Muscle metaboreflex control of coronary blood flow

ERIC J. ANSORGE,1 SACHIN H. SHAH,3 ROBERT A. AUGUSTYNIAK,1 NOREEN F. ROSSI,2 HEIDI L. COLLINS,1 AND DONAL S. O’LEARY1
1Department of Physiology, 2Department of Medicine, John D. Dingell Veterans Administration Medical Center, and 3Department of Surgery, Wayne State University School of Medicine, Detroit, Michigan 48201

Received 23 January 2002; accepted in final form 9 April 2002

Ansorge, Eric J., Sachin H. Shah, Robert A. Augustyniak, Nooreen F. Rossi, Heidi L. Collins, and Donal S. O’Leary. Muscle metaboreflex control of coronary blood flow. Am J Physiol Heart Circ Physiol 283: H526–H532, 2002.—We investigated the effect of muscle metaboreflex activation on left circumflex coronary blood flow (CBF) and vascular conductance (CVC) in conscious, chronically instrumented dogs during treadmill exercise ranging from mild to severe workloads. Metaboreflex responses were also observed during mild exercise with constant heart rate (HR) of 225 beats/min and β1-adrenergic receptor blockade to attenuate the substantial reflex increases in cardiac work. The muscle metaboreflex was activated via graded partial occlusion of hindlimb blood flow. During mild exercise, with muscle metaboreflex activation, hindlimb ischemia elicited significant reflex increases in mean arterial pressure (MAP), HR, and cardiac output (CO) (+39.0 ± 5.2 mmHg, +29.9 ± 7.7 beats/min, and +2.0 ± 0.4 l/min, respectively; all changes, P < 0.05). CBF increased from 51.9 ± 4.3 to 88.5 ± 6.6 ml/min, (P < 0.05), whereas no significant change in CVC occurred (0.56 ± 0.06 vs. 0.59 ± 0.05 ml·min⁻¹·mmHg⁻¹; P > 0.05). Similar responses were observed during moderate exercise. In contrast, with metaboreflex activation during severe exercise, no further increases in CO or HR occurred, the increases in MAP and CBF were attenuated, and a significant reduction in CVC was observed (1.00 ± 0.12 vs. 0.90 ± 0.13 ml·min⁻¹·mmHg⁻¹; P < 0.05). Similarly, when the metaboreflex was activated during mild exercise with the rise in cardiac work lessened (via constant HR and β1-blockade), no increase in CO occurred, the MAP and CBF responses were attenuated (+15.6 ± 4.5 mmHg, +8.3 ± 2 ml/min), and CVC significantly decreased from 0.63 ± 0.11 to 0.53 ± 0.10 ml·min⁻¹·mmHg⁻¹. We conclude that the muscle metaboreflex induced increases in sympathetic nerve activity to the heart functionally vasoconstrict the coronary vasculature.

WHEN EXERCISING skeletal muscle does not receive sufficient blood flow to meet metabolic demands, metabolites (e.g., lactic acid, H⁺, and diprotonated phosphate) accumulate and stimulate afferent neurons, which evoke a reflex increase in sympathetic nerve activity (SNA) and mean arterial pressure (MAP), known as the muscle metaboreflex (1, 2, 8, 13, 18–21, 23, 27). The capability of the metaboreflex to correct a blood flow deficit lies in its ability to increase perfusion pressure, which is achieved via increases in cardiac output (CO) and vasoconstriction within nonischemic vascular beds (15, 16, 21, 22). Both the increase in CO and its redistribution during metaboreflex activation is aimed at eliminating any existing mismatch between O2 delivery and O2 demand in the exercising skeletal muscle.

Previous studies (2, 28) in normal dogs have shown that during mild-to-moderate workloads, the major mechanism utilized by the muscle metaboreflex to improve blood flow to the ischemic muscle is to raise CO. This increase in CO is achieved via increases in heart rate (HR), ventricular performance, and central blood volume mobilization (18, 19, 22, 24). In contrast, when increases in CO are limited, such as during severe exercise when CO is already at or near maximal levels (2), or in heart failure when increases in ventricular performance are likely limited (8), peripheral vasoconstriction becomes the primary mechanism for muscle metaboreflex pressor responses.

At lower workloads, the muscle metaboreflex-induced increase in HR (and likely CO) occurs predominantly via increases in SNA (18). The muscle metaboreflex-induced increases in HR, CO, as well as often marked increases in ventricular afterload, would be expected to increase myocardial O2 demand and thereby cause a metabolic coronary vasodilation (5, 26). However, increases in SNA to the heart may also activate coronary vascular α-adrenergic receptors, which may thereby limit any metabolically induced vasodilation. Indeed, Gwirtz et al. (6, 7) showed that coronary α1-adrenergic receptor blockade significantly increased coronary blood flow (CBF) during exercise. In addition, Huang and Feigl (9) also showed that the increase in SNA to the heart during normal exercise activates coronary α-receptors, lowering total CBF, but the increase did help maintain a more uniform ventricular transmural blood flow by preferentially eliciting vasoconstriction in the epicardium, thereby improving the ratio of endocardial to epicardial blood flow. Although coronary α-adrenergic receptor activation dur-
ing exercise improves the uniformity of ventricular transmural flow, Gwirtz et al. (6, 7) showed that the restriction of total flow may limit the increases in ventricular performance inasmuch as the rate of myocardial shortening was significantly increased after coronary α1-receptor blockade. Thus increases in SNA to the heart during normal exercise promote vasodilation by increasing myocardial O2 demand and possible activation of vascular β2-adrenergic receptors (4). However, this vasodilation is functionally restrained by the concomitant activation of vascular α-receptors.

To our knowledge, the effect of activation of the muscle metaboreflex on CBF is unknown. Previously, Aung-Din et al. (3) demonstrated in anesthetized dogs that electrically induced static hindlimb contraction performed after β-adrenergic blockade elicited coronary vasoconstriction via activation of vascular α-adrenergic receptors. However, static muscle contraction activates both metabo- and mechanosensitive skeletal muscle afferents (11); thus the relative roles of these individual afferents in mediating the increase in SNA are unclear. In addition, anesthesia and acute surgical trauma can affect cardiovascular reflexes. We and others have shown that during submaximal exercise the muscle metaboreflex can elicit substantial increases in CO (1, 2, 22, 28), which coupled with the large increases in ventricular afterload, would be expected to elicit significant increases in myocardial O2 demand and hence metabolic coronary vasodilation (5, 17, 26). However, as workload approaches maximal levels, further metaboreflex-induced increases in CO are limited and the reflex increases in afterload are substantially smaller (2). In this setting, any further metaboreflex-induced increases in SNA likely do not produce marked increases in myocardial O2 demand (17). A similar lessening of increases in myocardial O2 demand with metaboreflex activation can occur at lower workloads if metaboreflex-induced increases in CO are experimentally prevented or pathophysiologically constrained (8, 22). In these settings, metaboreflex-induced increases in SNA to the heart may elicit coronary vasoconstriction inasmuch as the vasoconstrictor effect of activation of coronary vascular α-adrenergic receptors would potentially not be balanced by a substantial metabolic drive for vasodilation due to the increased myocardial work. Thus the present study was designed to test the effect of muscle metaboreflex on CBF and vascular conductance across workloads ranging from mild to severe exercise and during mild exercise wherein the normal large increases in HR and CO were prevented.

METHODS

All experiments were performed using nine conscious dogs (21–26 kg, 8 male and 1 female) selected for their willingness to run on a motor-driven treadmill. All procedures were reviewed and approved by the Institutional Animal Care Committee and conformed to National Institutes of Health guidelines.

Surgical preparation. Each animal was prepared in a series of surgical sessions with at least 1 wk between surgeries and between the last surgery and first experiment. For all procedures, anesthesia was induced with Pentothal Sodium and maintained with isoflurane. Cefazolin (500 mg iv) was given both before and after surgery and then cephalixin (30 mg/kg by mouth, 2 times/day) was given to avoid postoperative infection. During the surgical recovery, buprenorphine (0.015 mg/kg iv) and acepromazine (0.1 mg/kg im) were administered for pain control and sedation whenever necessary.

In the first surgical session, a left thorocotomy was performed at the fourth intercostal space and a blood flow transducer (Transonic Systems) was placed around the ascending aorta to measure CO. A second blood flow transducer was placed around the left circumflex coronary artery to measure CBF. Two sonomicrometry crystals were implanted in the epicardium of the left ventricle for experiments unrelated to this study. In addition, stainless steel electrodes were sutured to the apex of the left ventricle for future ventricular pacing. The edges of the pericardium were reaproximated and the chest was closed in layers.

In the second surgical session, a midventral approach was implemented for the placement of blood flow transducers (Transonic Systems) around the terminal aorta to measure hindlimb blood flow (HLBF) and a blood flow transducer was also placed on the left renal artery for studies unrelated to the present investigation. A vascular occluder (In Vivo Metrics) was placed around the terminal aorta distal to the flow probe. All side branches between the iliac arteries and the flow probe were ligated and severed. A catheter was inserted into a side branch of the aorta above the flow probe and occluder to measure MAP.

In the final surgical session, a fluid-filled catheter was inserted into the jugular vein and fed through the vein to the atrial-caval junction to measure central venous pressure (CVP). All cables, occluder tubing, and catheters were tunneled subcutaneously and exited through the skin between the scapulae.

Experimental procedures. All experiments were performed after the animals had fully recovered from surgery and were active and had regained presurgery eating habits. The animal was transported to the laboratory and allowed to acclimate to its surroundings for 15–30 min. The animal was then led to the treadmill, where the blood flow transducers were connected to the flowmeters (Transonic Systems). The MAP and CVP catheters were connected to pressure transducers (Transpac IV, Abbott Laboratories). All flow and pressure transducers were coupled to a recording system (model RS 3800, Gould). HR was measured via a cardiograph triggered by the CO signal. All data were sampled with a laboratory computer at 1,000 Hz and mean values for each cardiac cycle were saved on the computer for future analysis. Before the start of each experiment, the animal was directed to stand for at least 1 min to stabilize cardiovascular parameters.

The muscle metaboreflex was activated during mild, moderate, and severe treadmill exercise (3.2 km/h, 0% grade, 6.4 km/h, 10% grade, and 8.0 km/h, 15–20% grade) via graded reductions in hindlimb perfusion achieved by partially inflating the vascular occluder implanted on the terminal aorta. The treadmill was started, and after 3–5 min, all parameters reached steady state. The hindlimb occluder was then partially inflated, resulting in stepwise reductions in hindlimb perfusion. The occlusion was maintained until all parameters reached steady state in ~3–5 min.

On a separate day, the mild exercise experiment was repeated wherein HR was held constant via ventricular pacing at 225 beats/min and β1-adrenergic blockade was employed. The β1-adrenergic receptor antagonist atenolol (2.0 mg/kg) was administered systemically. Previously (22), we have shown that the combination of constant HR and β1-blockade abolished any rise in CO with muscle metaboreflex...
activation during mild exercise. Through this combination, CO was functionally held constant.

Statistical analysis. Each dog served as its own control. The data were analyzed, as previously described by Wyss et al. (28), to elucidate response patterns: 1) control values measured during free-flow exercise, 2) values measured at metaboreflex threshold, and 3) the values measured during the largest reduction in HLBF. One-minute averages of all cardiovascular output variables were taken during steady state and at each level of hindlimb vascular occlusion. During mild dynamic exercise, initial reductions of HLBF do not elicit metaboreflex responses (i.e., changes in MAP, HR, and CO). Once HLBF is reduced below a threshold level, additional reductions in HLBF elicit marked increases in MAP, HR, and CO. When measured output variables, such as MAP and HR, are plotted versus HLBF, the responses resemble a “dog leg” pattern. Accordingly, the data were approximated to two linear regressions, an initial response line, where no substantial change in MAP or HR occurred with initial reductions in hindlimb perfusion, and a pressor response line when further reductions in hindlimb perfusion elicited marked increases in MAP, HR, and CO. The intersection of the two regression lines approximates the threshold for muscle metaboreflex activation during mild exercise. In moderate exercise, often there is no apparent threshold for metaboreflex activation, and in this case, the threshold was ascribed as the value during free-flow exercise (no imposed occlusion). During severe exercise, no threshold was ever observed as previously described by Augustyniak et al. (2). During control experiments at mild and moderate exercise, the pattern of the changes in CVC did not fit the dual regression line model because little change in this variable occurred (see Fig. 2). Hindlimb occlusion can raise MAP via the metaboreflex and also due to the passive mechanical effects of the occluder. The rise in MAP due to the passive mechanical effects of the occluder was calculated as described by Augustyniak et al. (2). The rise in MAP due solely to the metaboreflex-mediated increases in CO and peripheral vasoconstriction (MAPactive) is the difference between the observed increase in MAP and that due solely to the mechanical effects of the occluder. Maximal values observed during muscle metaboreflex activation were compared with the values during free-flow exercise with the use of Student’s t-test. The changes in CBF, CVC, and MAP with metaboreflex activation were compared across workloads via ANOVA with repeated measures and individual means were compared using the test for simple effects. All data are presented as means ± SE.

RESULTS

Table 1 contains all mean hemodynamic data during standing rest and free-flow exercise at each workload.

Table 1. Average hemodynamic values at rest and free-flow exercise during mild, moderate, and severe exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest (3.2 km/h, 0%)</th>
<th>Mild Exercise (6.4 km/h, 10%)</th>
<th>Moderate Exercise (8.0 km/h, 15% or 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>104 ± 5.5</td>
<td>105 ± 5.2</td>
<td>113 ± 3.8</td>
</tr>
<tr>
<td>CO, 1 min</td>
<td>5.8 ± 0.48</td>
<td>7.80 ± 0.68</td>
<td>13.0 ± 1.0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>104 ± 7.1</td>
<td>131 ± 7.0</td>
<td>189 ± 4.5</td>
</tr>
<tr>
<td>HLBF, l/min</td>
<td>0.83 ± 0.06</td>
<td>1.60 ± 0.81</td>
<td>3.40 ± 0.20</td>
</tr>
<tr>
<td>CBF, ml/min</td>
<td>40.2 ± 3.4</td>
<td>52.0 ± 4.30</td>
<td>83.0 ± 7.0</td>
</tr>
<tr>
<td>CVC, ml·min⁻¹·mmHg⁻¹</td>
<td>0.42 ± 0.04</td>
<td>0.56 ± 0.06</td>
<td>0.80 ± 0.08</td>
</tr>
<tr>
<td>SV, ml</td>
<td>56.0 ± 4.8</td>
<td>60.0 ± 5.0</td>
<td>70.0 ± 4.6</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mean arterial pressure (MAP), cardiac output (CO), heart rate (HR), hindlimb blood flow (HLBF), coronary blood flow (CBF), coronary vascular conductance (CVC), and stroke volume (SV) during rest and free-flow exercise at each workload are shown.

Figure 1 shows an experiment during mild exercise, where initial reductions in hindlimb perfusion do not elicit increases in CO, MAP, or CBF. However, once the reductions in hindlimb perfusion fall below a threshold level, marked increases in CO, MAP, and CBF occur with muscle metaboreflex activation. Note that little change in CVC occurred with muscle metaboreflex activation.

Figure 2 shows average hemodynamic data as a function of HLBF during mild (n = 9), moderate (n = 9), and severe exercise (n = 6). During mild and moderate exercise, with muscle metaboreflex activation, MAPactive, CO, HR, and CBF were elevated with no significant change in CVC. Muscle metaboreflex activation during severe exercise yielded an attenuated rise in MAPactive and CBF (P < 0.05 vs. lower workloads) as well as no significant change in CO or HR. Muscle metaboreflex activation during severe exercise caused a significant reduction in CVC.

Figure 3 shows hemodynamic responses to muscle metaboreflex activation during mild exercise in control experiments and after combined constant HR and β1-adrenergic blockade (n = 6). Compared with control data, the rise in MAIactive with muscle metaboreflex activation was attenuated during constant HR and β1-adrenergic blockade. By employing constant HR and β1-adrenergic blockade, CO and HR were functionally held constant, thereby preventing any increase in either variable. In this setting with muscle metaboreflex activation, there was a marked reduction in the rise in CBF compared with the control experiment and CVC significantly decreased.

DISCUSSION

The major new finding in this study is that the muscle metaboreflex is capable of vasoconstricting the coronary vasculature. Previous studies (1, 2, 8, 13, 15, 16, 18–21, 23, 27) from our laboratory and others have shown that muscle metaboreflex activation increases SNA to the peripheral vasculature and the heart, which elicits regional vasoconstriction, increased HR, ventricular performance, and CO. During mild exercise, a clear threshold existed for metaboreflex activation whereas at heavier workloads any reduction in HLBF elicited metaboreflex responses. Thus, with muscle metaboreflex activation, there is a substantial
increase in myocardial work (e.g., significantly increased CO pumped against a substantially elevated afterload). Despite this elevation in myocardial work, coronary vasodilation was not observed with muscle metaboreflex activation during mild and moderate exercise. However, during severe exercise, the increase in myocardial work with metaboreflex activation was likely lessened (no significant increase in CO and a significantly smaller increase in afterload), and an attenuated rise in CBF occurred. In this setting, there was a significant reduction in CVC with muscle metaboreflex activation. Similarly, when the rise in myocardial work with metaboreflex activation was reduced experimentally via \(\beta_1\)-adrenergic blockade and constant HR, a significant decrease in CVC occurred. The pattern of the CVC responses with metaboreflex activation during severe exercise was similar to that during mild exercise with \(\beta_1\)-adrenergic blockade + constant HR, in that in both settings significant coronary vasoconstriction occurred. Despite the markedly different baseline levels for cardiac work, CBF, and CVC, the severe exercise and constant HR and \(\beta_1\)-blockade experiments demonstrated several similarities in the efferent responses. In both settings, there was no significant change in CO or HR, the rise in CBF was attenuated, and CVC decreased, indicating coronary vasoconstriction. In all settings, significant increases in CBF occurred with metaboreflex activation. These increases in CBF were not due to vasodilation of the coronary vasculature but occurred solely via the increases in perfusion pressure (e.g., MAP) inasmuch as CVC remained either unchanged (mild and moderate exercise) or significantly decreased (severe exercise and during mild exercise with constant HR and \(\beta_1\)-blockade) with metaboreflex activation. In pathophysiological states such as coronary artery disease, activation of the muscle metaboreflex may be deleterious inasmuch as metaboreflex-induced coro-
nary vasoconstriction may only exasperate an already reduced level of CBF and lead to myocardial ischemia, which could increase the risk for a cardiovascular event.

Previous reviews by Feigl (5) and Stone (25) have described that the direct effect of stimulation of sympathetic nerves to the heart results in tachycardia, increased myocardial contractility, an increase in aortic blood pressure, and marked rise in CBF. A secondary effect of SNA to the heart is α-adrenergic vasoconstriction. In response to static muscle contraction in anesthetized dogs, Aung-Din et al. (3) observed a 29.6% increase in CBF with no change in CVC. In addition, they found that after β-adrenergic blockade, static muscle contraction elicited a 30% decrease in CBF and a 53% increase in coronary resistance. The unmasking of sympathetic coronary α-receptor vasoconstriction by β-receptor blockade has been also observed in other studies (9, 12, 14). More recently, Gwirtz et al. (6, 7) have shown that α-adrenergic vasoconstriction limits the rise in CBF during exercise and may also limit increases in cardiac function because the rate of myocardial shortening was enhanced with α1-receptor blockade during exercise.

Fig. 2. Average levels of the observed MAP (●), passive MAP (▲), active MAP (MAPactive ■), CO, HR, CBF, and CVC plotted as a function of HLBF during mild (n = 9), moderate (n = 9), and severe exercise (n = 6). During mild and moderate workloads, MAPactive, CO, HR, and CBF increased with metaboreflex activation with no significant change in CVC. Note that during severe exercise, no increases in CO or HR occurred, the rise in CBF was small, and a significant decrease in CVC occurred. ∗ P < 0.05 vs. free-flow exercise; NS, no significant change from free-flow exercise.
The rise in SNA observed with exercise and its concomitant activation of \( \alpha \)-adrenergic receptors may assist in preserving the regional distribution of myocardial blood flow. Huang et al. (9) observed that during moderate to heavy workloads, the ratio of left ventricular blood flow through the inner myocardial layer to the outer layer was better maintained in the region where \( \alpha \)-receptors were intact than in the region where \( \alpha \)-receptors were pharmacologically blocked. This may be a consequence of an apparent preferential effect of sympathetic nerve stimulation on the epicardial vessels (10). In this setting, \( \alpha \)-adrenergic vasoconstriction helps to maintain a uniform distribution of myocardial blood flow during exercise by limiting epicardial vasodilation, thereby facilitating a greater degree of blood flow through endocardial vessels, which are more susceptible to narrowing by systolic compression (5, 25). Thus the \( \alpha \)-adrenergic vasoconstriction observed during muscle metaboreflex activation may improve the match between myocardial metabolism and blood flow across the ventricular wall by altering the transmural distribution of blood flow; however, this has yet to be investigated.

Recently, Hammond et al. (8) reported the rise in MAP with muscle metaboreflex activation during heart failure was due almost solely to the decrease in total vascular conductance (TVC). Although a sustained tachycardic response was observed, there was a reduction in stroke volume (SV), thereby preventing a rise in CO. The fall in TVC, as well as marked increases in

*Fig. 3. Average levels of observed, passive, and active MAP (as denoted in Fig. 2), CO, HR, CBF, and CVC plotted as a function of HLBF during muscle metaboreflex activation during mild exercise (control) and after combined constant HR and \( \beta_1 \)-adrenergic blockade (\( n = 6 \) in each group). By employing constant HR and \( \beta_1 \)-adrenergic blockade, CO and HR were functionally held constant and with muscle metaboreflex activation the increases in MAPactive and CBF were attenuated and a significant decrease in CVC occurred. *\( P < 0.05 \) vs. free-flow exercise; NS, no significant change from free-flow exercise.
arterial levels of plasma norepinephrine, indicates extremely high levels of SNA in this condition. Although Gwirtz et al. (6, 7) concluded that the normal rise in SNA to the heart limits increases in ventricular performance via vasoconstriction of the coronary vessels, with the extreme rise in SNA with muscle metaboreflex activation in heart failure (total renal vasoconstriction was observed in some experiments), it is possible that the failure to raise CO in this setting maybe due to marked coronary vasoconstriction.

In summary, activation of the muscle metaboreflex during dynamic exercise can vasoconstrict the coronary vasculature. Muscle metaboreflex activation elicits substantial increases in SNA to the heart, which increases myocardial work that would be expected to cause significant coronary vasodilation. However, no vasodilation was observed at lower workloads in this setting, and metaboreflex activation during severe exercise as well as during mild exercise when increases in cardiac work were attenuated (via β1-blockade + constant HR), significant decreases in CVC were observed. Thus the coronary vascular response to muscle metaboreflex activation was dependent on whether substantial increases in myocardial O2 demand occurred.

The authors thank Sue Harris for expert technical assistance. This study was supported by National Heart, Lung, and Blood Institute Grant HL-55473 and a joint award from the Departments of Defense and Veterans Affairs.

REFERENCES


