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Muscle pump does not enhance blood flow in exercising skeletal muscle

JASON J. HAMANN, ZORAN VALIC, JOHN B. BUCKWALTER, AND PHILIP S. CLIFFORD
Medical College of Wisconsin and Veterans Affairs Medical Center, Milwaukee, Wisconsin 53295

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Hamann, Jason J., Zoran Valic, John B. Buckwalter, and Philip S. Clifford. Muscle pump does not enhance blood flow in exercising skeletal muscle. *J Appl Physiol* 94: 6–10, 2003. First published August 16, 2002; 10.1152/jappphysiol.00337.2002.—The muscle pump theory holds that contraction aids muscle perfusion by emptying the venous circulation, which lowers venous pressure during relaxation and increases the pressure gradient across the muscle. We reasoned that the influence of a reduction in venous pressure could be determined after maximal pharmacological vasodilation, in which the changes in vascular tone would be minimized. Mongrel dogs ($n = 7$), instrumented for measurement of hindlimb blood flow, ran on a treadmill during continuous intra-arterial infusion of saline or adenosine (15–35 mg/min). Adenosine infusion was initiated at rest to achieve the highest blood flow possible. Peak hindlimb blood flow during exercise increased from baseline by 438 ± 34 ml/min under saline conditions but decreased by 27 ± 18 ml/min during adenosine infusion. The absence of an increase in blood flow in the vasodilated limb indicates that any change in venous pressure elicited by the muscle pump was not adequate to elevate hindlimb blood flow. The implication of this finding is that the hyperemic response to exercise is primarily attributable to vasodilation in the skeletal muscle vasculature.

contraction; dog; vasodilation; exercise hyperemia; muscle contraction

THE SKELETAL MUSCLE PUMP HAS long been considered to be a rapid, localized mechanism by which blood flow could be increased to active skeletal muscle (4). It is believed that muscle contraction aids muscle perfusion by emptying the venous circulation, which lowers venous pressure during relaxation, increasing the pressure gradient across the muscle, thus facilitating an increased arterial inflow (4, 8, 19). Unfortunately, a direct test of this hypothesis is not feasible because current methodologies do not allow direct measurement of venous pressure within muscle. To date, the strongest evidence for the muscle pump has come from investigations in which blood flow was measured in contracting muscles with venous pressure manipulated by positioning the limb above or below the level of the heart (5, 11, 20, 24). The rationale for these investigations was that contraction-induced changes in venous pressure would be greater with the limb below the

heart. The enhanced blood flow response to a single contraction (24) or rhythmic exercise (11, 20) when the limb was positioned below the heart was attributed to the muscle pump. On the other hand, several investigations (9, 12, 14) have failed to find evidence for an influence of the muscle pump on blood flow in contracting skeletal muscle. These negative results may result from the nonphysiological nature of the electrically stimulated contractions employed in these investigations. As suggested by Laughlin (8), the muscle pump may be more effective in dynamic exercise than during stimulated contractions due to sequential fiber activation rather than simultaneous activation of all fibers. Whether the muscle pump serves to increase skeletal muscle perfusion during exercise is an issue of continuing debate.

Because muscle blood flow is a function of the arteriovenous pressure gradient and vascular tone, we reasoned that the influence of a reduction in venous pressure could be determined after maximal pharmacological vasodilation in which the changes in vascular tone would be minimized. From a theoretical standpoint, it should be possible to further elevate arterial inflow in the dilated vasculature by a reduction in downstream venous pressure. In this investigation, we pharmacologically vasodilated the vasculature of the dog hindlimb before the commencement of treadmill exercise. The experiments tested the hypothesis that the muscle pump is capable of enhancing blood flow under conditions where the skeletal muscle vasculature is vasodilated.

METHODS AND PROCEDURES

All experimental procedures were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the American Physiological Society's "Guide for the Care and Use of Laboratory Animals" [DHEW Publication No. (NIH) 85-23, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205]. Seven mongrel dogs (18–22 kg) were selected for their willingness to run on a motorized treadmill. Separate, sterile surgeries were performed to instrument the animals for measurement of arterial blood pressure, hindlimb blood flow, and intra-arterial drug infusion. For all surgical procedures, anesthesia was induced with thiopental sodium (15–

Address for reprint requests and other correspondence: P. S. Clifford, VA Medical Center, Anesthesia Research 151, 5000 W National Ave, Milwaukee, WI 53295 (E-mail: pcliff@mcw.edu).

30 mg/kg; Gensia Pharmaceuticals, Irvine, CA). After intubation with a cuffed endotracheal tube, a surgical level of anesthesia was maintained with 1.5% halothane (Halocarbon Laboratories, River Edge, NJ) and 98.5% oxygen. Postoperatively, animals were given an analgesic for pain management (0.3 mg of buprenorphine hydrochlorine; Reckitt and Coleman, Kingston-upon-Hull, UK) and treated with antibiotics for 10 days (1 g of cefazolin sodium; Apothecon, Princeton, NJ). For measurement of arterial blood pressure, the carotid arteries were exteriorized for percutaneous cannulation (13, 16). Measurement of hindlimb blood flow was accomplished by implantation of 4-mm ultrasonic transit-time flow probes (Transonic Systems, Ithaca, NY) around the external iliac artery of each hindlimb. Flow probe cables and connectors were tunneled under the skin to the back and externalized for access. Intra-arterial drug infusion was permitted by insertion of a heparinized catheter (0.045 in. OD, 0.015 in. ID, 60 cm length; Data Science International, St. Paul, MN) into a side branch of the femoral artery. The catheter was tunneled under the skin to the back of the dog and externalized for vascular access. Catheters were flushed daily with saline and filled with a heparin lock (100 IU heparin/ml in 50% dextrose solution) to maintain patency. At least 2 days elapsed between the final surgery and any experimental procedures.

All experiments were performed in a laboratory in which the temperature was maintained below 20°C. On the day of an experiment, animals were brought into the laboratory and placed in a sling where they rested while the flow probes were connected to a transit-time flowmeter (Transonic Systems). A 20-gauge intravascular catheter (Insyte, Becton-Dickinson, Sandy, UT) was inserted retrogradely into the lumen of the carotid artery and attached to a solid-state pressure transducer (Ohmeda, Madison, WI) for measurement of arterial pressure. After calibration of the pressure transducer and flow probes, the dog was placed on a treadmill.

Preliminary experiments were performed with each dog to determine the peak iliac blood flow to treadmill exercise at 3.0 miles/h (mild intensity) and to determine the rate of intra-arterial adenosine infusion required to elevate blood flow considerably above this level. There were 2 days of experiments. On one day, while the dog rested on the treadmill, an infusion pump infused adenosine (Sigma, St. Louis, MO) intra-arterially at a constant rate (15–35 mg/min) to achieve the highest blood flow possible. When blood flow had stabilized, treadmill exercise commenced at 3.0 miles/h while adenosine infusion continued. On another day, exercise was performed while saline (control) was infused at the same rate as the adenosine infusion before and during exercise. For each trial, the dog ran on the treadmill for a period of 1 min. The order of the two trials was randomized.

Arterial blood pressure and external iliac blood flow were recorded at 100 Hz directly to a computer (Macintosh G3) using a MacLab system (ADInstruments, Castle Hill, Australia). Data were analyzed off-line using MacLab software. In both trials, baseline measurements were averaged over the 5-s immediately before commencement of exercise and during the period of peak blood flow between 10 and 15 s of exercise. Previous experiments in this laboratory (2) demonstrated that the peak exercise blood flow in the dog is achieved over this interval. An α -level of $P < 0.05$ was used to establish statistical significance during all analyses. Statistical analyses of the data were performed with paired *t*-tests. All data are expressed as means \pm SE.

RESULTS

Figure 1 is an original tracing of the hindlimb blood flow response obtained in the experimental limb of one dog at commencement of treadmill exercise (3 miles/h) during saline (control) and adenosine infusion (vasodilated). Under the control condition, there was an immediate and rapid increase in iliac blood flow from the baseline at the onset of treadmill exercise, which reached a peak response 15 s into exercise. This hindlimb blood flow response is typical of the responses observed at onset of treadmill exercise in this laboratory. As expected, intra-arterial infusion of adenosine elevated baseline blood flow. The initiation of exercise with continued adenosine infusion failed to increase blood flow. In fact, in this case, there was an immediate, albeit small, decrease in hindlimb blood flow. It can also be seen from this tracing that the vasodilated limb blood flow remained below the baseline over the interval when blood flow peaked during the control trial.

Figure 2 summarizes the baseline and peak exercise blood flow values for the experimental limb under control and vasodilated conditions. Under control conditions, baseline blood flow with the dog resting on the treadmill averaged 137 ± 16 ml/min. After the commencement of exercise, blood flow increased significantly ($P < 0.01$), averaging 575 ± 37 ml/min between 10 and 15 s. With the dog resting on the treadmill, intra-arterial infusion of adenosine increased the baseline blood flow to 973 ± 41 ml/min. During exercise with continued infusion of adenosine, limb blood flow between 10 and 15 s was 946 ± 57 ml/min ($P > 0.05$). The magnitude of the change in hindlimb blood flow during exercise is depicted in Fig. 3. Under control conditions, exercise elicited an increase in blood flow of 438 ± 34 ml/min. In contrast, when the hindlimb was vasodilated, exercise produced a decrease in blood flow of 27 ± 18 ml/min.

During infusion at rest, mean arterial blood pressure was 106 ± 4 mmHg in the control trial and was not

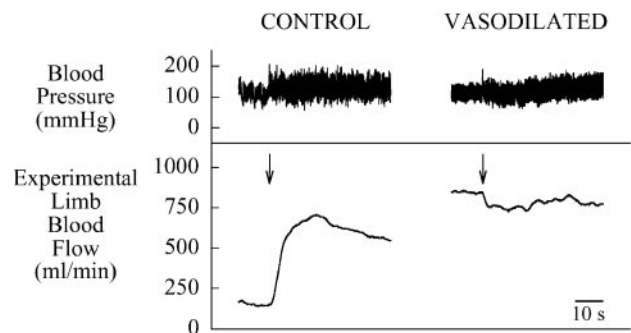


Fig. 1. Original tracings of mean blood flow (0.1-Hz filter) from the experimental hindlimb of 1 dog showing the transition from rest to treadmill exercise during an intra-arterial infusion of saline (control) or adenosine (vasodilated). Arrows indicate the commencement of exercise. Note that commencement of exercise was associated with an immediate and rapid increase in blood flow under control conditions. However, during vasodilation of the hindlimb with adenosine, there was not an increase in blood flow at the onset of exercise.

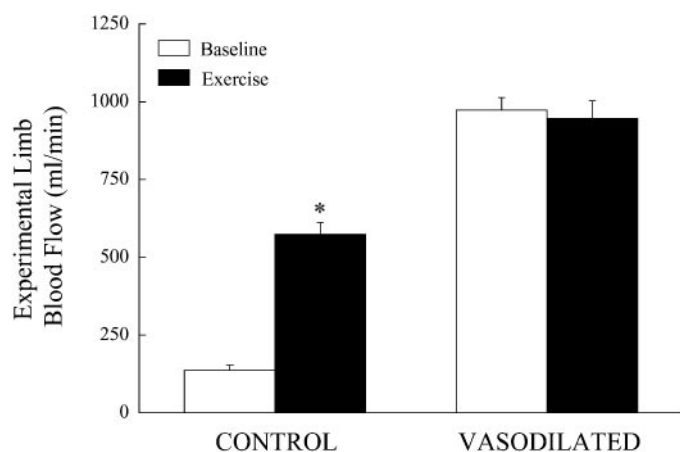


Fig. 2. Summary of the blood flow responses to treadmill exercise during control and vasodilated conditions. Baseline represents the average blood flow taken in during the 5 s immediately preceding the commencement of treadmill exercise. Exercise denotes a 5-s average blood flow taken between 10 and 15 s of exercise. Values are means \pm SE. * $P < 0.01$.

different from adenosine infusion (112 ± 1 mmHg). Mean arterial pressure between 10 and 15 s of exercise was not different between trials (113 ± 4 and 108 ± 2 mmHg for saline and adenosine, respectively)

DISCUSSION

The purpose of this study was to determine whether the muscle pump could increase blood flow to exercising skeletal muscle under conditions where the vasculature was artificially vasodilated. The fact that the blood flow to the vasodilated limb did not increase on commencement of exercise indicates that any change in venous pressure elicited by the muscle pump was not sufficient to elevate blood flow through the limb. This finding suggests that the initial increase in skeletal muscle blood flow on initiation of exercise is primarily attributable to local vasodilation in the skeletal muscle vasculature rather than a change in perfusion pressure evoked by the muscle pump.

The muscle pump theory holds that muscle contraction aids muscle perfusion by emptying the venous circulation, which lowers venous pressure during relaxation, increasing the pressure gradient across the muscle, thus facilitating an increased arterial inflow (4, 8, 19). The conceptual basis for the understanding of the muscle pump comes from an extension of Ohm's law, which describes flow through a vessel as the product of the pressure gradient along the vessel and vascular conductance, $\dot{Q} = (P_a - P_v) \times \text{conductance}$ (where P_a and P_v are arterial and venous pressures, respectively). Current technical limitations do not permit direct measurement of venous pressure with skeletal muscle; therefore, investigators have been forced to make inferences about venous pressure within muscle from indirect measurements and calculations. We reasoned that the influence of a change in muscle perfusion pressure (i.e., decrease in venous pressure) on blood flow could be determined if the skeletal muscle vasculature was vasodilated before commencement of exer-

cise. Under conditions in which the hindlimb is maximally vasodilated with adenosine, changes in local vascular tone are minimized and the effect of the muscle pump should be manifest. A straightforward interpretation of our data is that the magnitude of the change in venous pressure elicited by the muscle pump was inadequate to elevate blood flow at the onset of exercise.

An essential, yet speculative, feature of the muscle pump theory is the notion that veins are tethered to the surrounding tissue, resulting in an abrupt decrease in venous pressure at the beginning of relaxation (8). Several laboratories have attempted to quantify the venous pressure required to achieve the augmented blood flow observed during muscle contractions. Their calculations provide estimates ranging from -30 mmHg in dogs to -400 mmHg in exercising humans (8, 15, 18, 23). Whether negative venous pressures of this magnitude can be produced is not known. However, in our opinion, negative venous pressures would be unlikely to affect arterial inflow due to a vascular waterfall effect. A vascular waterfall effect is a situation that exists when blood flow through the muscle is determined by the difference between the arterial pressure and the critical opening pressure of the veins (17), not the absolute venous pressure. There is experimental evidence to support the idea that the microcirculation of skeletal muscle serves as a vascular waterfall and venous pressure changes elicited by muscle contraction do not influence arterial inflow (12, 14, 21). From the above argument, it seems doubtful that the initial hyperemic response to exercise can be accounted for solely by changes in venous pressure elicited by the muscle pump.

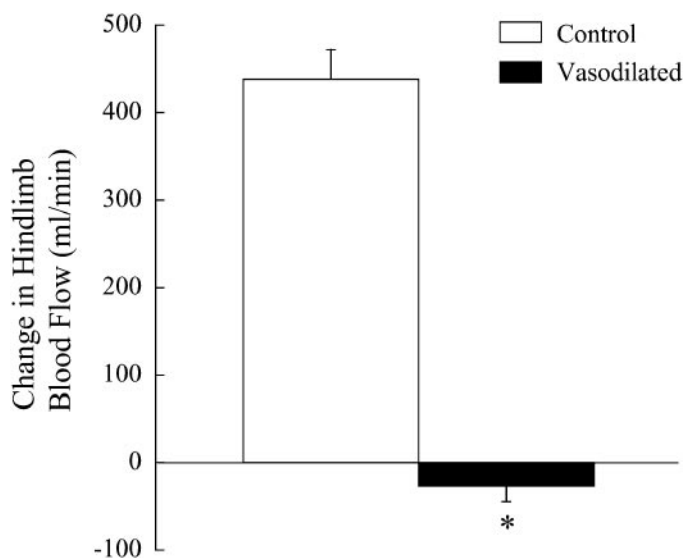


Fig. 3. Magnitude of the change in hindlimb blood flow resulting from the onset of treadmill exercise during control and vasodilated conditions. The change in blood flow was determined as the difference between the resting baseline and the level obtained between 10 and 15 s of exercise. Commencement of treadmill exercise resulted in no significant change in flow in the vasodilated hindlimb. Values are means \pm SE. * $P < 0.01$.

On the other hand, there is evidence to support the concept that the muscle pump can influence blood flow to contracting skeletal muscles. Mechanical forces of contraction have been shown to be sufficient to initiate and maintain blood flow across an isolated muscle vascular bed (19). Several key studies have been performed based on the idea that contraction-induced changes in venous pressure would be greater when resting venous pressure was raised by manipulating the position of the exercising limb. Steady-state leg blood flows were higher in human volunteers exercising in a head-up tilted posture compared with the supine posture (5, 11). Similarly, forearm blood flow was higher with the arm positioned below the heart than when the arm was above the heart (20, 24). In addition, Tschakovsky et al. (24) employed rapid cuff inflations of the forearm to mimic the mechanical effect of muscle contraction. Rhythmic cuff inflations increased forearm blood flow when the arm was positioned below the heart but not above the heart. The enhanced blood flow response to contractions or cuff inflations when the limb was positioned below the heart provide evidence to support a role for the muscle pump in regulating skeletal muscle blood flow during exercise.

Several authors have concluded that the exercise hyperemia observed in their studies was the result of changes in perfusion pressure elicited by the muscle pump acting in concert with rapid metabolic vasodilation (11, 20, 24, 25). The paramount question regarding the muscle pump is as follows: in the absence of concurrent vasodilation, can the muscle pump elevate blood flow? To address this issue, Naamani et al. (14) maximally vasodilated diaphragm and gastrocnemius muscle of anesthetized dogs before initiating contractions. Their data showed that muscle contractions did not further increase blood flow, except in the case of spontaneous contractions of the diaphragm. To this end, data from the companion manuscript (3) support the concept that blood flow is not augmented by the muscle pump in maximally vasodilated gastrocnemius muscle of anesthetized dogs. One drawback of the *in situ* exercise model used by Naamani et al. (14) and Dobson and Gladden (3) is that electrical stimulation simultaneously activates all the fibers within the muscle (synchronous contractions). The relevance of the nature of contraction, whether elicited physiologically or by electrical stimulation, has prompted discussion as to whether the muscle pump is more effective in dynamic exercise when the muscles are contracting asynchronously (8). Support for this notion was based on the fact that spontaneous diaphragmatic contractions elevated flow (14). In the present investigation, the state of vasodilation of the hindlimb vasculature was fixed by infusion of a potent vasodilator and voluntary contractions were performed by conscious dogs. Under these conditions, the muscle pump failed to increase blood flow to the exercising muscle.

There are several advantages to our experimental approach compared with previous investigations. First, we used conscious animals that performed dy-

namic exercise on a treadmill. It has been suggested that the muscle pump may be more effective in dynamic exercise than in models of exercise (8). Unlike *in vitro/in situ* models of exercise, which produce synchronous contractions via electrical stimulation, conscious locomotory exercise produces contractions that are asynchronous in nature. Second, blood flow to the exercising hindlimbs was measured continuously by using transit-time ultrasonic flow probes. This enabled us to follow the time course of changes in hindlimb blood flow at the onset of treadmill exercise. Third, the limited instrumentation employed in this investigation should have had minimal effects on venous vascular mechanics. Laughlin and Schrage (9) emphasized the possibility that extensive instrumentation may alter the vascular mechanics of the venous circulation. Fourth, our experimental model affords the ability to produce local vasodilation of one hindlimb via intra-arterial infusion of pharmacological agents (adenosine) without the confounding effects of systemic cardiovascular alterations.

A potential limitation to this investigation results from the elevated arterial inflow rates employed. The ability of the muscle pump to elevate blood flow is theoretically dependent on the enhanced arteriovenous pressure gradient following muscle contraction. Under conditions of high arterial inflow, the duration of an enhanced pressure gradient would be shortened due to the rapid refilling of the venous volume displaced during muscle contraction. In the present investigation, elevated resting blood flows may have reduced the ability of the muscle pump to function when contractions were initiated, but it seems unlikely that this factor could account for the total absence of a muscle pump effect.

It is clear from continuous recordings of venous outflow (1, 3, 22) that skeletal muscle contraction expels blood from the veins within the muscle. If venous expulsion has no effect on arterial inflow, as indicated by the present data, does it serve another physiological function? Initially, the muscle pump was considered an aid to venous return (7, 22). Skeletal muscle contraction causes translocation of blood from the venous circulation toward the heart, which contributes to the increase in cardiac output at the commencement of exercise. However, the volume of blood pumped out by each contraction is determined by the volume of blood contained in the intramuscular veins and capillaries, which is a function of the arterial inflow. In other words, the muscle pump can only expel the volume of blood provided by the arterial inflow. This issue bears a remarkable similarity to the debate in the late 1970s about the factors controlling cardiac output (6, 10). Guyton (6) argued that cardiac output is dependent on venous return and that the heart can only pump what has been returned to it. We believe that this is analogous to the relationship that exists between venous outflow and arterial inflow to contracting skeletal muscle. The venous outflow is regulated by the arterial inflow and not vice versa.

In this study, we isolated the effect of the muscle pump on the initial hyperemic response to dynamic exercise by pharmacologically vasodilating the vasculature of the hindlimb before the commencement of dynamic exercise. The data reveal that the muscle pump cannot by itself elevate skeletal muscle blood flow under conditions of high arterial inflow. Thus it is our contention that rapid vasodilation must occur at exercise onset to immediately increase blood flow to the working skeletal muscles. Further research is needed to identify the local mechanism(s) that provides the link between muscle activation/contraction and local vasodilation.

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