Effects of ischemia on $\dot{V}O_2$, tension, and vascular resistance in contracting canine skeletal muscle

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GORMAN, M. W., J. K. BARCLAY, AND H. V. SPARKS. *Effects of ischemia on $\dot{V}O_2$, tension, and vascular resistance in contracting canine skeletal muscle.* J. Appl. Physiol. 65(3): 1075–1081, 1988.—This study examined the changes in O_2 consumption ($\dot{V}O_2$), vascular resistance, and tension development during skeletal muscle contractions at reduced flow. We tested the hypothesis that when $\dot{V}O_2$ is limited by O_2 supply, the skeletal muscle vasculature is not maximally dilated because of the fall in contractile force that accompanies the decrease in O_2 supply. During 30 min of ischemic contractions, tension fell by 45 ± 4% and $\dot{V}O_2$ fell 54 ± 1% from preischemic levels. The O_2 cost per unit tension did not change compared with nonischemic muscles. After the initial flow reduction, flow fell an additional 16 ± 3% over 30 min. Adenosine infusion after 30 min of ischemic contractions increased flow by 42 ± 3% but increased $\dot{V}O_2$ by only 9.8 ± 2.3% and had no effect on tension development. When perfusion pressure was returned to normal after 30 min of ischemic contractions, twitch tension did not begin to recover within 20 min but tetanic tension showed a small improvement. $\dot{V}O_2$, although increased, remained well below the preischemic level. These results suggest that because of the reduced tension during ischemic contractions, the O_2 supply-to-consumption ratio is nearly normal, which could explain the presence of the vasodilator reserve. The defect in tension development is long lived, producing a "stunned" muscle in which excess O_2 supply does not restore function or $\dot{V}O_2$ to normal.

blood flow; exercise; vascular smooth muscle; adenosine

IN CONTRACTING SKELETAL MUSCLE, the linear relationship between O_2 consumption and blood flow (11) leads to the conclusion that blood flow is determined by muscle performance (metabolism) under normal conditions. When blood flow to a contracting muscle is reduced, there is a decrease in tension development, an increase in O_2 extraction, and a decrease in vascular resistance (2, 8, 14). In this situation the logical conclusion is that the normal cause and effect relationship is reversed: the flow level during ischemia determines the level of muscle performance and metabolism. At a certain level of ischemia when tension development is reduced, one would expect that the muscle resistance vessels should be maximally dilated to maximize blood flow. In the heart, however, flow reductions of ~50% do not produce maximum vasodilation (1, 5, 7, 15). We wished to determine whether this is also true in contracting skeletal muscle and to examine the effect of such ischemia on O_2 consumption and tension development. Our results indicate that a vasodilator reserve exists under certain ischemic conditions, and that the flow-to-oxygen consumption ratio is similar to that during free-flow contractions. These results suggest that during ischemic contractions the flow-metabolism relationship observed under conditions of free flow can be maintained because of the reduction in tension development and O_2 use. Since the release of vasodilator metabolites may be indirectly related to the flow-to-metabolism ratio, this could explain the lack of maximal vasodilation during ischemia severe enough to reduce tension development.

We also examined muscle performance following reperfusion after 30 min of ischemic exercise. While twitch tension did not improve during 20 min of reperfusion, tension during tetanic stimulation began to recover. This suggests that the origin of "stunned" muscle may lie in the excitation-contraction process and not within the contractile proteins.

METHODS

We anesthetized 18 mongrel dogs of both sexes with pentobarbital sodium (30 mg/kg iv); additional 30-mg doses were administered as required. Each animal received heparin (1,000 U/kg) before any cannulation. After tracheal intubation the animal was mechanically ventilated at a rate and tidal volume that maintained arterial P_{CO_2} at 30–40 Torr. Arterial P_{O_2} (92 ± 7 Torr) and pH 7.40 ± 0.02) were adjusted as necessary by the addition of 100% O_2 to the inspired air and by infusion of isotonic sodium bicarbonate. Blood gases and pH were measured using a Corning pH/blood gas analyzer.

All arteries feeding and veins draining the left gastrocnemius-plantaris muscle group were left intact. Arteries to and veins from other hindlimb areas were tied. Each preparation was completely freed from surrounding tissue with the exception of the muscle origin on the femur, which was not disturbed. A covering of moist gauze and plastic film minimized heat and water loss from evaporative drying of the preparation. The venous outflow passed through tubing connecting the femoral vein close to the preparation with the same femoral vein at the inguinal triangle. Venous blood samples were obtained from a 19-gauge butterfly infusion set inserted through the wall of the tubing close to the muscle.

The blood perfusing the muscle was drawn from a cannula in the right femoral artery and passed through tubing into a cannula placed in the left artery just proximal to the main branches entering the muscle. This tubing passed through either a Mohrman (13) or a Sigmamotor pump, which was used to control blood flow. A Statham pressure transducer attached to a sidearm of the arterial tubing distal to the pump continuously monitored perfusion pressure to the preparation. Systemic blood pressure was monitored from either the left gracilis artery or from the arterial tubing proximal to the pump. The arterial tubing contained a cannulating type electromagnetic flow probe, which we calibrated via timed blood collections at the conclusion of each experiment. Arterial occlusions provided a check of the flow probe zero.

Isometric contractions resulted from stimulation of the distal stump of the sciatic nerve of the preparation at 4 Hz. Brief, repetitive tetanic contractions resulted from stimulation for 150 ms at 40 Hz once per second. Each stimulus of 9 V and 0.2 ms was supramaximal for a given muscle. We monitored isometric tension development with a pneumatic myograph, which was calibrated with weights, or a modified Grass FT-03 force transducer. Each muscle was at the optimum length as determined from a length tension relation for that muscle.

Arterial and venous paired 1-ml blood samples were drawn anaerobically and stored in crushed ice before blood gas analysis. In the majority of experiments, an inline AVOX analyzer (16), which was calibrated by comparison with the results of the blood gas samples, was used to obtain the arteriovenous O_2 content difference. After passing through the AVOX, the blood was returned via a funnel to the contralateral femoral vein. In the remainder of the experiments, O_2 content was determined with a Lexington Instruments Lex-O_2-Con analyzer.

An injection of pentobarbital sodium humanely killed the animal at the end of the experiment. The experimental muscles were removed, cleared of connective tissue and fat, and weighed for normalization of developed tension, blood flow, and O_2 consumption to the wet weight of muscle.

Experimental protocol. Before the twitch contractions, the muscle contracted for 2 min of 60 brief, tetanic contractions per minute. After allowing the flow to return to control, the muscle was stimulated for 60–65 min at 4 twitches/s. During the first 8 min, muscle flow was increased to maintain perfusion pressure constant at 125 Torr. In time control experiments (n = 5) this pressure was maintained for the duration of the experiment. In the experimental groups, at 8 min perfusion pressure was decreased to a level that reduced the flow to ~50% of its steady-state value. The new perfusion pressure was reached in two to three steps over 1 min because of autoregulation of muscle flow. This perfusion pressure was then maintained for 30 min, while stimulation at 4 Hz continued. We then switched to brief tetanic contractions at 1 Hz for 30 s, followed by a resumption of 4-Hz twitches. In eight muscles, adenosine (10^{-2} M) was then infused intra-arterially at 1–2 ml/min for a period of 5 min. After a 5- to 10-min recovery period from the adenosine infusion, ischemia was terminated by returning perfusion pressure to 125 Torr. Reperfusion was continued for 20 min, during which time the muscle was continually stimulated at 4 twitches/s with intermittent bouts of tetanic stimulation. In some experiments we stimulated the muscles at 6–8 twitches/s briefly after the adenosine infusion to determine the effect of a higher metabolic rate on blood flow during ischemia. In experiments using the Lex-O_2-Con, arterial and venous samples were drawn just before twitch stimulation, at 8 min of stimulation, at 10, 20, and 30 min of ischemia, and at 10 and 20 min of reperfusion.

In five experiments we followed the same protocol but with a series of changes in muscle length at 8 min and after 30 min of ischemia. Muscle length was decreased in two steps from the optimal length and then was returned to optimal length. Arterial and venous paired 1-ml blood samples were drawn at each length when a steady state had been reached. These length change patterns were also performed at 8 and 38 min in the time control experiments.

In five experiments we measured the distribution of muscle blood flow with 15-μm radioactive microspheres. Before use the microspheres were agitated for at least 30 min using a vortex mixer and an ultrasonic bath; ~10 μCi of microspheres labeled with either ^{85}Sr, ^{51}Cr, or ^{141}Ce were then mixed with 1 ml of arterial blood and injected into the arterial tubing proximal to the pump during a 30-s interval. The first sphere injection was made after 5 min of 4-Hz contractions under free-flow conditions, the second injection after 30 min of ischemic contractions, and the final injection during adenosine infusion into the contracting ischemic muscle. At the conclusion of the experiment, the muscles were sectioned into 40–45 pieces, weighing from 50 mg to 4 g, and were counted for each isotope in a Packard Instruments multichannel analyzer. Counts were corrected for overlap from other isotopes, and flow was calculated for each muscle segment using a flow per counts per minute factor derived from the total muscle flow and the total counts per minute of each isotope in the muscle. Flow distribution was analyzed by calculating the mean and relative dispersion (SD/mean) for each measurement according to methods described by King et al. (10).

Calculations and statistical analysis. O_2 uptake was calculated as the product of the arteriovenous O_2 content difference and blood flow. O_2 uptake per contraction was determined by dividing the net O_2 uptake (stimulation O_2 uptake − resting O_2 uptake) by the number of twitches per minute. When time control and experimental muscles were compared as a function of time, we used mixed model analysis of variance (12) to determine whether the two groups differed. Comparison of specific time points between and within groups was done with Tukey's test. Linear regression was used to determine the relation between O_2 uptake per contraction and developed tension. The 0.05 level of significance was accepted for all statistical tests. All values presented are means ± SE.

RESULTS

The values for twitch tension, blood flow, and O_2 uptake at 8 min of stimulation in control and experimental groups (just before lowering perfusion pressure) were not significantly different. Control muscles developed 743.6 ± 41.2 N/kg of tension, whereas the muscles in the experimental group averaged 653.3 ± 42.2 N/kg. The O_2 uptake and blood flow in the control group after 8 min of 4-Hz contractions were 90.2 ± 7.1 $\mu mol \cdot kg^{-1} \cdot s^{-1}$ and 95.0 ± 13.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, respectively. The corresponding values for the experimental group were an O_2 uptake of 83.5 ± 5.0 $\mu mol \cdot kg^{-1} \cdot s^{-1}$ and a blood flow of 92.9 ± 11.8 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. The O_2 delivery (blood flow × arterial O_2 concentration) averaged 1.6 ± 0.1 times the O_2 demand (as measured by O_2 uptake) in both groups. The O_2 consumption at rest was not different with control muscles averaging 4.5 ± 0.9 $\mu mol \cdot kg^{-1} \cdot s^{-1}$ and experimental muscles 3.6 ± 0.4 $\mu mol^{-1} \cdot kg^{-1} \cdot s^{-1}$. Thus the muscles in the two groups were equivalent before the period of ischemia.

When blood flow was decreased to 50% of the 8-min value for 30 min, twitch tension decreased significantly from the time control values and remained depressed during 20 min of reperfusion (Fig. 1). The ratio of twitch tension to tetanic tension decreased from 0.39 ± 0.04 before ischemia to 0.30 ± 0.03 after 30 min ($P < 0.05$). The ratio decreased further to 0.22 ± 0.02 ($P < 0.05$) during reperfusion because the tetanic tension recovered more quickly than twitch tension. Significantly, the twitch tension stayed depressed despite the increased blood flow and O_2 delivery during reperfusion.

Blood flow data are presented in Fig. 2. In control muscles there was a slow decline in flow during 4-Hz contractions between the 8- and 38-min points, which was not statistically significant. In ischemic muscles, reperfusion led to flows equivalent to those in the control group.

The effect of ischemia on the ratio of blood flow to O_2

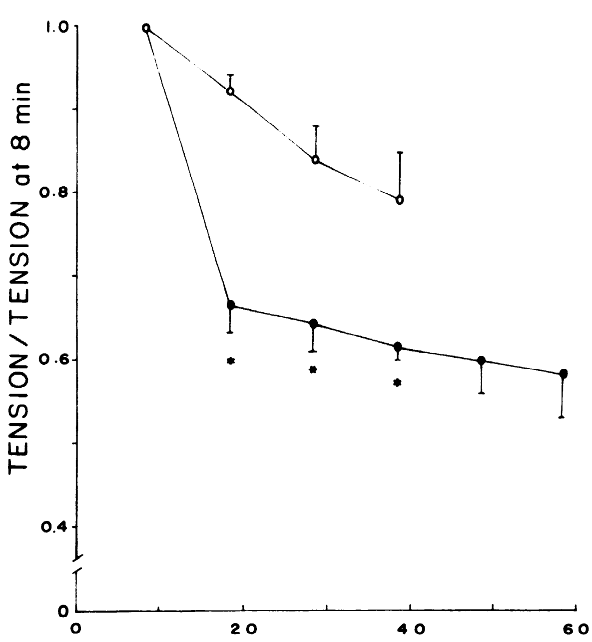

FIG. 1. Changes in twitch tension observed with time in control experiments (○) and with ischemia starting at 8 min followed by reperfusion at 38 min (●). * $P < 0.05$ compared with corresponding time control value.

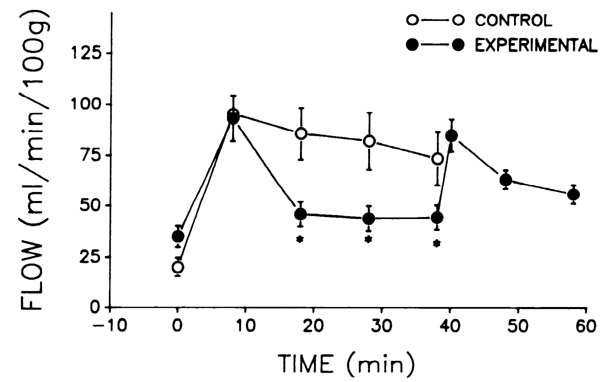

FIG. 2. Muscle blood flows. *Time 0* represents resting flow; all other flows are during 4-Hz contractions. *Time at which experimental muscles were ischemic. Since flow was not an independent variable during ischemia, no statistical test at those times is appropriate.

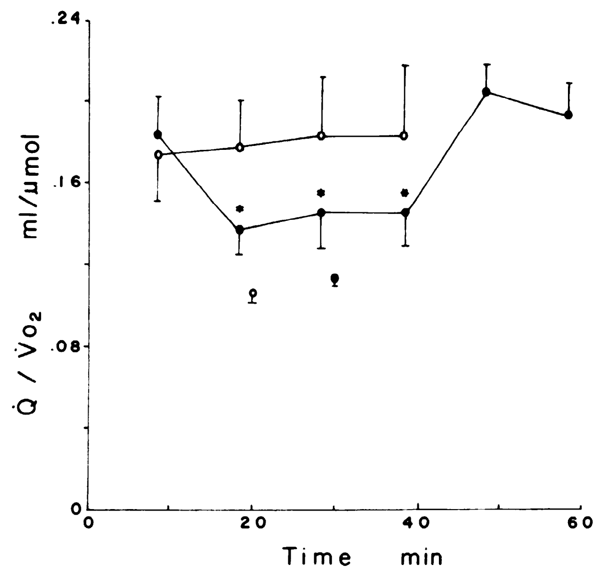

FIG. 3. A comparison of the effect of ischemia and reperfusion (●) and of time (○) on ratio of blood flow ($\dot{Q}$) to O_2 uptake ($\dot{V}O_2$). Ischemia was begun at 8 min and reperfusion at 38 min. Lower values indicated at 20 and 30 min are theoretical minimum ratios that could be reached for control and ischemic muscles assuming 100% O_2 extraction. * $P <$ 0.05 compared with 8-min point.

uptake is depicted in Fig. 3. When compared with their own control point, the ratio in ischemic muscles decreased an average of 0.045 ± 0.008 ml/μmol in the first 10 min ($P < 0.05$) and remained depressed for the duration of the ischemic period. However, the ratios in ischemic muscles were not significantly different from the time control group. The effect of ischemia on the blood gases and O_2 content in venous blood is presented in Table 1. The venous P_{O_2} decreased ~6 Torr with the 50% reduction in flow.

The O_2 cost of a Newton of twitch tension was not significantly different between control and experimental groups and did not change during the experimental period despite progressive muscle fatigue (Fig. 4). The somewhat higher means and the large standard errors in the experimental group resulted from one animal with high values. The results in Fig. 4 indicate that total O_2 consumption declines in parallel with tension during ischemia. We further analyzed the O_2 consumption in terms of tension-dependent and tension-independent O_2

TABLE 1. *Blood gases and O_2 concentration in venous blood from control and ischemic muscles*

	Time, min			
	8	18	28	38
$P\bar{v}_{CO_2}$, mmHg				
C	58.3±2.6	56.6±3.2	51.0±2.0	50.4±1.6
I	47.4±1.8*	51.8±3.3	52.3±3.1	50.9±1.6
$P\bar{v}_{O_2}$, mmHg				
C	27.9±3.3	28.3±3.4	27.4±2.8	27.9±3.9
I	25.9±2.1	20.5±2.5	19.4±2.6	20.4±2.6*
$C\bar{v}_{O_2}$, mM				
C	3.4±0.4	3.4±0.3	3.8±0.4	3.7±0.4
I	3.1±0.3	1.8±0.4	1.9±0.5	2.0±0.5*

Values are means ± SE. $P\bar{v}_{CO_2}$, mixed venous P_{CO_2}; $P\bar{v}_{O_2}$, mixed venous P_{O_2}; $C\bar{v}_{O_2}$, concentration of O_2 in mixed venous blood; C, control; I, ischemic. * $P < 0.05$ control vs. ischemic muscles.

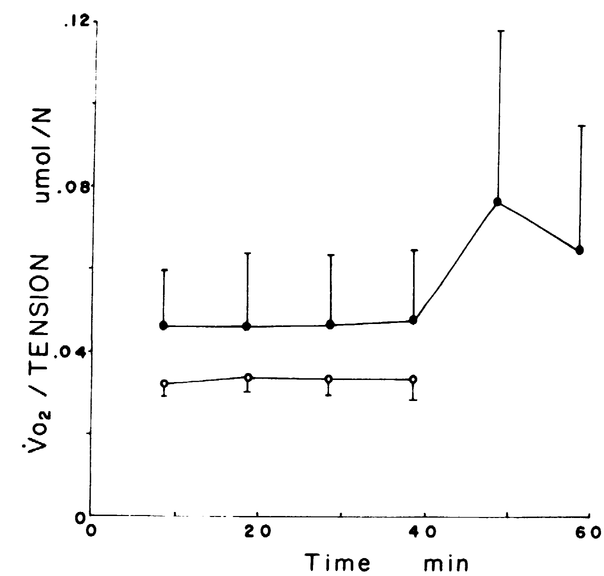

FIG. 4. Effect of time (○) and of ischemia and reperfusion (●) on O_2 cost of tension development. $\dot{V}O_2$, O_2 uptake.

uptake by varying tension through changes in muscle length before and after ischemia (Fig. 5). Tension-independent O_2 uptake is given by the y-intercept of the linear regression curve of O_2 uptake per contraction on twitch tension. Tension-dependent O_2 uptake is the slope of this linear regression line. There was no significant difference between the slope or intercept of the regression lines determined after 8 min of contractions for the control and experimental groups. Neither intercept nor slope of the regression line calculated after 38 min of contractions in control muscles was significantly different from the 8-min values. Both intercept and slope were decreased significantly by 30 min of ischemia in the experimental muscles.

Adenosine was infused after 30 min of ischemic contractions in eight dogs. In these dogs, the flow after 8 min of 4-Hz contractions at normal perfusion pressure was 85.2 ± 8.4 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. At the onset of the ischemic period, this flow was reduced to 42.0 ± 4.8 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. The perfusion pressure was reduced to 48 ± 3 Torr. During 30 min of 4-Hz contractions at this reduced perfusion pressure, flow fell further to 34.8 ± 3.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. Adenosine infusion at the reduced perfusion pressure raised this flow to 49.2 ± 5.4 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. As was the case after reperfusion, the increased flow during adenosine infusion did not result in increased tension development.

The heterogeneity of muscle blood flow, expressed as the relative dispersion, was 0.30 ± 0.03 during contractions at free flow, 0.37 ± 0.04 after 30 min of ischemic contractions, and 0.42 ± 0.06 with ischemic contractions plus adenosine infusion ($n = 5$). None of these changes was statistically significant. A histogram of the composite flow distributions during ischemic contractions with and without adenosine is shown in Fig. 6. Of a total of 209 muscle segments analyzed, adenosine did not increase the flow in 29 segments (14%).

DISCUSSION

The results indicate that under the conditions of our experiments *1)* the O_2 uptake per unit tension development is unchanged from control during 30 min of ischemic contractions, *2)* maximal vasodilation is not achieved during ischemic contractions, *3)* the flow-to-O_2 uptake ratio during ischemic exercise is nearly the same as during free flow, *4)* when free flow is restored after 30 min of ischemic contractions, tetanic tension begins to recover but 4-Hz twitch tension does not, and *5)* both the tension-dependent and tension-independent O_2 uptake were significantly decreased by ischemia.

Twitch tension did not show any recovery from its depressed ischemic level in these experiments after up to 20 min of reperfusion. This may be analogous to the phenomenon of "stunned" myocardium, in which ischemic but noninfarcted regions of myocardium fail to recover full tension development for up to a week after reperfusion (4). Tetanic tension, although still greatly depressed, did begin to recover in these experiments. This suggests that the myocytes are capable of greater performance if presented with a sufficient stimulus (i.e., greater calcium release from sarcoplasmic reticulum). The origin of "stunning" may therefore lie at least partly in excitation-contraction coupling rather than in the contractile proteins.

The results of the experimental series to estimate the tension-independent and tension-dependent O_2 uptake also support the involvement of at least the excitation-contraction coupling process in the effects of ischemia. This approach minimizes the contribution of glycolytic ATP production, which could be appreciable during ischemia, and assumes that the O_2 uptake of a skeletal muscle represents the resynthesis of the majority of the ATP consumed during a contraction. The regression analysis used here is based on the model of Chapman and Gibbs (6), which utilizes the concept that when a muscle contracts but does not develop tension, the O_2 consumed represents the energy cost of processes that are independent of tension development in the muscle cell. The y-intercept of the tension vs. O_2 uptake per contraction regression line established by changing the muscle length estimates the O_2 uptake associated with the processes involved in activation, including the active transport of calcium ions. This component has been named the tension-independent O_2 uptake. One assump-

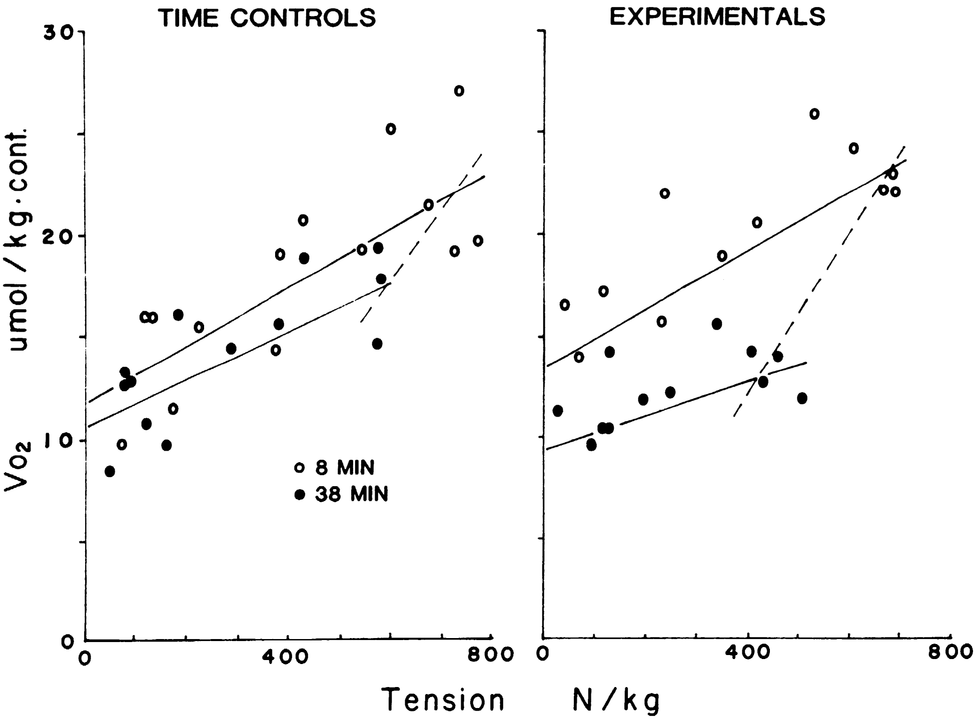

FIG. 5. Effect of 30 min of contractions in time control muscles (*left*) and of 30 min of ischemic contractions (*right*) on relation between tension and O_2 uptake ($\dot{V}O_2$) per contraction. Values obtained at 8 (○) and at 38 min (●) of contractions are presented for majority of experiments. - - -, Regression lines for decreasing tension due to fatigue at constant length (data points not shown). These demonstrate that total $\dot{V}O_2$ declines with tension. Tension was also varied by decreasing muscle length (——) in an attempt to separate total $\dot{V}O_2$ into activation (intercept) and tension development (slope) components. Solid regression line at 8 min for control experiments was $y = 0.015 \pm 0.001x + 11.6 \pm 1.2$, whereas for ischemia experiments it was $y = 0.014 \pm 0.002x + 13.1 \pm 1.7$. At 38 min, regression line for control experiments was $y = 0.012 \pm 0.002x + 10.3 \pm 1.0$, and for ischemia experiments it was $y = 0.008 \pm 0.002x + 9.3 \pm 1.22$. Slope and intercept for experimental muscles at 38 min are significantly different from values at 8 min ($P < 0.05$, *t* test). Data points for —— and - - - are the same at highest tension.

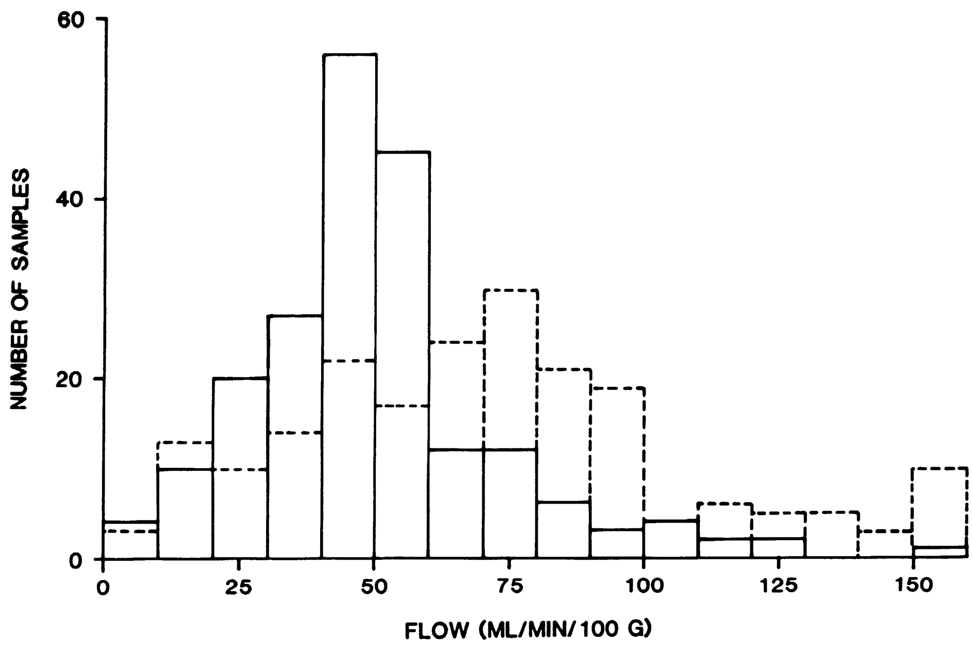

FIG. 6. Distribution of microsphere blood flows after 30 min of ischemic contractions (——) and during ischemic contractions plus adenosine infusion (- - -). Data are from 209 muscle segments from 5 muscles. Segments with flows ≥150 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ have been consolidated in the highest flow category.

tion underlying this approach is that the tension-independent O_2 uptake is constant across a wide range of muscle lengths. If this assumption is accepted, then the slope of the regression line represents the O_2 cost of the processes involved in the generation of tension, or the tension-dependent O_2 uptake. The shortening of the muscle length to decrease developed tension would slightly overestimate the value of the intercept (18), but because the procedure was the same with all muscles, any differences observed in the present experiments should be due to experimental treatment. The observation that the tension-independent O_2 uptake was reduced with ischemia suggests that excitation-contraction coupling has been altered by this degree of ischemia. The tension-dependent O_2 uptake was also reduced, indicating an ischemia-induced alteration in the ATP-requiring steps in tension generation.

Calculations of O_2 uptake per unit tension development (Fig. 4) indicate that this ratio is the same for both ischemic and control muscles and does not change during 30 min of 4-Hz stimulation. This finding argues against the hypothesis that the decreasing tension development in ischemic muscle results from a fall in the free energy available from ATP hydrolysis (9). If this were true, the muscle would require more ATP per unit tension development, and we would have expected to see the O_2 consumption per unit tension rise during the 30 min of ischemic contractions. This constant O_2 uptake per unit tension development seems at first analysis to conflict with the observation of a decreased tension-dependent O_2 uptake after 38 min of ischemia (Fig. 5). The mechanism of the tension change in these techniques, however, is entirely different. The tension in Fig. 4 is changing because of progressive muscle fatigue at a constant muscle length (see Fig. 1), whereas in Fig. 5 the tension was varied by changing muscle length and the degree of overlap between the myofilaments. The data in Fig. 4 indicate that total O_2 consumption declines in parallel with tension, and Fig. 5 attempts to separate the cause of the total consumption decline into activation and tension development components. Both components were decreased by ischemia.

We found that the ischemic muscles were not maximally dilated even though the flow reduction was severe enough to produce definite fatigue. Similar findings have been reported for the heart (1, 5, 7, 15). One explanation for the residual vasodilator reserve might be that the flow reduction was very heterogeneous and that areas of unreduced flow were responsible for the vasodilator reserve. The microsphere experiments allow us to reject this possibility. Both the flow decrease during ischemia and the increase during adenosine infusion were seen in virtually every muscle segment examined. Although segments with flows of <30 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ during ischemic contractions were less likely to dilate to adenosine than segments with higher flows, flow was reduced below control in the 86% of segments that did dilate in response to adenosine. Because we did not analyze any muscle segments <50 mg, however, we cannot rule out the possibility that flow heterogeneity at the microcirculatory level might account for the vasodilator reserve. The radioactive microsphere technique could not detect such microheterogeneity. Another possible explanation for the ischemic vasodilator reserve could be that adenosine dilations represent a pharmacological level that cannot be achieved physiologically. Although we attempted to produce vasodilation after 30 min of ischemic contractions with interventions such as tetanic stimulation, 6-Hz stimulation, or increasing muscle length, the dilations seen with adenosine could not be achieved. Unfortunately, these interventions increase the component of vascular resistance due to extravascular compression, which makes interpretation of this result difficult. Whether this pharmacologically demonstrated vasodilator reserve can ever be achieved physiologically must, therefore, remain an open question.

The findings of a near normal flow-to-O_2 uptake ratio and a residual vasodilator reserve could be related, if metabolic vasodilator production is driven by the O_2 supply-to-demand ratio (3, 17). Thus the flow-to-O_2 uptake ratio may not have decreased enough to produce maximal vasodilation. The exact identity of the signal for vasodilator production is not known. Although the flow-to-O_2 consumption ratio drops at the onset of ischemic contractions, the ratio during ischemia is remarkably close to the ratio in control muscles (Fig. 3). A plot of the flow-to-O_2 uptake ratio at various stimulation frequencies during free flow (Fig. 7) demonstrates that the ratio during 4-Hz contractions is very near the absolute minimum value. Thus very little additional O_2 extraction is possible when flow is reduced, and tissue Po_2 must fall as a result. The fall in tissue Po_2, as well as other changes due to reduced flow (such as reduced intracellular pH), brings about changes in the cellular environment that decrease all aspects of muscle function. The decreases in function reduce energy demand (as reflected by O_2 consumption). This forms a negative-feedback loop that tends to stabilize the cellular environment during ischemic contractions. Thus the cellular environment can be defended over a wide range of flow reductions at the cost of reduced muscle performance. Because the cellular environment is linked to vascular conductance by release of vasoactive metabolites, the relative constancy of cellular environment through decreased performance could explain the lack of maximal vasodilation we observed. Maximal vasodilation might, therefore, only be achieved when ischemia is severe enough to reduce tension development to near zero.

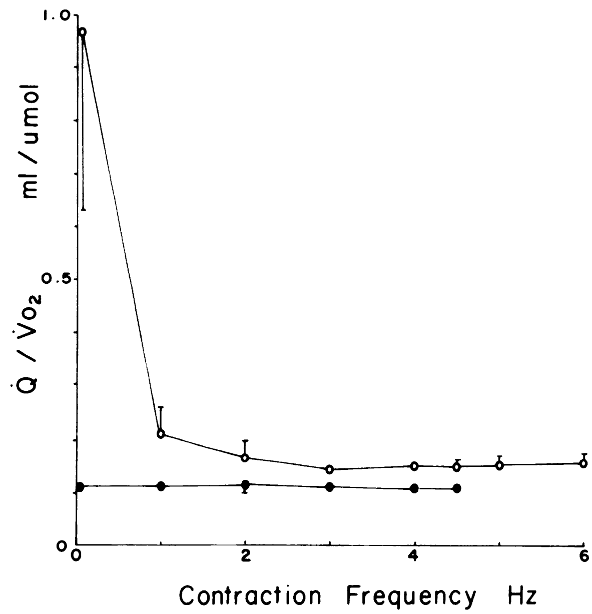

FIG. 7. Relation between contraction frequency and blood flow ($\dot{Q}$)-to-O_2 uptake ($\dot{V}o_2$) ratio under free-flow conditions (○) and theoretical minimum ratio assuming complete O_2 extraction (●). Data are from previous studies in this laboratory with the same muscle preparation ($n = 6$).

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