output (31, 32). Finally, terminal aortic occlusion is expected to decrease right atrial pressure to the extent that terminal aortic (muscle) blood flow is diverted to more compliant vascular beds in the remainder of the circulation (21, 31). Our observations that right atrial pressure was either well maintained or was increased during reflex activation indicate that factors which tend to increase atrial pressure at least offset and often overwhelm those factors that tend to reduce atrial pressure.

Several factors associated with muscle chemoreflex activation are expected to raise right atrial pressure. The rise in heart rate is expected to cause a small (0.5 mmHg) rise in right atrial pressure owing to the reduction in the “capacitance” of the ventricular chambers (26); i.e., averaged over time, the ventricles in essence “store” a certain volume of blood, and tachycardia reduces this volume and transfers it to the venous system (26). More importantly, activation of the sympathetic nervous system is expected to raise right atrial pressure via splanchnic vasoconstriction (2) and splanchnic venoconstriction (6). In dogs, the spleen can contribute importantly to reflex-induced blood volume mobilization (33). The substantial increases in right atrial pressure attending the pressor responses produced during mild exercise with constant cardiac output, and during moderate exercise when cardiac output rose, strongly indicate that the muscle chemoreflex evoked splanchnic vasoconstriction and venoconstriction causing blood volume to be expelled into the central circulation.

Distribution of Cardiac Output

Although we did not determine the complete distribution of cardiac output during these pressor responses, probable targets for its distribution can be surmised. Our study provides direct evidence that the kidneys do not receive any of the augmentation in upper body blood flow provided by the increase in cardiac output and the redistribution of terminal aortic flow, which together amounted to ~3 l/min. Renal vasoconstriction was well matched to the rise in arterial pressure such that we measured only modest (15%) reductions in renal blood flow. In a similar experiment, Mittelstadt and co-workers (15) found that there was no consistent change in renal blood flow. In another study, these investigators found that forelimb blood flow rose by 100–200 ml/min during pressor responses to muscle ischemia (14). If a single forelimb (axillary artery flow) constitutes one-fourth of the total upper body musculature, then up to 1 l/min (33%) of the rise in blood flow can be accounted for by skeletal muscle. A likely target for a substantial portion of the total rise in blood flow is the heart. Myocardial blood flow is expected to rise considerably owing to the large increases in heart rate and systemic pressure that accompany reflex activation. Again, the increments in right atrial pressure we observed indicate that the muscle chemoreflex evoked splanchnic vasoconstriction and venoconstriction and thus blood flow to this region likely fell.

Additional Experiments With Constant Mean Arterial Pressure

The increases in arterial pressure that accompany muscle chemoreflex activation in the present study confound our understanding of the full potential of the muscle chemoreflex to alter right atrial pressure in two important ways. First, although the compliance of the arterial system is low relative to the venous system, a significant amount of blood can be transferred from the venous system into the arterial system owing to the large (50–75 mmHg) changes in arterial pressure that occurred. Second, the arterial baroreflexes attenuate muscle chemoreflex responses evoked by partial vascular occlusion of active muscle (27). Thus to more fully reveal the potential of the muscle chemoreflex to influence right atrial pressure, we felt it would be useful to activate the reflex in a setting where mean arterial pressure does not change.

Figure 4 illustrates responses from two dogs prepared with atrioventricular block as described previously (28, 31, 32), in which the muscle chemoreflex was activated by rapid complete inflation of a terminal aortic occlusion cuff during steady-state treadmill exercise (25). Mean arterial pressure was maintained constant by computer-controlled ventricular pacing (18). In both experiments, right atrial pressure underwent a small, initial rise immediately after terminal aortic occlusion. This rise likely reflects the transfer to central
veins of blood volume from arteries located distal to the occlusion cuff secondary to the large (100 mmHg) decrease in hindlimb arterial pressure produced by complete occlusion. The rapid nature of this initial rise signifies that this blood volume is rapidly pumped to the central circulation by the skeletal muscle pump (29). This experiment reveals that the combination of a reduction in cardiac output, needed to maintain mean arterial pressure constant, and peripheral vasoconstriction unopposed by arterial baroreflexes leads to potent (e.g., 7 mmHg) increments in right atrial pressure. These two examples likely shed light on the extent to which the muscle chemoreflex might influence cardiac filling pressure in settings where arterial pressure changes little (5) and/or where ventricular function is impaired (e.g., heart failure).

Comparison With Other Mechanisms That Raise Right Atrial Pressure

The carotid sinus baroreceptor reflex has been shown to induce relatively small changes in right atrial pressure. For example, Bennett et al. (1) showed that right atrial pressure rose only 0.8 mmHg in response to carotid occlusion when cardiac output was maintained constant by ventricular pacing in atrioventricular-blocked dogs with blocked vagus nerves. Carotid occlusion induced a 50% fall in total vascular conductance and thus a 50% rise in arterial pressure (1). This rise in arterial pressure is nearly identical to the rise induced by the muscle chemoreflex in the present study in which cardiac filling pressure rose by 2.3 mmHg (i.e., 3 times greater) when cardiac output was maintained constant. Thus the capacity of the muscle chemoreflex to raise right atrial pressure appears to be much greater than that of the carotid sinus baroreceptor reflex. As a consequence, the muscle chemoreflex appears to exert a much greater influence on cardiac output. For example, carotid occlusion raised cardiac output by only 0.7 l/min in conscious resting dogs with severed aortic depressor nerves (20), i.e., far less than the 2 l/min increments we observed despite similar increases in arterial pressure in the two experiments.

The skeletal muscle pump has been estimated to mobilize 5–10 ml/kg body wt and can raise right atrial pressure by 4–5 mmHg (4, 8, 32). Thus the muscle chemoreflex appears to be as potent as the muscle pump in raising right atrial pressure inasmuch as right atrial pressure would have been expected to rise by 5 mmHg if cardiac output had been maintained constant during moderate exercise.

In summary, when active skeletal muscles are underperfused, a rise in cardiac output induced by the muscle chemoreflex constitutes an important adjustment, because it increases the total blood flow available to be distributed among organs competing for flow. Inasmuch as increments in heart rate and contractility provide limited means of raising cardiac output owing to the inverse relationship that exists between cardiac output and right atrial pressure in the intact circulation, the ability to maintain or increase cardiac filling pressure is important if the muscle chemoreflex is to function effectively. We found that the muscle chemoreflex evokes hemodynamic adjustments that can elicit marked increases in right atrial pressure. Muscle chemoreflex effects on right atrial pressure work in concert with increases in heart rate and contractility such that sizable increases in cardiac output are produced when blood flow to active muscle is reduced during exercise.
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