Blood flow response to muscle contractions is more closely related to metabolic rate than contractile work

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Hamann, Jason J., Heidi A. Kluess, John B. Buckwalter, and Philip S. Clifford. Blood flow response to muscle contractions is more closely related to metabolic rate than contractile work. J Appl Physiol 98: 2096–2100, 2005. First published February 3, 2005; doi:10.1152/japplphysiol.00400.2004.—The magnitude of the blood flow response to exercise has been linked to both the contractile work performed and the metabolic cost of the activity. Under certain conditions, contractile work and metabolic cost may be dissociated. This study examined the blood flow response to trains of contractions when contraction duration was manipulated under conditions of similar tension-time indexes (isometric analog of work). Previous investigations have shown that trains of short-duration contractions have a greater ATP utilization, which may result from an augmented ion transport required for muscle activation and relaxation. On the basis of these findings, we hypothesized that the blood flow response would be greater to a train of short-duration contractions than a train of long-duration contractions. Canine gastrocnemius-plantaris muscle (n = 8) was isolated, and blood flow assessed with an ultrasound flow probe placed around the popliteal artery. The sciatic nerve was stimulated to produce two contraction protocols that resulted in similar contraction-to-rest ratios: short duration: 0.25 s/0.75 s vs. long duration: 1 s/3 s. In accord with the design of the experiment, the tension-time indexes were identical for the two contraction protocols (short: 18.6 ± 1.0 vs. long: 18.6 ± 1.0 K N⋅s). Steady-state oxygen consumption was greater in the short-duration contractions (17.2 ± 0.9 ml/100 g⋅1⋅min⁻¹) than in the long-duration contractions (11.7 ± 0.7 ml/100 g⋅1⋅min⁻¹). Similarly, the steady-state blood flow was greater in contractions of short duration (125 ± 7 ml/min) compared with long-duration contractions (92 ± 7 ml/min). Contractions of short duration resulted in significantly higher oxygen consumptions and blood flows compared with contractions of long duration despite the same total contractile work. The blood flow response to muscle contraction appears to be more closely associated with muscle metabolism than contractile work performed.

exercise; skeletal muscle; hyperemia; oxygen consumption

SKELETAL MUSCLE BLOOD FLOW increases in response to contractile activity, the magnitude of which appears to be associated with indexes of muscle contractile work and metabolic cost. This relationship has been demonstrated by a coupling of blood flow to running speed (21), contraction frequency (5, 8, 23), power output (28), and oxygen consumption (VO₂) (1, 2, 7, 25). However, it is unclear from these investigations which factor, contractile work or metabolic rate, exerts more influence on steady-state blood flow.

Although there is general agreement that muscle contractile work and metabolic cost are related, they may be dissociated under certain conditions. Data from several investigations suggest that the duration of each muscle contraction can significantly affect the metabolic energy requirements of contracting muscle (19, 26, 30). Under conditions of similar muscle contractile work, short-duration contractions resulted in significantly higher VO₂ and rate of ATP utilization (6, 9, 19). The difference in metabolic rate between short- and long-duration contractions is independent of force generation and believed to be the result of augmented ATP utilization required for ion transport of muscle activation and relaxation in short-duration contractions (6, 9, 19, 31). Because steady-state blood flow is thought to be controlled by the production of metabolic vasodilators, metabolic sequelae related to contraction duration may have some implications for local blood flow control. However, the blood flow response to repetitive muscle contractions of short and long duration is not known.

In the present study, we sought to examine the blood flow response to short- vs. long-duration contractions under conditions where the tension-time indexes (TTI; isometric analog of work) remained constant. These manipulations were intended to help clarify whether blood flow is more closely related to muscle contractile work or metabolic rate. A recent investigation using the same experimental preparation found that short-duration contractions yielded a higher VO₂ but that blood flow was held constant (19). We hypothesized that the magnitude of the blood flow response to a train of short-duration contractions would be greater than to a train of long-duration contractions even though the TTIs were matched.

METHODS

All experimental procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the American Physiological Society’s Guiding Principles in the Care and Use of Animals. Eight mongrel dogs (19–24 kg) of either sex were studied under this experimental protocol. Each animal was obtained after an overnight fast. Anesthesia was induced with 100 mg/kg α-chloralose and 500 mg/kg urethane given intravenously, and a deep surgical plane of anesthesia was maintained with a constant infusion of 20 mg⋅kg⁻¹⋅h⁻¹ α-chloralose and 100 mg⋅kg⁻¹⋅h⁻¹ urethane. The animals were intubated with auffed endotracheal tube and ventilated with room air by using a mechanical ventilator (Harvard Apparatus, Dover, MA). End-tidal CO₂ was measured with an infrared analyzer (Ohmeda, Miami, FL) and adjusted to 35–40 Torr by alterations in respiratory frequency. Core temperature was measured with a rectal thermometer and maintained at ~37°C with a heating pad placed under the animal. All animals were euthanized with an overdose of anesthetic and potassium chloride at the end of the experiments.

Surgical preparation. The left gastrocnemius-plantaris (GP) muscle group was surgically isolated as previously described (15, 18, 32). Briefly, a medial incision was made through the skin of the left

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hindlimb from the mid thigh to the ankle. To expose the GP, the insertion tendons of the muscles overlying the GP were cut and the muscles retracted. The arterial circulation to the GP was isolated to perfusion by the popliteal artery. Venous outflow from the GP was isolated to the popliteal vein. Blood flow was measured with a transit-time ultrasonic flow probe (Transonic Systems, Ithaca, NY) placed around the left popliteal artery. Arterial blood pressure was measured by using a cannula inserted retrogradely into the lumen of the carotid artery and attached to a solid-state pressure transducer (Abbott, North Chicago, IL). The carotid artery cannula also provided a site for arterial blood sampling. A catheter in a side branch of the left popliteal vein provided the site for venous blood sampling.

A portion of the calcaneus, with the tendons of the GP attached, was cut and connected via a short coupler to an isometric load cell (model SM-250, Interface, Scottsdale, AZ). The load cell was calibrated with known weights before each experiment. After surgical isolation of the GP, the muscle was bathed in saline heated to 37°C, and covered with saline-soaked gauze and a thin piece of plastic to prevent drying and cooling. Both the femur and the tibia were fixed to the base of the force platform by using bone screws and connecting rods. The sciatic nerve was exposed and isolated near the GP. The distal stump of the nerve, 1.5–3.0 cm in length, was wrapped with two wire loops (catalog no. 7920, A-M Systems, Carlsborg, WA) for stimulation. Isometric tetanic contractions were evoked by stimulation with trains of stimuli (0.2-ms pulse duration, 40-Hz frequency) at 10× motor threshold. The minimum current required to elicit a visible contraction was defined as the motor threshold.

Before each experiment, the optimal length ($L_o$) of the GP was determined by progressively lengthening as the muscle was stimulated (1-s contraction) until a peak in developed tension (total minus resting tension) was observed. Once surgical isolation of the GP was complete, all equipment was in place, and $L_o$ was determined, the muscle was allowed to rest for a minimum of 10 min while blood gases and pH were measured (model ABL520, Radiometer, Copenhagen, Denmark). If necessary, metabolic acidosis was corrected with intravenous infusion of sodium bicarbonate. When all blood values were within normal limits, the experiment commenced.

Experimental protocol. Each GP was stimulated for two 150-s contraction periods in a balanced-order arrangement. As designed, the two contraction periods had stimulation patterns that resulted in similar duty cycles (1.3 contraction-to-relaxation ratio) with the differences in the two contraction periods being in the contraction duration (short duration 0.25-s stimulation/0.75-s relaxation vs. long duration 1-s stimulation/3-s relaxation) and number of contractions. A representative sample of the muscle contractile force produced by the two stimulation patterns is presented in Fig. 1. The contraction periods were matched for total time of muscle stimulation and number of stimulation impulses. The two contraction periods were separated by 30 min of rest.

Measurements. Arterial blood pressure, popliteal blood flow, and muscle force production were displayed continuously and stored by using a Maclab data-acquisition system sampling at 100 Hz (AD Instruments, Castle Hill, Australia). Data were analyzed offline by using Maclab software for the calculation of the hemodynamic and muscle force data. Baseline hemodynamic measurements were averaged over the 10 s immediately preceding each contraction period. Steady-state blood flow and blood pressure were averaged over the last 10 s of each contraction period. Initial and final force values were determined as the highest force attained for the first and last individual contraction within a contraction period. The total TTI was calculated by integrating the muscle force tracings for the entire contraction period. This measure provides an index of external work and does not account for internal work performed by the muscle against series elastic elements. Muscle fatigue was calculated as the force produced during the final contraction expressed as a percentage of the initial contractile force for each contraction period. Steady-state arterial and venous blood samples were drawn simultaneously, under anaerobic conditions, at rest and during the last few seconds of each stimulation period for the determination of muscle VO2. Blood samples were analyzed with a blood-gas analyzer (modelABL520, Radiometer) and hemoximeter (model OSM3, Radiometer) set for canine blood. VO2 by the GP was calculated from blood flow and arteriovenous oxygen content difference. It has been shown previously that muscle blood flow and VO2 are near steady state by the end of a 2-min contraction period in this preparation (4). Immediately after termination of the experiment, the GP was removed, dissected free of connective tissue, and weighed.

Statistical analysis. Statistical analyses of differences in blood pressure, blood flow, muscle force production, and blood values between the two protocols were performed by using a paired t-test. Data are presented as means ± SE. The level of statistical significance was set at $P < 0.05$.

RESULTS

Mean muscle weight of the GP ($n = 8$) removed at the end of the experiments was $94 ± 4$ g. There were no differences in baseline blood flows between contractions of short duration ($23 ± 4$ ml/min) and long duration ($24 ± 5$ ml/min). Baseline blood pressure was also not different between short- ($160 ± 4$ mmHg) and long-duration ($161 ± 3$ mmHg) contractions. Resting VO2 of the GP before contractions averaged $0.5 ± 0.1$ ml/100 g−1·min−1.

Figure 2 summarizes the steady-state blood flow and VO2 values for the GP under conditions of short- and long-duration contractions. As can be seen in the figure, short-duration contractions resulted in significantly greater muscle blood flow and VO2 compared with long-duration contractions. To further examine the relationship between muscle blood flow and VO2, we calculated the increase in muscle blood flow per unit increase in VO2 (Δblood flow/ΔVO2) for each animal for both protocols. The ratios were not different ($P = 0.57$) between short- (6.1 ± 0.4) and long-duration (6.0 ± 0.5) contractions. It should be noted that blood pressure was not different during the two contraction protocols (short, $161 ± 4$ vs. long, $160 ± 3$ mmHg).

![Fig. 1. Original tracings of muscle force from the gastrocnemius-plantaris muscle group during the 2 contraction periods in 1 dog. The arrow indicates the start of the contraction period with 4 s of data presented. During the long-duration contraction protocol (solid line), there is 1 contraction for every 4 contractions in the short duration contraction protocol (dashed line). Note that during the baseline period the muscle force is not zero because the muscle has been set to optimal length.](http://jap.physiology.org/doi/10.1152/jappl.00003.2005)
Data for muscle force production are presented in Table 1. In accordance with the experimental protocol, TTI was not different between the two contraction protocols ($P > 0.05$). Figure 3 is a summary of the muscle force production during the two contraction periods. The short- and long-duration contractions displayed a similar rate of decline in force production during the contraction periods.

Table 2 presents the blood values corresponding to the two contraction protocols. There were no significant differences between steady-state blood gases and indexes of acid-base balance during the two contraction protocols. However, short-duration contractions exhibited a greater oxygen extraction than did the long-duration contractions.

### DISCUSSION

The purpose of this study was to determine whether repetitive muscle contractions of short duration result in a greater blood flow response than repetitive contractions of long duration under conditions of identical contractile work (TTI). The major new finding from this investigation is that trains of short-duration contractions result in significantly higher blood flows compared with trains of long-duration contractions. As expected, metabolic rate, as determined by muscle $V\dot{O}_2$, was also higher during contractions of short duration even though contractile work was the same between the two contraction protocols. These results provide direct evidence that the blood flow response to repetitive contractions is more closely related to muscle metabolism than contractile work.

Numerous investigations have shown that blood flow is related to work performed and/or the metabolic cost of the activity (1, 2, 5, 7, 8, 21, 23, 25, 28). However, in these previous studies, no attempts were made to determine which factor, contractile work or metabolic rate, determines steady-state blood flow. Although contractile work and metabolism are generally thought to be related, they may be dissociated under certain conditions. There are two examples of this: 1) heavy-intensity constant-workload exercise and 2) manipulations of frequency and duration of contraction at constant work rate.

During constant-load heavy-intensity exercise, muscle $V\dot{O}_2$ may be greater than predicted from the $V\dot{O}_2$/work rate relationship during moderate-intensity exercise. This additional increment in muscle $V\dot{O}_2$ is referred to as the slow component of $V\dot{O}_2$. During the $V\dot{O}_2$ slow component, muscle $V\dot{O}_2$ uptake and limb blood flow increase in concert (3, 20, 22, 27, 34). The coupling of blood flow with muscle metabolism rather than work rate during the slow component is in agreement with the results of the present investigation.

In a variety of modes of locomotion, the metabolic cost is increased with increased contraction frequency (11, 24, 33). Data collected during steady-state contractions by Hogan et al. (19) showed a dissociation of contractile work and metabolism on the basis of duration of contraction. When total contraction time was kept constant, trains of short-duration contractions had a higher energy cost than trains of long-duration contractions. However, the data were collected under constant blood flow and $V\dot{O}_2$ were significantly higher during short- vs. long-duration contractions. There were no significant differences between steady-state blood gases and indexes of acid-base balance during the two contraction protocols. However, short-duration contractions exhibited a greater oxygen extraction than did the long-duration contractions.

### Table 1. Values of muscle force during the two contraction protocols

<table>
<thead>
<tr>
<th>Contraction Duration</th>
<th>Long</th>
<th>Short</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial developed force, N</td>
<td>559±26</td>
<td>467±19*</td>
</tr>
<tr>
<td>Final developed force, N</td>
<td>498±28</td>
<td>391±12*</td>
</tr>
<tr>
<td>Fatigue index, %</td>
<td>89±2</td>
<td>84±2</td>
</tr>
<tr>
<td>TTI, kN·s</td>
<td>18.6±1.0</td>
<td>18.6±1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. TTI, tension-time index. *Significantly different from long-duration contractions, $P < 0.05$.

### Table 2. Steady-state blood values during the two contraction protocols

<table>
<thead>
<tr>
<th></th>
<th>Long</th>
<th>Short</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{aO_2}$, Torr</td>
<td>81±4</td>
<td>80±4</td>
</tr>
<tr>
<td>$P_{aCO_2}$, Torr</td>
<td>45±1</td>
<td>45±2</td>
</tr>
<tr>
<td>$C_{aO_2}$, vol%</td>
<td>20.0±0.8</td>
<td>19.8±0.9</td>
</tr>
<tr>
<td>$O_2$ extraction, %</td>
<td>61±2</td>
<td>67±2*</td>
</tr>
<tr>
<td>pH,</td>
<td>7.37±0.01</td>
<td>7.35±0.01</td>
</tr>
<tr>
<td>[HCO$_3^-$], mM</td>
<td>24.9±0.4</td>
<td>24.5±0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. $P_{aO_2}$, arterial $P_{O_2}$; $P_{aCO_2}$, arterial $P_{CO_2}$; $C_{aO_2}$, content of arterial $O_2$; $pH$, arterial pH; [HCO$_3^-$], bicarbonate concentration. *Significantly different from long-duration contractions, $P < 0.05$.
flow conditions and provide no insight as to the effect of enhanced energy demands on blood flow. We utilized the demonstrated difference in energy costs between contractions of varying duration to determine whether muscle blood flow is more strongly coupled to contractile work performed or metabolic rate. Using the same experimental preparation as Hogan et al., we found that short-duration contractions have a higher metabolic demand and a correspondingly elevated blood flow.

Recently, muscle VO$_2$ and blood flow were measured during knee-extensor exercise performed at low and high contraction frequencies under conditions of similar power output (14). Similar to the present findings, both metabolic demand and blood flow were greater during high-frequency contractions. It should be pointed out that maintaining a constant total power output (internal and external) in the knee-extensor model required estimation of the internal power, whereas no estimation was performed in the present study.

The total metabolic energy cost for muscle contraction is determined by the summed ATPase activity of the muscle. In addition to the ATP required by the actomyosin ATPase for force generation (i.e., contractile work), ATP is also utilized for nonforce generating processes such as Ca$^{2+}$ sequestering by the sarcoplasmic reticulum and membrane ion pumping (i.e., Na$^+$-K$^+$ pump). Numerous investigations have shown that the metabolic energy requirements are influenced by contraction duration (19, 26, 30). During a single contraction, the ATP cost is greater at contraction onset than the cost to maintain the developed force (12, 13, 16, 29). The increased ATP utilization during the onset of muscle contraction is used to support ion transport related to activation and relaxation (6, 9). Because short-duration contractions have a higher metabolic requirement and because steady-state blood flow during exercise is thought to be controlled by metabolically produced vasodilator substances, we questioned whether the magnitude of the blood flow response would also be higher. The present data show a greater blood flow and VO$_2$ during short-duration contractions. This finding provides evidence that muscle contractile work is not the primary determinant of blood flow and supports the idea that steady-state blood flow is sensitive to changes in metabolic rate. The present data also extend the findings from a previous investigation showing that the blood flow response to a single contraction is not determined solely by muscle contractile work (17).

How does the enhanced metabolic rate with short-duration contractions result in an augmented muscle blood flow? Traditionally, it has been thought that skeletal muscle fibers govern their own blood flow through the release of vasoactive metabolites produced in accordance with the metabolic demand of the tissue. This view of local blood flow control has been termed the “metabolic theory.” Although it has been argued that the time required for metabolite production, accumulation, and diffusion is too long to account for the initial increase in blood flow at the onset of exercise, during steady-state exercise (as in the present study), this temporal factor is not an issue. During steady-state exercise, the estimated energy costs from aerobic and anaerobic pathways is greater in short-duration contractions (19). Therefore, it is reasonable to assume that substrates or products of metabolism are responsible for regulating steady-state blood flow. Although many metabolic vasodilators (e.g., adenosine, ATP, H$^+$, lactate, nitric oxide, oxygen) have been suggested to play a role in exercise hyperemia, none has been shown to be essential for steady-state blood flow control. For a recent review of the evidence for and against potential vasodilators involved in exercise hyperemia, see Clifford and Hellsten (10). In the present investigation, muscle VO$_2$ and blood flow were both higher during trains of short-duration contractions than during trains of long-duration contractions. Because muscle contractile work was identical between the contraction protocols, it appears from the present data that a factor related to muscle metabolism influences steady-state blood flow. The idea that blood flow is linked to metabolism is supported by the fact that the ratio of the increase in blood flow for a given increase in muscle VO$_2$ was not different between the two contraction protocols. This finding substantiates the conclusion that the increase in blood flow was coupled to the increase in VO$_2$. However, the present data provide no additional insight as to the specific substance(s) that links the blood flow to metabolic rate.

In conclusion, our data show that, under conditions of identical contractile work, blood flow is higher during a train of short-duration contractions than during a train of long-duration contractions. In addition, the present investigation supports the finding that short-duration contractions have a higher energy cost than contractions of long duration. Taken together, it appears that short-duration contractions have a higher blood flow response due to a greater metabolic demand and suggests that the blood flow response to repetitive contractions is more closely associated with muscle metabolism than contractile work.

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