Flow-generating capability of the isolated skeletal muscle pump

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Sheriff, Don D., and Richard Van Bibber. Flow-generating capability of the isolated skeletal muscle pump. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1502–H1508, 1998.—We sought to test directly whether the mechanical forces produced during rhythmic muscle contraction and relaxation act on the muscle vasculature in a manner sufficient to initiate and sustain blood flow. To accomplish this goal, we evaluated the mechanical performance of the isolated skeletal muscle pump. The hindlimb skeletal muscle pump was isolated by reversibly connecting the inferior vena cava and terminal aorta with extracorporeal tubing in 15- to 20-kg anesthetized pigs (n = 5). During electrically evoked contractions (1/s), hindlimb muscles were made to perfuse themselves by diverting the venous blood propelled out of the muscles into the shunt tubing, which had been prefilled with fresh arterial blood. This caused arterial blood to be pushed into the distal aorta and then through the muscles (shunt open, proximal aorta and vena cava clamped). In essence, the muscles perfused themselves for brief periods by driving blood around a “short-circuit” that isolates muscle from the remainder of the circulation, analogous to isolated heart-lung preparations. Because the large, short shunt offers a negligible resistance to flow, the arterial-venous pressure difference across the limbs was continuously zero, and thus the energy to drive flow through muscle could come only from the muscle pump. The increase in blood flow during normal heart-perfused contractions (with only the shunt tubing clamped) was compared with shunt-perfused contractions in which the large veins were preloaded with extra blood volume. Muscle blood flow increased by 87 ± 11 and 110 ± 21 (SE) ml/min in the first few seconds after the onset of shunt-perfused and heart-perfused contractions, respectively (P > 0.4). We conclude that the mechanical forces produced by muscle contraction and relaxation act on the muscle vasculature in a manner sufficient to generate a significant flow of blood.

muscle blood flow; skeletal muscle veins; muscle vascular conductance; muscle vascular resistance; metabolic vasodilation; functional hyperemia; muscle venous pump; venous return; venous function; venous physiology; vascular capacitance; blood pressure; muscle contraction; exercise

WHEN VENOUS VALVES are competent, the skeletal muscle pump enables two important adjustments to exercise. First, it provides a substantial portion of the total energy expended to drive the flow of blood around the peripheral circulation. It probably provides all of the force that propels the flow of blood from active muscles back to the heart (20). In addition, the muscle pump can assist its own perfusion in tall animals such as upright humans by increasing the arterial-venous pressure difference across the muscle. It does this by transiently eliminating the hydrostatic component of venous pressure in the dependent legs, thereby harnessing the persistent arterial hydrostatic pressure to assist the left ventricle in driving flow through the microcirculation of skeletal muscle (7). Second, at the onset of exercise, muscle contraction transfers blood volume from muscle veins to the central circulation (5, 9, 19). This blood volume redistribution then provides a ventricular filling pressure that is adequate for the high cardiac outputs attained during exercise (12, 16, 19).

Recently, Laughlin (13) suggested that the muscle pump might also assist muscle perfusion independent of its cancellation of the large hydrostatic component of muscle venous pressure. For example, restoring forces imposed during muscle relaxation could suddenly pull open tethered veins, thereby creating negative intravascular pressures that would further increase the arterial-venous pressure difference across the muscle (13). In this way, the vascular system could capture a portion of the energy expended by skeletal muscle in producing the mechanical activity of contraction and relaxation and harness this energy to assist the perfusion of muscle. The finding that rhythmic contraction and relaxation of muscle at the onset of locomotion cause a sudden (1–2 s) rise in “calculated” muscle vascular conductance (actually a “virtual conductance” across a pump) supports this proposal (18). This sudden rise in “conductance” is not explained by known metabolic, neural, myogenic, or hydrostatic influences and is presumed to be caused by the muscle pump (18). In addition, the finding that physiological recruitment of “maximally” vasodilated muscle (diaphragm) causes an increase in blood flow at constant perfusion pressure (14) provides further support for this idea. An alternative presumption is that the sudden rise in conductance is caused by the “instantaneous” action of as yet unidentified vasodilator substances (3).

Our objective was to test directly whether the mechanical forces produced during rhythmic muscle contraction and relaxation act on the muscle vasculature in a manner sufficient to initiate and sustain blood flow. Our approach was to measure the blood flow in active muscles in a situation where the left ventricle could not provide energy to drive muscle perfusion. We examined how the muscle pump works in isolation by creating an extracorporeal shunt between the inferior vena cava and the terminal aorta. The shunt could be controlled so that blood flow was driven through contracting hindlimb muscles either 1) in the normal heart-perfused manner with the shunt clamped or 2) by only the forces provided by the active muscles themselves. The hindlimbs muscles were made to perfuse themselves by diverting the venous blood propelled out of the
muscles into the shunt tubing, which had been prefilled with fresh arterial blood. This caused arterial blood to be pushed into the distal aorta and then through the muscles. In essence, the active muscles perfuse themselves by driving blood flow around a short circuit that isolates the muscles from the remainder of the circulation in a manner that is analogous to the isolated heart-lung preparations that have greatly increased our understanding of the mechanics of the ventricular pumps. Analyzing in this way, we found that skeletal muscle is an effective pump.

METHODS

All procedures involving the use of animals were reviewed and approved by the Institutional Animal Care and Use Committee and were in conformance with the National Institutes of Health “Guide for the Care and Use of Laboratory Animals” [Department of Health and Human Services Publication No. (NIH) 85–23, Revised 1985].

Surgical Preparation

Five pigs (15–20 kg) were administered ketamine (35 mg/kg) and xylazine (5 mg/kg) intramuscularly followed by intravenous pentobarbital sodium (25 mg/kg). Mechanical ventilation with room air was begun shortly after tracheal intubation. The terminal aorta and inferior vena cava were exposed via a midline abdominal incision. Approximately 3- to 5-cm segments of these vessels were dissected free of surrounding tissue, and side branches emanating from these segments were ligated and sectioned. The isolated segments of the inferior vena cava and terminal aorta were tied, and short sections of stiff-walled tubing (PE-360), which in turn were connected to larger bore flexible tubing (3/8-in. ID, 9/16-in. OD Silastic), were inserted into the proximal and distal sections of these two vessels to form extracorporeal loops. These loops were interconnected by a short section of tubing to create a reversible shunt. This preparation is shown schematically in Fig. 1. These cannulations were completed within 10–20 min after the vessels were tied. The hindlimbs were freely perfused via the aortic and caval loops (shunt clamped) except for brief periods as noted below in Experimental Protocols. The animals were supine throughout the experiment. Large-bore tubing was used both because it would provide a low-resistance pathway for flow and because it could be prefilled with fresh arterial blood during each reversible isolation of the muscle pump. In this way, the muscle pump was harnessed to eject venous blood into the venous end of the shunt tubing, which in turn would cause arterial blood to be “pushed” back into the arterial supply of the muscles. In this way, the isolated muscle pump perfused itself with arterial blood, not with venous blood as might otherwise be expected.

Experimental Procedures

A cannulating-type electromagnetic transducer was placed in the aortic cannula distal to the shunt for measurement of arterial inflow to the hindlimbs. Arterial and venous pressures were measured with strain gauge transducers connected via tubing to needles inserted directly into the extracorporeal tubing. All three signals were displayed on a chart recorder and digitized at 250 Hz, and the averaged values of each signal were written to the fixed disk of a microcomputer twice per second. The zero level of flow was established by damping the arterial tubing distal to the blood flow transducer.

Experimental Protocols

Heart-perfused muscle contractions. Blood flow during electrically induced contractions of hindlimb muscles was measured while blood flowed freely from the aorta through the muscle (shunt clamped) as depicted in Fig. 1A. The quadriceps muscles were electrically activated bilaterally through needles inserted directly into the anterior aspects of the thighs. The legs were unrestrained, and muscle contractions caused extension of the knee and flexion of the hip. Between contractions, the legs returned passively to the resting position (possibly assisted by stretch reflex-induced contractions of antagonist muscles).

The muscle stimulation parameters chosen were those reported by Folkow et al. (6) to elicit the largest increments in blood flow to the hindlimbs of cats. They were as follows: pulse duration, 0.2 ms; amplitude, 10–20 V; frequency, 60 Hz; train duration, 200 ms; rate, 1/s. The muscles were typically stimulated for 20–30 s and then allowed to rest until the measured variables returned to baseline values (usually 2–3 min).

Shunt-perfused muscle contractions. Shortly before the muscles were activated, the venous outflow tubing proximal to the shunt was clamped, and the shunt was opened. During this time, blood flowed from the aorta across the shunt into the veins. This flushed the shunt blood into the veins and filled the shunt tubing with fresh arterial blood. The arterial inflow tubing proximal to the shunt was then clamped, causing arterial inflow to fall to zero. The muscles were activated as described above (see Heart-perfused muscle contractions) beginning a few seconds after the arterial tube was clamped. In this setting, depicted in Fig. 1B, blood pressure in the tubing simultaneously represents arterial and venous pressure because the large, short shunt offers a low resistance pathway for flow.

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A

To muscle

From muscle

\[ \text{Q} \]

Shunt

\[ \text{Pa} \]

Aorta

IVC

B

To muscle

From muscle

\[ \text{Q} \]

Shunt

\[ \text{Pa} \]

Aorta

IVC

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Fig. 1. Schematic depiction of isolated muscle pump preparation. A: normal (cardiac) perfusion. B: muscles perfuse themselves by driving blood through a shunt directly back into arteries supplying muscles. Shunt tubing is large and prefilled with arterial blood so that muscles perfuse themselves with arterial blood for short periods of time. IVC, inferior vena cava; P, pressure; a, arterial; v, venous; Q, flow.
negligible resistance to flow. Therefore, the arterial-venous pressure difference across the limbs is continuously zero, and thus the energy to drive the flow of blood around the circuit can come only from the muscle pump. The muscles were typically stimulated for 20–30 s immediately after which the shunt was clamped and normal (cardiac) perfusion was reinstated by opening the arterial inflow and venous outflow tubes. Shunt-perfused muscle contractions were carried out within minutes of the heart-perfused contractions to which they were compared.

Statistical Analysis

Data are presented as means ± SE. The increments in blood flow after 10 s of contractions in the two settings were compared with a paired t-test.

RESULTS

Figure 2 depicts pressure and flow generated by the isolated skeletal muscle pump with the hindlimb circulation configured as depicted in Fig. 1B. Each pressure and flow pulse results from the mechanical activity associated with a single electrically evoked contraction of hindlimb muscles.

Figure 3 illustrates the experimental protocols and provides examples from a single pig of the responses typically observed. Figure 3A shows the rise in blood flow and changes in blood pressures that accompanied electrically evoked, rhythmic muscle contraction and relaxation under the normal heart-perfused condition. Blood flow was elevated above baseline in the second data point and rose from 310 to 440 ml/min within 3 s after the onset of muscle activity. Arterial pressure was well maintained, and venous pressure rose slightly.

Figure 3B shows the responses in the same animal when the muscle pump was isolated by uncoupling the heart from the hindlimb circulation (shunt perfused). Approximately 30 s lapsed from the end of the trace in Fig. 3A to the beginning of the trace in Fig. 3B. In the experiment depicted in Fig. 3B, the venous outflow tubing was clamped at the point 1 ~45 s before the onset of muscle activity. This caused venous pressure to rise slowly to ~30 mmHg. The shunt was opened at point 2 ~30 s before the first contraction, and this caused venous pressure to rise steeply until it equaled arterial pressure. Arterial inflow continued despite the absence of a pressure difference between the arteries and large veins, indicating that the smaller veins were not fully engorged with blood and that hindlimb blood volume was increasing at a rate equal to the arterial inflow. The arterial inflow tube proximal to the shunt
was clamped at point 3 ~10 s before stimulation. This caused blood flow to fall quickly to zero and arterial and venous pressures to fall to ~20 mmHg at time 0. Blood flow rose from 0 to 103 ml/min immediately after the onset of rhythmic muscular activity. This rise in blood flow nearly equaled the rise seen at the onset of heart-perfused contractions (Fig. 3, inset). Arterial and venous pressures rose 15 mmHg immediately after the onset of contractions. Thereafter, both pressures slowly fell during the period of muscular activity. The shunt was clamped for 5 s at point 4 to reestablish the zero level of blood flow about midway through the period of muscular activity. This was done to verify that electromagnetic activation of adjacent muscle did not interfere with the electromagnetic measurement of flow. The shunt was clamped and the arterial and venous tubes were opened at point 5 ~10 s after the cessation of muscular activity. This caused arterial pressure to rise markedly and venous pressure to fall. Importantly, the peak flow observed during recovery from muscular activity was similar to the flow seen at the same time in Fig. 3A during normal perfusion.

Figure 4 shows the initial (10 s) effect of muscle contraction and relaxation on blood flow from five pigs in both the heart-perfused and the shunt-perfused conditions. The increase in blood flow ranged from 58 to 175 ml/min (mean, 110 ± 21 ml/min) during heart-perfused contractions and from 60 to 118 ml/min (87 ± 11 ml/min) during shunt-perfused contractions (means are based on 1 experiment from each of the 5 pigs). The initial rise in flow was not significantly different between the two conditions (P > 0.4).

DISCUSSION

We found that the isolated skeletal muscle pump is capable of rapidly initiating and sustaining blood flow. The observed flow was achieved despite a lack of a pressure difference across the active muscles measured in the arteries and large veins in a setting where the left ventricle could not contribute energy for muscle perfusion. This result provides evidence that the mechanical forces produced during rhythmic muscle contraction and relaxation act on the muscle vasculature in a manner sufficient to generate blood flow. Although estimates of the blood volume-mobilizing (1, 2, 19–21), venous pressure-lowering (17, 21), and virtual conductance-raising (18) capabilities of the muscle pump have been provided previously, to our knowledge our study is the first to evaluate directly the effectiveness of the blood flow-generating capability of the isolated muscle pump.

Potential Limitations

There are a number of considerations to our approach of isolating the muscle pump that should be addressed. For example, we measured flow through the shunt tubing, not microcirculatory flow per se. It is assumed that blood flowed across the microcirculation back into veins; alternatively, blood may have only flowed across the shunt tubing and then accumulated within arteries. Several factors support the validity of the assumption that blood flowed through the microcirculation of the active muscle during shunt-perfused muscle contractions. First, if blood volume were simply transferred from small limb veins to limb arteries (i.e., no microcirculatory flow), arterial pressure would be expected to rise progressively throughout the period of muscular activity. Our results are clearly in contrast to this expectation. Although pressure initially rose at the onset of activity (Fig. 3B), thereafter pressure slowly fell despite continued mechanical activity of the muscles that sustained the flow of blood across the shunt into the arteries. The observation that pressure within the arteries slowly fell despite sustained inflow indicates that blood drained off faster than it was replaced. Second, it is unlikely that each succeeding muscle contraction expelled a small fraction of the blood volume originally contained in the veins because even mild contractions eject a large fraction of the blood volume contained in muscle veins (2, 5, 12, 19, 21). Rather, it is more likely that the veins were refilled by inflow from the microcirculatory vessels between each contraction. Third, because the shunt offers a negligible resistance to flow, the pressure difference across the limbs from large arteries to large veins was continuously zero, meaning there was no pressure gradient to drive flow across any regions in the hindlimbs that were not contracting skeletal muscle. Taken together, these factors indicate that a large fraction of the flow measured in the shunt tubing was propelled through the microcirculation of the quadriceps muscles.

The continuous fall in pressure during shunt-perfused muscle contractions (Fig. 3B) suggests that not all of the blood pumped by the muscle completed the circuit through its own microcirculation back to the veins; that is, if this circuit were perfectly isolated,
pressures would be expected to remain relatively stable throughout the period of muscle contractions. The fall in pressure suggests that blood volume escaped from the circuit. This could occur if blood volume was redistributed from relatively noncompliant to relatively compliant regions (e.g., from muscle to skin) within the hindlimbs, or if blood volume was pumped out of the hindlimbs via collateral venous drainage. The consistent finding that pressure was lower during periods of zero flow (essentially a “mean circulatory filling pressure” for the isolated hindlimbs) after contractions ceased than before they began implies a loss of blood volume from the hindlimbs (assuming that resting hindlimb vascular capacitance was little altered by brief periods of muscular activity). Alternatively, arteriolar dilation could cause pressure to fall by reducing the resistance through which the muscle pump drives flow. However, arteriolar vasodilation would be expected to raise flow, not lower it, and would not be expected to alter the postcontraction (zero flow) blood pressure. Muscle fatigue could also lead to diminished flow, but again, this would not be expected to reduce the postcontraction (zero-flow) pressure.

We expanded the blood content of the large veins during shunt-perfused contractions above the volume they normally contain. The reason for doing so relates to the high compliance of veins relative to arteries and the fact that the venous segment proximal to the last set of venous valves would in effect act as an extension of the terminal aorta to which it was directly connected. Thus the blood volume contained within the hindlimbs had to be large enough to ensure that this venous segment could be distended with arterial-like pressures without compromising the filling of the remaining vascular sections. We presume that the flow-generating capability of the skeletal muscle pump, isolated in this manner, is dependent on the volume of blood contained within it, as is true for the circulation as a whole (10); that is, the flow it generates could be increased (within limits) or decreased (e.g., with no volume there can be no flow) by increasing or decreasing the volume of blood contained within the hindlimbs. The observation that pressure and flow fell in parallel during shunt-perfused contractions provides evidence that the blood flow generated by the isolated muscle pump is dependent on the blood volume it contains. Importantly, we have demonstrated that the muscle pump can initiate and sustain blood flow despite a subnormal “arterial” pressure and an abnormally high “venous” pressure, both of which are expected to diminish flow.

Finally, by making the muscle pump eject blood into the arteries, we made it mimic the function of the heart. Thus, although we anatomically uncoupled the heart from the muscle vasculature, we did not delete the physiological function normally provided by the heart. Rather, we substituted the muscle pump in place of the heart by having the muscle pump perform an action (arterial refilling) that it does not ordinarily perform. Nevertheless, our results demonstrate that the mechanical forces produced during contractions cause blood to be propelled through the muscle vasculature in the absence of energy contributed by the heart.

Comparison of Heart-Perfused and Shunt-Perfused Muscle Contractions

We found that the increase in blood flow generated by the isolated muscle pump was similar to the increase in blood flow that accompanied identical contractions during normal (cardiac) muscle perfusion. Flow increased rapidly at the onset of both types of contractions; the immediate rise in blood flow at the onset of locomotion has been used as an argument for the importance of the muscle pump (18). As expected, the values of blood flow in the present study were lower than those observed during locomotion possibly because the muscle pump is less effective during electrically evoked contractions than during locomotion (13).

For the direct comparison of shunt-perfused vs. heart-perfused contractions to serve as a useful measure of the effectiveness of the muscle pump, the physical and chemical conditions in the arterial bed and microcirculation should be closely similar with respect to the stimuli that govern vascular smooth muscle tone. First, the muscles were at least initially perfused with arterial blood when the muscles were shunt perfused, not venous blood as might be expected. The shunt was opened before the onset of contractions, and this filled the shunt tubing with fresh arterial blood. The shunt then acted as a “reservoir” during shunt-perfused contractions. Inasmuch as the highest shunt flow we observed was ~100 ml/min, the volume of tubing containing arterial blood was ~50 ml, and contractions were carried out for only 20–30 s, little or no venous blood probably reached the muscles during contractions. Second, metabolic vasodilation is probably delayed after the onset of 1/s contractions (8, 15, 18), and even if rapid vasodilation occurred, we would expect it to be similar in the two conditions. Third, although the arterial distending pressure was different in the two conditions, myogenic responses to large changes in arterial pressure have little effect on muscle vascular conductance at the onset of exercise (18). Fourth, the blood flow observed seconds after shunt-perfused contractions ceased (and normal perfusion of the muscle was reinstated) was not substantially greater than the blood flow observed at the same time point after heart-perfused contractions, despite the possibility that venous blood could potentially have reached the muscles by this time after shunt-perfused contractions. The lack of a reactive hyperemia indicates that the muscles were not abnormally dilated during shunt-perfused contractions.

The lack of a reactive hyperemia is somewhat unexpected given the low arterial pressure and the presumed lack of blood flow to inactive regions (see below) that were imposed for close to 1 min. One explanation for this lack is that the arterial pulse pressure generated by the isolated muscle pump during shunt perfusion equaled or exceeded the pulse pressure generated by the left ventricle during normal (cardiac) perfusion.
These pressure pulsations could sustain myogenic vaso-

motor tone.

The vascular resistance against which the isolated muscle pump drove flow caused large vein pressure to be higher during shunt-perfused contractions than during heart-perfused contractions. Because the pressure in large veins can be viewed as the afterload against which the muscle pump ejects blood, the abnormally high venous pressure might limit the pumping capacity of the muscle pump, just as an abnormally high arterial pressure can limit ventricular stroke volume (11). However, calf contractions performed by human subjects can eject blood under thigh cuffs inflated to 90 mmHg (1) and can expel blood against the 100 mmHg venous hydrostatic pressure that develops during quiet standing. Venous pressure was typically 50 mmHg or less during shunt-perfused contractions in our experiments. Taken together, these observations indicate that the muscle pump has a relatively low “afterload” sensitivity.

Flow rose somewhat more abruptly at the onset of shunt-perfused contractions than at the onset of heart-perfused contractions. This is not unexpected. The flow we measured represents venous outflow from the muscles during shunt-perfused contractions, whereas it represents arterial inflow to the muscles during heart-perfused contractions. The venous blood ejected during a first contraction causes venous outflow to rise instantaneously in heart-perfused conditions (6), whereas arterial inflow may be initially impeded during a freely perfused contraction (4). Also, the time course of responses during heart-perfused contractions is further complicated by 1) the fact that there are two pumps arranged in series but likely operating at different frequencies, causing greater second-to-second variability of blood flow during heart-perfused compared with shunt-perfused contractions in Fig. 4; and 2) blood circulated through both active and inactive regions during heart-perfused contractions, whereas it only circulated through active muscle during shunt-perfused contractions.

The total flow generated by the isolated muscle pump (e.g., ~100 ml/min in Fig. 3B) was much less than the total flow observed during heart-perfused muscle contractions (e.g., ~450 ml/min in Fig. 3A). This is not surprising given that the arterial-venous pressure difference across the inactive tissues of the hindlimbs was zero during shunt perfusion, whereas the pressure difference across inactive regions was normal (e.g., ~70 mmHg) during heart-perfused muscle contractions. Thus a substantial portion of the flow measured during heart-perfused contractions was probably directed to inactive regions. For example, if the resting quadriceps muscles receive one-fourth of the resting terminal aortic flow, then a flow equal to three-fourths of the resting flow was directed to inactive regions during heart-perfused contractions. Conversely, presumably all of the measured flow during shunt-perfused contractions went to the active muscles.

The foregoing discussion supports the validity of comparing the initial increase in blood flow seen at the onset of shunt-perfused and heart-perfused muscle contractions and reveals that active skeletal muscle is an effective pump.

Summary

The mechanical forces produced during rhythmic muscle contraction and relaxation act on the muscle vasculature in a manner sufficient to generate blood flow. The muscle pump can initiate and sustain a significant flow despite the lack of a pressure difference across the active muscles measured in the arteries and large veins, when energy imparted by the heart and a significant hydrostatic component to blood pressure are both lacking, and under conditions where arterial pressure is abnormally low and venous pressure is abnormally high, both of which are expected to diminish flow.

This work was presented in part at the American Physiological Society intersociety meeting, “The Integrative Biology of Exercise,” in October 1996 in Vancouver, British Columbia, Canada, and was published in abstract form (Physiologist 39: A41, 1996).

This work was supported by National Heart, Lung, and Blood Institute Grant HL-46314.

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Received 19 August 1997; accepted in final form 23 January 1998.

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