MUSCLE BLOOD FLOW RESPONSE TO CONTRACTION:
INFLUENCE OF VENOUS PRESSURE

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ABSTRACT

The skeletal muscle pump is thought to be at least partially responsible for the immediate muscle hyperemia seen with exercise. We hypothesized that increases in venous pressure within the muscle would enhance the effectiveness of the muscle pump and yield greater postcontraction hyperemia. In nine anesthetized beagle dogs, arterial inflow and venous outflow of a single hindlimb were measured with ultrasonic transit-time flowprobes in response to 1 sec tetanic contractions evoked by electrical stimulation of the sciatic nerve. Venous pressure in the hindlimb was manipulated by tilting the upright dogs to a 30° angle in the headup or headdown positions. The volume of venous blood expelled during contractions was 2.2±0.2, 1.6±0.2, and 1.4±0.2 ml with the head up, horizontal, and head down positions, respectively. Although altering hindlimb venous pressure influenced venous expulsion during contraction, the increase in arterial inflow was similar regardless of position. Moreover, the volume of blood expelled was a small fraction of the cumulative arterial volume following the contraction. These results suggest that the muscle pump is not a major contributor to the hyperemic response to skeletal muscle contraction.

Key Words: exercise, hyperemia, muscle pump, vasodilation, dog
INTRODUCTION

It is well known that during exercise there is an elevation in blood flow to exercising skeletal muscle. The muscle pump is hypothesized to elevate skeletal muscle blood flow by mechanical factors (16). As the muscle contracts, it compresses the veins within the muscle and expels the venous contents towards the heart. Upon relaxation, it is hypothesized that the muscle fibers which are tethered to the walls of the veins, open the lumen of the compliant vessels and create low pressure (7, 9). Because the venous circulation contains one way valves, one way flow is assured and the enhanced arteriovenous pressure gradient results in an increase in arterial inflow to skeletal muscle (7).

Studies employing both human and animal models have shown that skeletal muscle blood flow is significantly elevated within 1 sec following the release of a brief tetanic contraction (1, 15, 18). Despite this rapid blood flow response in vivo, direct observations of arteriolar diameter reveal that dilation of the skeletal muscle arterioles occurs more slowly (4, 6, 21). Because activation of the muscle pump is temporally compatible with the immediate increase in blood flow seen at the onset of exercise, this observation has been used as prima facie evidence that the muscle pump must be responsible for the rapid increase in skeletal muscle blood flow with the initiation of exercise (16).

Fundamental to the muscle pump theory of blood flow control is that muscular contraction lowers venous pressure within the active muscle thus widening the arteriovenous pressure gradient. However, the relationship between venous pressure within the muscle prior to contraction and the ability of the muscle pump to produce skeletal muscle hyperemia is a question open for investigation (8). In the present study, baseline venous pressure in the canine hindlimb was manipulated by postural changes. As arterial pressure remained constant with
postural changes and venous pressure was elevated in the headup position, we reasoned that
maximal contraction of the hindlimb muscles should produce larger decreases in venous pressure
in the head up position compared to the head down position. Thus, we hypothesized muscle
contraction would elicit larger increases in skeletal muscle blood flow in the headup position.

METHODS

All experimental procedures were conducted in accordance with the American
Physiological Society's Guiding Principles in the Care and Use of Animals, and were approved
by the Institutional Animal Care and Use Committees of the VA Medical Center and the Medical
College of Wisconsin. Nine purpose bred beagle dogs (13±0.5 kg, mean±SEM) were used in
this study. Anesthesia was induced with bolus intravenous infusion of 100 mg/kg α-chloralose
and 500 mg/kg urethane into the antecubital vein and was maintained with continuous
intravenous infusion of 20 mg/kg/hr α-chloralose and 100mg/kg/hr urethane. The animals were
intubated and ventilated with room air using a mechanical ventilator (Harvard Apparatus, Dover,
MA). Respiratory tidal volume was set to 15 ml/kg and end-tidal Pco₂, measured with an
infrared analyzer (Ohmeda, Miami, FL), was kept in a range between 35 and 40 mmHg by
adjusting respiratory frequency. Arterial blood samples were regularly taken for measurement of
arterial Po₂, Pco₂ and pH (model ABL-30, Radiometer, Copenhagen, Denmark). If necessary,
metabolic acidosis was corrected with slow intravenous infusion of sodium bicarbonate. Body
temperature of the dogs was maintained via a heating pad (Gaymar, Orchard Park, NY).

Initial surgical procedures were performed in supine position. The carotid artery was
dissected and an intravascular catheter (18 gauge) was inserted retrogradely into the lumen and
attached to a solid-state pressure transducer (Ohmeda) placed at the level of the dog's heart for
measurement of systemic arterial blood pressure. Through an abdomino-inguinal incision, an
external iliac artery and vein were exposed and transit-time ultrasound flow probes (Transonic Systems, Ithaca, NY) placed around them for measurement of arterial inflow and venous outflow of the hindlimb. An acoustic couplant (model 1181, Nalco) was used to displace air within the probe's measurement window. In order to reduce hindlimb collateral blood flow, the internal iliac artery and vein, as well as all visible side branches within the femoral triangle were ligated. The dog's head was then positioned in a stereotaxic apparatus (Stoelting, Wood Dale, IL) secured on an aluminum platform and the torso extended by caudal tension applied via a hip-pin clamp in order to place the dog in a normal upright posture (horizontal position). To alter hindlimb venous pressure the platform was tilted at a 30° angle to situate the dog in head up (hindlimb below the heart) or head down (hindlimb above the heart). This resulted in a difference of ~25 mmHg in hindlimb venous pressure between the head down and head up position.

Contraction of the hindlimb muscles was evoked by electrical stimulation of the distal end of the sciatic nerve, which had been previously dissected and cut to avoid centrally conducted impulses along afferent nerve fibers. Two stimulating electrodes consisting of 0.20-mm-diameter Teflon coated stainless steel wires (A-M Systems, Everett, WA) were inserted into the nerve and then wrapped tightly around it in order to provide constant stimulation in all positions. To prevent movement upon hindlimb contraction that could potentially move the position of the ultrasound flow probe, the leg was secured at the ankle to the platform, insuring that all muscle contractions were isometric in nature. The minimal current required to elicit an observable contraction was defined as the motor threshold (MT) and all contractions were performed at 10 times this intensity (10 x MT). The order (headup, horizontal, or headdown) in which the influence of venous loading was examined was randomly assigned for each dog and
duplicate contractions were performed in each of the three experimental postures. The mean of
the two responses for each dog was used for statistical analysis.

*Data analysis.* Systemic arterial blood pressure and blood flow signals were
continuously recorded and stored on microcomputer (Apple G3 Power PC) using a MacLab data-
acquisition system (AD Instruments, Castle Hill, Australia) sampling at 100 Hz. Baseline was
calculated off-line as the 10 sec period prior to commencement of contraction. Peak arterial and
venous blood flows in response to contraction were recorded. In addition, since the effects of the
muscle pump should be evident in the first cardiac cycle following contraction (19), we analyzed
the arterial blood flow in the first beat following release of contraction. The volume of venous
blood expelled from the muscle during contraction was calculated by integrating the area under
the venous flow curve from the beginning of contraction to the point where venous flow returned
to baseline. Cumulative arterial blood volume passing through the limb in response to the
contraction was calculated as the integral of the area under the arterial flow curve starting at the
beginning of contraction and ending at the point where arterial blood flow returned to baseline.

*Statistical analysis.* To examine the hemodynamic response to contraction, a two-way
(time x position) repeated-measures analysis of variance was used to examine the effect of
contraction on difference in postcontraction hyperemia, heart rate, and blood pressure. One-way
repeated-measures analysis of variance was employed to examine the effect of contraction on
volume of blood expelled from venous system. Where significant F-ratios were found, a Tukey's
post hoc test was performed. Data are expressed as means ± SEM. The level of statistical
significance was set at P < 0.05.

RESULTS
Figure 1 contains original tracings from an individual dog showing blood pressure, hindlimb arterial and venous blood flow in response to a 1 sec tetanic contraction with the 3 different body positions. Figure 2 shows in more detail that there was an immediate, rapid expulsion of blood from the veins with muscle contraction. Blood flow returned to baseline (and went below baseline) within the duration of the contraction. In contrast, in every condition the arterial hyperemic response started immediately upon the release of contraction, peaked within 3-5 sec, and lasted for about 20 sec.

Data regarding the blood pressure and heart rate during the experiment are presented in Table 1. There was not a significant (p>0.05) effect of position nor was there a significant (p>0.05) effect of contraction on arterial pressure. In contrast, heart rate increased significantly (p<0.05) as posture of the dog changed from head down to head up. A 1 sec tetanic contraction did not affect (p>0.05) heart rate at any position.

Figure 3 summarizes changes in venous outflow from the hindlimb at each position. There were no significant (p>0.05) differences in baseline venous flow among the three positions. However, changes in posture significantly influenced the peak venous blood flow measurement during the 1 sec contraction, with the highest in the head up position. Figure 4 depicts the total blood volume expelled from the veins during the contraction under each condition. The blood volume expelled during the contraction was greatest (p<0.05) for the head up position.

Figure 5 shows the arterial blood flow response to the 1 sec tetanic contraction in the three different postures. Baseline arterial blood flows were not significantly (p>0.05) different among the positions. Muscle contraction produced significant (p<0.05) increases in blood flow during the first cardiac cycle following release of contraction, which were not significantly
(p>0.05) different among the positions. The peak blood flow response was also not significantly
(p>0.05) different among the positions. In addition, there was no significant (p>0.05) difference
in the cumulative volume of arterial inflow in response to muscle contraction with the 3 different
postural positions (figure 6).

DISCUSSION

There are two new important findings in the present study. First, the magnitude of the
increase in arterial blood flow to canine skeletal muscle with a brief tetanic contraction, whether
examined over the first cardiac cycle or at peak, was independent of the venous pressure in the
muscle over the range of pressures studied. Second, the volume of blood expelled by a single
contraction was a small fraction of the total increase in blood flow accumulated. These results
suggest that the muscle pump is not a major contributor to skeletal muscle hyperemia in response
to a single contraction.

Although there is an immediate increase in blood flow to active skeletal muscle with the
onset of exercise (1, 10, 11, 15, 17, 18, 20), the mechanism(s) by which this rapid increase in
blood flow occurs has remained elusive. The muscle pump theory has been proposed as a rapid,
local mechanism by which blood flow to active skeletal muscle can be regulated. The premise
behind the muscle pump theory is that muscle contractions empty the venous circulation
resulting in lower venous pressure during the relaxation phase. The reduction in venous pressure
increases the pressure gradient across the muscle vascular bed and enhances muscle perfusion.
Ideally, to support this hypothesis one need only measure the fluctuations in venous pressure
within the muscle. Unfortunately, because of the presence of venous valves and the probability
of damaging valves by inserting a catheter, it has been technically impossible to measure
pressure in the venules of skeletal muscle, so investigators have been forced to make inferences about the muscle pump from indirect data.

In accordance with the muscle pump theory, we expected that the elevated venous pressure in the muscles of the hindlimb with the dog in the headup position would permit a greater contraction-induced reduction in venous pressure which would translate to a higher blood flow response in the headup compared to the headdown position. The results indicate that changes in position altered venous pressure and influenced the amount of blood stored in the veins of hindlimb. Muscle contraction expelled significantly more blood from the venous circulation in the head up position compared to the head down position \(2.15 \pm 0.23 \text{ ml}\) vs \(1.37 \pm 0.17 \text{ ml}\), but did not affect the magnitude of muscle hyperemia following contraction, whether measured over the first cardiac cycle or at the peak. As shown in figure 5, the contraction-induced increase in arterial inflow was similar regardless of position. Thus, contrary to our hypothesis, enhanced muscle pump effectiveness was dissociated from subsequent arterial hyperemia, which is inconsistent with the concept that the muscle pump plays a predominant role in the blood flow response to a single contraction. These results add to the accumulating evidence that there is limited influence of the muscle pump on the contraction-induced increases in blood flow \(2, 5, 9, 12, 14, 15\).

By definition, the muscle pump can only influence blood flow for as long as venous pressure is reduced. Once arterial inflow replaces the volume of blood expelled during contraction, venous pressure is restored, and there can be no further effect of the muscle pump on blood flow. Therefore, the proportion of skeletal muscle hyperemia attributable to the muscle pump should be directly related to the volume of blood needed to replace the blood that was expelled from the veins by the contraction. In the present study, comparing the venous blood
volume (~2 ml) expelled by the muscle contraction to the cumulative arterial blood volume response (>30 ml) following contraction reveals that the venous volume is a relatively small proportion of the cumulative arterial volume. The amount of blood flow for which the muscle pump can be responsible is a small percentage (~6%) of the total. Furthermore, at the prevailing venous blood flows, this volume would have been refilled in <1 sec, whereas the peak blood flows were observed at ~4 sec. This temporal dissociation of the peak muscle pump effect from the peak blood flow effect argues against a predominant role of the muscle pump in contraction-induced hyperemia. In the aggregate, the above findings suggest that another mechanism (vasodilation) produces the majority of skeletal muscle hyperemia associated with a single contraction.

In contrast to our findings, other laboratories have provided evidence that the manipulation of venous pressure within the muscle enhances the effectiveness of the muscle pump. Like the present study, these studies investigated the blood flow response to contraction following venous pressure manipulations by positioning the contracting limb above or below the heart (3, 11, 17, 18). An augmented blood flow response to a single contraction (18) or rhythmic contractions (3, 11, 17) with the limb positioned below the heart was attributed to the muscle pump by these authors. It is possible that these conflicting results indicate a greater role for the muscle pump in skeletal muscle hyperemia associated with voluntary contractions compared to electrically stimulated contractions. One might speculate that for the muscle pump to be fully effective, natural patterns of muscle fiber recruitment are necessary. Nevertheless, electrically stimulated muscle contractions elicit large increases in skeletal muscle arterial blood flow indicating substantial skeletal muscle hyperemia which appears independent of the actions of the muscle pump.
Some of the support for a role for the muscle pump in the immediate increase in skeletal muscle blood flow at the onset of exercise has been spawned by the perception that skeletal muscle vasodilation occurs slowly and can not be responsible for the immediate hyperemia. The evidence for delayed vasodilation comes from \textit{in situ} and \textit{in vitro} preparations where vessels were directly visualized. Results from the cremaster muscle (4) and hamster retractor muscle (6) show a latency for vasodilation of 5-20 sec, with the delay related to vessel size. Wunsch et al. (21) investigated the response of first-order arterioles to various agents (adenosine, acetylcholine, NO, K’) and found a latency of at least 4 sec between exposure of the arterioles to these compounds and the beginning of vasodilation. On the other hand, Marshall and Tandon (13) showed that 1 sec tetanic contractions of rat spinotrapezius muscle evoked dilation of terminal arterioles in less than 2 sec. A recent publication from Tschakovsky et al. (19) argued that vasodilation, not an increase in muscle pump effectiveness, explains the contraction intensity-related increases in blood flow in the first cardiac cycle following release of contraction. This argument is strongest for contractions performed with the arm above heart level since it seems unlikely that the muscle pump would be capable of substantial reductions in venous pressure with the arm in this position. In view of the disagreement on this topic, it is obvious that further investigation is warranted to establish the time course of vasodilation at the onset of exercise.

In conclusion, although altering hindlimb venous pressure influenced venous expulsion during contraction, the increase in arterial inflow was similar regardless of position. Moreover, the volume of blood expelled was a small fraction of the cumulative arterial volume following the contraction. These results suggest that the muscle pump is not a major contributor to the hyperemic response to skeletal muscle contraction.
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REFERENCES


FIGURE LEGENDS

Fig. 1. Original tracings from an individual dog showing blood pressure, external iliac arterial and venous blood flow in the three experimental postures. One sec tetanic contractions were elicited by electrical stimulation of cut sciatic nerve in head down (A), horizontal (B), and head down (C) positions. The black bar shows the 1 sec contraction. Note the increased response in venous expulsion as the dog was transferred from head down to head up position.

Fig. 2. Overlapping tracings of arterial and venous mean blood flow during a 1 sec tetanic contraction (identified by horizontal bar) in a single dog. Note the rapid ejection of blood from the veins concurrent with the mechanical obstruction to arterial inflow.

Fig. 3. Venous blood flow response to muscle contraction. Baseline blood flow was similar in the three postural positions, but peak blood flow was significantly increased as the dogs were transferred from head down to head up position. * Significantly different from baseline, P<0.05.
† Significantly different from horizontal position, P<0.05.

Fig. 4. Total muscle venous blood volume expelled during a 1 sec tetanic muscular contraction. There was significant increase in the volume expelled from the veins of the hindlimb in the head up position compared to head down and horizontal postures. * Significantly different from horizontal position, P<0.05.
Fig. 5. Arterial blood flow response to muscle contraction. Shown are the significant increases from baseline to first beat and peak blood flow in all three experimental postures. There were no significant differences in baseline, first beat, or peak flows achieved among the three conditions.

* Significantly different from baseline, P<0.05.

Fig. 6. Total increase in hindlimb arterial blood volume in response to a 1 sec tetanic muscular contraction. There was not a significant difference in the increase in the arterial blood volume in response to the muscle contraction between the three conditions (p>0.05).
Table 1. Blood pressure and heart rate responses to tetanic contractions under three different postures.

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<th>BLOOD PRESSURE (mmHg)</th>
<th>HEART RATE (beats per minute)</th>
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<tr>
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<td>HEAD DOWN</td>
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</tr>
<tr>
<td>HORIZONTAL</td>
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<td>130±4</td>
</tr>
<tr>
<td>HEAD UP</td>
<td>134±5</td>
<td>132±4</td>
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Values are means ± SE. *Significantly different from horizontal position.
Figure 1

A) HEAD DOWN

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<th>Venous Blood Flow (ml/min)</th>
<th>Arterial Blood Flow (ml/min)</th>
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<td>1000</td>
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B) HORIZONTAL POSITION

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C) HEAD UP

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Figure 1
Venous blood flow (ml/min)

- **baseline**
- **peak**

**Figure 3**
Figure 4

Expelled venous volume (ml)

HEAD DOWN  HORIZONTAL  HEAD UP

*
Arterial blood flow (ml/min)

Figure 5

HEAD DOWN
- Baseline
- First beat
- Peak

HEAD UP
- Baseline
- First beat
- Peak

Horizontal
- Baseline
- First beat
- Peak

0 100 200 300 400 500

Figure 6

Cumulative arterial volume (ml)

HEAD DOWN  HORIZONTAL  HEAD UP