Time Course of Vascular Resistance and Venous Oxygen Changes following Brief Tetanus of Dog Skeletal Muscle

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ABSTRACT
The time courses of vascular resistance and venous blood oxygen (O₂) saturation following a brief tetanus of isolated dog calf muscle were studied during free-flow (constant-pressure), high constant-flow (>30 ml/100 g min⁻¹), and low constant-flow (<24 ml/100 g min⁻¹) perfusion. A monophasic decrease in resistance followed a 1-second tetanus during either free-flow or high constant-flow perfusion. The transient decrease in vascular resistance during high constant-flow perfusion returned to control before the return of the decrease in end-capillary oxygen tension. Thus, it seems unlikely that the vascular response to a brief tetanus during free-flow or high constant-flow perfusion was controlled by a factor related to oxidative metabolism.

A biphasic resistance response followed a brief tetanus during low constant-flow perfusion. This vascular response had a longer duration than the response during free-flow or high constant-flow perfusion. It returned to control with approximately the same time course as that for tissue O₂ consumption and could therefore be controlled by factors related to oxidative metabolism. These findings support the hypothesis that exercise hyperemia is due to multiple factors. Moreover, they indicate that, under the conditions of free-flow perfusion or high constant-flow perfusion, the vascular response to a brief tetanus is not solely controlled by factors directly associated with tissue oxidative metabolism.

KEY WORDS
flow washout  exercise hyperemia  metabolic vasodilator  constant-flow perfusion  blood flow  constant-pressure perfusion

Several factors contributing to exercise hyperemia have been identified (1-3), and most of these factors have been implicated as metabolic vasodilators on the basis of two criteria: (1) steady-state exercise produces changes in the venous level of the substance which correlate with changes in the vascular resistance and (2) the substance produces vasodilation when it is infused into the arterial supply of resting skeletal muscle. However, such experiments are difficult to interpret, because steady-state exercise produces many alterations in the chemical composition of the venous effluent which may be correlated with, but are not causes of, the changes in resistance. In addition, the effect of a vasodilator substance on arteriolar tone is probably more closely related to its interstitial concentration than it is to its venous concentration (4). These concentrations differ if a significant transcapillary diffusion gradient exists; the existence of such a gradient depends on both the specific substance and the experimental situation (5). Moreover, an altered arterial concentration of certain suspected vasodilators, such as lowered oxygen (O₂), may cause the release of other vasodilators from skeletal muscle so that the direct effect of the test substance on vascular smooth muscle may be obscured.

Mellander and Johansson (3) recognized the difficulties involved in elucidating the mechanism of exercise hyperemia and listed criteria for assessing suspected controllers of exercise hyperemia. One of the criteria is the parallel time course of changes in the suspected factor and changes in resistance during exercise transients. Clearly, changes in the factor controlling exercise hyperemia must occur.
simultaneously with, or before, alterations in vascular resistance. There is a wide range in the rate of return of resistance to control levels following steady-state exercise, depending on the duration and the intensity of the preceding exercise (6, 7). Some investigators (8, 9) have noted discrepancies between the time courses of alterations in suspected metabolic vasodilators and changes in resistance, and several others have studied the time course of changes in resistance with exercise (10, 11). We do not know, however, of a systematic investigation of the dynamics of exercise hyperemia and suspected metabolic vasodilators. The present study compares the dynamics of changes in resistance and venous O₂ produced by a brief tetanus of skeletal muscle.

Methods

Male mongrel dogs weighing 20—25 kg were anesthetized with sodium pentobarbital (35 mg/kg, iv). They were heparinized (500 units/kg plus 100 units/kg hour⁻¹) just prior to artificial perfusion of the hind limb.

The calf muscles were isolated in a manner similar to that reported by Kjellmer (4). All structures in the popliteal region except the popliteal artery (more strictly called the femoral artery at this point) and vein and the femur were transected. We did not pack the medulla of the femur with cotton as Kjellmer did, because we found that this procedure did not stop the small amount of collateral flow which supplies the calf muscles via the bone. Venous outflow was never more than 2 ml/100 g min⁻¹ when the popliteal artery was clamped. Within the error of measurement, we could not detect differences between arterial inflow and venous outflow in the steady state. The calf was skinned and the paw removed. The popliteal vein was cannulated just proximal to the popliteal junction, and the effluent returned to a reservoir connected to the contralateral femoral vein. Venous outflow pressure was held constant at approximately 5 mm Hg. From a side tap in the venous cannula, a portion of the venous effluent was drawn at constant flow (2.3 ml/min) through a cuvette densitometer (Gilford 103 I.R.) for continuous monitoring of the venous hemoglobin saturation. All tubing was either Silastic or polyethylene, and there was little or no evidence of thrombotic material attached to the tubing at the end of the day. In constant-pressure experiments, flow through the calf muscle preparation was monitored with an electromagnetic flowmeter (Carolina 301) with a probe placed on the popliteal artery and calibrated by timed collection of venous effluent. In constant-flow experiments, blood from the contralateral femoral artery flowed through a finger pump and into the cannulated popliteal artery. Resistance, in units of mm Hg/min 100 g⁻¹ ml⁻¹, was calculated by dividing the perfusion pressure by the flow. Conductance was calculated as the reciprocal of vascular resistance.

Muscle exercise was controlled by supramaximal electrical stimulation (2—10 v, 0.1 msec) of the distal end of the sectioned sciatic nerve. A 1-second train of stimuli at a frequency of 32 impulses/sec was used to produce a brief tetanic contraction. Isometric tension production by the gastrocnemius was measured by attaching a strain gauge to a fragment of the calcaneus attached to the Achilles tendon. The other calf muscles contracted isometrically, since their tendons were clamped against the distal ends of the tibia and fibula by several turns of copper wire. We studied the time course of the vascular response to a brief tetanus during three types of perfusion: (1) free-flow (constant-pressure) perfusion, (2) high constant-flow (>30 ml/100 g min⁻¹) perfusion, and (3) low constant-flow (<24 ml/100 g min⁻¹) perfusion.

For our purposes, it was necessary to distinguish between three processes which can be viewed as muscle O₂ consumption. The first process can be termed whole-muscle O₂ consumption, which is flow multiplied by the instantaneous arterial-venous O₂ difference. The second process, which can be termed tissue O₂ consumption, is the rate of blood-tissue O₂ transfer and is flow multiplied by the instantaneous arterial-end-capillary O₂ difference. The time course of change in tissue O₂ consumption may differ from that of change in whole-muscle O₂ consumption because of the distribution of venous transit times. The third process, actual O₂ use in oxidative phosphorylation, follows a time course different from tissue O₂ consumption if tissue O₂ stores are changing. Throughout, we attempted to account for the dispersion effects of venous vascular transit with the procedure outlined below. In certain instances, we attempted to estimate the effects of tissue O₂ capacitance, using the approach outlined in the Appendix.

Correction for Vascular Transit Delays on O₂ Measurements—With constant O₂ delivery (constant flow and constant arterial O₂ content), changes in the O₂ content of the venous effluent indicate changes in whole-muscle O₂ consumption. However, these changes in venous O₂ content do not give the correct time course for changes in tissue O₂ consumption (blood-tissue O₂ transfer) because of the distribution of transit times of blood between capillaries and the venous measuring site (12). Wilde (18) dealt with this problem both graphically and with an ingenious mechanical analogue when he was investigating the pulsatile release of potassium from heart muscle. More sophisticated, but equivalent, mathematical techniques involving convolution have been used to describe the effects of catheter transit on the shape of indicator-dilution curves (14—16). Rather than use the difficult process of deconvolution to remove the effects of vascular transit from our venous O₂ measurements, we used convolution to predict how assumed time courses of increased tissue O₂ consumption would appear as O₂ saturation changes at the venous measuring site. Our application of the convolution integral is as follows:

\[ O₂(t) = \int_{0}^{T} O₂(T) \delta(t - T) \, dt \]
where $O_2(t) = \text{blood } O_2 \text{ content measured at an external venous site as a function of time, } O_2(t) = \text{blood } O_2 \text{ content at capillaries as a function of time, } h(t) = \text{distribution of vascular transit delays between capillaries and the measuring site, and } T = \text{variable of integration.}$

To properly apply this formula, it is necessary to assume that vascular transit effects during a particular observation are linear and time invariant (15). Since blood $O_2$ content sums linearly, the effects of vascular transit on blood $O_2$ content may be described by a linear transformation (16). In the constant-flow (pump-perfused) situation, we assumed that the distribution of vascular transit delays did not vary with time during a particular maneuver.

Capillary-to-oximeter transit time distribution was estimated from the distribution of times for transit of the entire bed. This distribution was experimentally determined in each preparation and at each flow used by recording the time course of appearance of intravascular dye (indigo carmine) at the oximeter after injection of an intra-arterial bolus. This method combines catheter and densitometer dynamics with those of actual vascular transit. We compared the dye transit observed at rest and during exercise at the same flow rate in several preparations. Since there was no difference between dye transit during exercise and rest, we usually determined the distribution of intravascular transit times with the muscle at rest.

We were interested in attempting to compare the time course of the vascular response to a brief tetanus with the various events related to increased muscle $O_2$ use. There are two ways in which skeletal muscle $O_2$ use could be expected to exert a vasodilating effect on vascular smooth muscle. First, it could lower the oxygen tension $(P_o_2)$ around vascular smooth muscle directly. Several anatomical studies (17-19) have demonstrated that small distributing arterioles run transversely across muscle fibers and therefore are exposed to different levels of external $P_o_2$ along their length. If $P_o_2$ were controlling smooth muscle tone, vascular resistance should be correlated with some sort of spatial average of arteriolar wall $P_o_2$ exposure. Since exchange vessels are in contact with the environment of the arterioles, end-capillary blood $P_o_2$ is probably as good an approximation as any of the net $P_o_2$ exposure of long segments of arterioles. We mean by end-capillary blood that blood which is in contact with the last segment of the vascular bed involved in diffusion exchange. If lowered $P_o_2$ causes the vasodilation associated with a brief tetanus, the changes in $P_o_2$ to which arterioles are exposed must occur at least simultaneously with, if not prior to, the changes in resistance. To determine whether this relationship existed in our experiments, we assumed that end-capillary blood $P_o_2$ followed the same time course as the vascular response since this time course is the slowest $P_o_2$ time course compatible with $P_o_2$ control of resistance. We then used an oxyhemoglobin saturation curve for canine blood (10) to give the corresponding time course of end-capillary blood hemoglobin saturation. In each preparation, the total extra $O_2$ consumed could be calculated from the flow rate and the area under the observed venous $O_2$ saturation response. Through an iterative procedure, we were able to select that end-capillary $P_o_2$ response which had the shape of the vascular response and produced the total extra $O_2$ consumption observed experimentally. Then we used the dye transit data and the convolution equation to predict the time course and the magnitude of these assumed events as observed at the oximeter site. By comparing the predicted venous $O_2$ response with the actual venous $O_2$ response, we then could test the validity of the original proposition that $P_o_2$ changes at least as fast as the vascular response. A mathematical statement of procedure appears as model I in the Appendix.

The second way in which increased muscle $O_2$ use could cause relaxation of vascular smooth muscle is by the release from skeletal muscle cells of a vasodilator substance associated with increased oxidative metabolism. For such a substance to be responsible for the vasodilation observed with a brief tetanus, the rate of oxidative metabolism must follow a time course at least as rapid as that of the vascular response, assuming instantaneous release and build up of the substance in the interstitium and instantaneous effect on vascular smooth muscle. Any significant time lag due to any of these processes would require an even faster time course of increased oxidative metabolism. We picked the slowest possible time course for prediction. We employed the second model discussed in the Appendix, including the convolution integral, to predict how we would expect this particular time course for oxidative metabolism to change venous $O_2$ at the oximeter site. The model accounts for changes in tissue $O_2$ stores and thereby relates the time course of change in oxidative metabolism to the corresponding time course of blood-tissue $O_2$ transport and thus the time course of alteration in end-capillary blood $O_2$ content. The convolution integral was used to account for vascular transit smearing and to predict venous $O_2$ saturation measurements. The possibility that increased oxidative metabolism follows the same time course as does the decrease in vascular resistance following a brief tetanus was evaluated by comparing the predicted and the measured venous $O_2$ saturation response. The Appendix contains a description of the model which was used to account for the dynamics introduced by tissue $O_2$ capacitance as well as a discussion of the assumptions made in formulating it.

In the cases of altered tissue $P_o_2$ and increased oxidative metabolism we chose the slowest possible time course compatible with participation in the control of the vascular response and then predicted the corresponding venous $O_2$ saturation time course. If the observed venous time course was still slower, it seems unlikely that $O_2$ could have been involved in the vascular response. If the observed venous time course was faster than the predicted one, $O_2$ could have caused the vascular response. The Appendix contains the equations which explicitly state the process by which the predictions were determined.

Various parameters of the predicted and the observed venous $O_2$ curves were used to perform statistical tests for the significance of differences among curves. We used Student's t-test (20) to evaluate the significance of differences.

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Results

Vascular Response to a Brief Tetanus.—As illustrated in Figure 1, one of two distinct types of alteration in resistance followed a brief tetanus; the type of alteration that occurred depended on the mode of perfusion. During either free-flow or constant-flow perfusion at 30 ml/100 g min⁻¹ or more, a monophasic decrease in resistance followed a brief tetanus and caused a monophasic increase in flow (Fig. 1A) or a monophasic decrease in perfusion pressure (Fig. 1B). The time course of this monophasic resistance response was similar for free-flow and high constant-flow perfusion.

In contrast, a biphasic decrease in resistance consistently followed a brief tetanus when the flow rate was constant at less than 24 ml/100 g min⁻¹ (Fig. 1C). The biphasic response appeared to result from the addition of a second slower phase to the resistance decrease which followed a brief tetanus at high flow. When a second period of tetanus occurred during the vascular response to the first one (Fig. 1D), there was little addition of the first phases but substantial summation of the second phases.

To compare the time courses of the vascular response observed during the three perfusion conditions, we digitized all individual responses at 2-second intervals and then normalized them on a 0-1 scale. The mean time courses for the conductance responses during constant-pressure perfusion and constant-flow perfusion at high rates (>30 ml/100 g min⁻¹) are plotted in Figure 2. The time courses for the vascular response were virtually identical with these two types of perfusion. The response was characterized by a rapid increase in vascular conductance which reached a peak value within 6 seconds after the onset of stimulation and then a monotonic decrease in conductance which reached the control level within 50 seconds.

The mean normalized resistance responses obtained during constant-flow perfusion at high (>30 ml/100 g min⁻¹) and low (<24 ml/100 g min⁻¹)
rates are presented in Figure 3. In contrast to the monophasic response during high constant-flow perfusion, the resistance response following a brief tetanus during low constant-flow perfusion had two distinct phases. During the first 20 seconds after the 1-second tetanus, the response with low constant-flow perfusion was not distinguishable from that with high constant-flow perfusion. Thereafter, the response with low constant-flow perfusion returned to control more slowly than that with high constant-flow perfusion. In two of four dogs, the response with low constant-flow perfusion exhibited a second resistance minimum which occurred 25-35 seconds after the tetanus. In two dogs, the return to control was slowed during this time period, but there was no second minimum.

The mean vascular resistance response observed during high and low constant-flow perfusion are replotted in Figure 4 on a semilogarithmic scale. During high constant-flow perfusion, the recovery phase of the conductance response following a brief tetanus was well approximated by a monoexponential return to control with a rate constant of 0.1/sec. After the initial peak, the resistance response during low constant-flow perfusion began as the same monoexponential recovery, but an abrupt change in the time course occurred approximately 20 seconds after stimulation. Recovery was dramatically slowed during a period lasting approximately 10 seconds. Thereafter, resistance approached control at a more rapid rate. An exponential decay with a rate constant of 0.017/sec, corresponding to the fastest possible rate of flow removal of most substances from skeletal muscle, is also indicated in Figure 4 for purposes of later discussion. It represents the rate at which an infinitely diffusible substance which is equally soluble in blood and tissue would be cleared from the total tissue volume by a flow of 100 ml/100 g min⁻¹.

The resistance response to twin brief tetani spaced 10 seconds apart during low constant-flow perfusion is illustrated in Figure 1D. A biphasic response followed the second stimulus. The magnitude of the rapid phase of this response was only slightly larger than that of the rapid phase of the vascular response to the first stimulus. It did not represent the algebraic sum of two responses to a single tetanus (Fig. 1C). However, the slow phase of the response which followed the second of the twin stimuli (Fig. 1D) was much larger than that which was present in the vascular response to a single tetanus at the same low constant flow (Fig. 1C). To permit further analysis, we defined the second phase of the response with low constant-flow perfusion as that portion of the response which was not present in the response to the same stimulus during high constant-flow perfusion. For example, the magnitude and the time course of the slow phase of the response illustrated in Figure 1C

![Figure 3: Normalized decrease in vascular resistance following a 1-second tetanus during high (●) and low (○) constant-flow perfusion. High-flow curve is the average of 39 trials in five dogs, and low-flow curve is the average of 34 trials in four dogs. Vertical bars indicate ± 1 so.](image)

![Figure 4: Semilogarithmic plot of normalized decrease in vascular resistance following a 1-second tetanus during high (●) and low (○) constant-flow perfusion. Points are means from Figure 3. Broken line indicates monoexponential decay at a rate constant (k) of 0.017/sec.](image)
would be obtained by subtracting from it the response with high constant-flow perfusion shown in Figure 1B. Similarly, the slow phase of the response following twin stimuli (Fig. 1D) was obtained by subtracting the response with high constant-flow perfusion to twin stimuli (not illustrated). Twin stimulation increased the magnitude of the first phase only 11% ($P < 0.06$) but increased the magnitude of the second phase 185% ($P < 0.003$).

Venous $O_2$ Response to Brief Tetanus.—Figure 5 (top) shows the results for a typical high-flow experiment and compares the observed venous hemoglobin saturation response with the venous $O_2$ response predicted by assuming a time course for end-capillary $P_{O_2}$ equal to that of the observed resistance response or the venous $O_2$ response predicted by assuming a time course for increased oxidative metabolism equal to that of the resistance response. Also illustrated are various measurements which were used as parameters to describe both the observed and the predicted venous $O_2$ transient. Table 1 contains the values for these parameters for each of the five high-flow experiments as well as the average results. The procedure used for making the two predictions is outlined in detail in the Methods and the Appendix.

The delay time between tetanus and the onset of decreased venous $O_2$ saturation was longer for both predicted curves than it was for the observed curve. Table 1 shows a significant difference between observed and predicted values for the time from tetanus to the half-minimum response. Both predicted curves also reached a lower minimum venous $O_2$ saturation than that which was observed. This point is demonstrated in Table 1 by significant differences in both minimum percent saturation and maximum change in venous saturation. Both predicted venous $O_2$ saturation curves returned to control levels more rapidly than did the observed curves. Despite the delayed onset, the absolute time from tetanus to half-return was significantly shorter for the curves predicted by assuming that end-capillary $P_{O_2}$ followed the same time course as resistance than it was for the observed curves. For either prediction, the time from peak to half-return was significantly shorter than it was for the observed curves. Thus we found significant differences between predicted and observed values for nearly all the parameters used to describe these curves. In general, when compared with the observations, the predicted venous $O_2$ saturation curves for the high-flow experiments (1) were delayed in onset, (2) showed larger changes, and (3) returned to control more rapidly. Except for time of onset, the differences from the observed curve were most pronounced for the prediction based on the assumption that vessel wall $P_{O_2}$ controls vascular resistance.

We used a similar approach to examine the venous $O_2$ saturation responses to a brief tetanus in the low-flow experiments. For these experiments, we only made predictions based on the assumption that vessel wall $P_{O_2}$ controls vascular resistance. At low flow the vascular resistance response was biphasic, and it was possible to base predictions on the assumption that $P_{O_2}$ controls the entire vascular response, only the fast phase of the vascular response, or only the slow phase. The fast phase was defined by monoexponential extrapolation to control level using the initial resistance recovery
TABLE 1
Parameters Describing Observed and Predicted Venous O₂ Saturation Response following 1-Second Brief Tetanus at High Constant Flow

<table>
<thead>
<tr>
<th>Dog</th>
<th>Parameter</th>
<th>Observed</th>
<th>Predicted</th>
<th>Observed</th>
<th>Predicted</th>
<th>Observed</th>
<th>Predicted</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vessel P₀₂</td>
<td>57.9</td>
<td>67.3</td>
<td>70.0</td>
<td>63.7</td>
<td>61.4</td>
<td>74.6</td>
<td>65.9</td>
<td>46.7</td>
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<tr>
<td></td>
<td>O₂ consumption</td>
<td>30.9</td>
<td>24.5</td>
<td>11.3</td>
<td>17.4</td>
<td>19.8</td>
<td>18.3</td>
<td>14.8</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>Minimum % saturation (a)</td>
<td>74.1</td>
<td>57.9</td>
<td>67.3</td>
<td>61.4</td>
<td>63.7</td>
<td>74.6</td>
<td>65.9</td>
<td>46.7</td>
</tr>
<tr>
<td></td>
<td>Maximum change in % saturation (b)</td>
<td>14.7</td>
<td>30.9</td>
<td>24.5</td>
<td>11.3</td>
<td>19.8</td>
<td>18.3</td>
<td>14.8</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>Time from tetanus to half-minimum (c)</td>
<td>13.1</td>
<td>17.2</td>
<td>12.4</td>
<td>16.3</td>
<td>19.0</td>
<td>22.3</td>
<td>19.2</td>
<td>19.2</td>
</tr>
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<td></td>
<td>Time from tetanus to half-return (d)</td>
<td>46.9</td>
<td>34.1</td>
<td>53.0</td>
<td>36.1</td>
<td>38.1</td>
<td>47.4</td>
<td>38.1</td>
<td>47.4</td>
</tr>
<tr>
<td></td>
<td>Time from peak to half-return (e)</td>
<td>24.9</td>
<td>42.7</td>
<td>28.0</td>
<td>42.3</td>
<td>12.1</td>
<td>41.8</td>
<td>11.8</td>
<td>41.8</td>
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<tr>
<td></td>
<td>Flow (ml/100 g min⁻¹)</td>
<td>30.5</td>
<td>12.7</td>
<td>41.5</td>
<td>14.3</td>
<td>33.9</td>
<td>15.4</td>
<td>44.1</td>
<td>11.8</td>
</tr>
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</table>

P values are for paired comparison of observed with each of predicted parameters (Student's t-test). Letters in parentheses indicate parameters illustrated in Figure 5.

rate (Fig. 4). The slow phase was then defined as the difference between this extrapolation and the entire resistance response. Only the predictions based on the slow phase of the biphasic resistance response are presented in Figure 5 (bottom) and Table 2. In two of the four low-flow experiments, we were unable to base predictions on either the entire resistance curve or the rapid phase alone, because those restrictions on the shape of the tissue P₀₂ curve required negative P₀₂ values to yield the correct amount of total extra O₂ consumption. In the two experiments where this phenomenon did not happen, predictions based on the assumption that P₀₂ controls either the entire resistance response or only the rapid phase of the vascular response yielded the same differences between predicted and observed curves as noted for the high-flow experiments. In contrast, predictions based on the assumption that vessel wall P₀₂ controls only the slow phase of the vascular response showed much better agreement with the venous O₂ saturation response. As shown in Figure 5 (bottom), the predicted and the observed curves agreed well. The minimum value and the maximum decrease for O₂ saturation were the same for predicted and observed curves (Table 2). The downswing of the predicted curves lagged behind that of the observed curves as was the case at high flow. The observed curves returned to control more quickly than did the predicted curves as judged from the time between tetanus and half-return (Table 2). Thus, at low flow, the predicted curves lagged behind the observed curves but had the same minimum.
### TABLE 2

Parameters Describing Observed and Predicted Venous O₂ Saturation Response following 1-Second Brief Tetanus at LowConstant Flow

<table>
<thead>
<tr>
<th>Dog</th>
<th>Observed Vessel P₀₂</th>
<th>Predicted Vessel P₀₂</th>
<th>Minimum % saturation</th>
<th>Maximum change in % saturation</th>
<th>Time from tetanus to half-minimum (sec)</th>
<th>Time from tetanus to half-return (sec)</th>
<th>Time from peak to half-return (sec)</th>
<th>Flow (ml/100 g min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog 6</td>
<td>64.1</td>
<td>64.5</td>
<td>22.8</td>
<td>14.3</td>
<td>50.0</td>
<td>24.0</td>
<td>23.7</td>
<td></td>
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<tr>
<td>Dog 7</td>
<td>79.2</td>
<td>78.4</td>
<td>13.1</td>
<td>8.0</td>
<td>78.8</td>
<td>58.8</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>Dog 3</td>
<td>45.6</td>
<td>48.2</td>
<td>36.0</td>
<td>26.9</td>
<td>60.1</td>
<td>22.1</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Dog 5</td>
<td>23.3</td>
<td>21.6</td>
<td>43.0</td>
<td>32.7</td>
<td>75.8</td>
<td>31.8</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td></td>
<td>29.4 ± 6.9</td>
<td>17.6 ± 4.1</td>
<td>65.7 ± 6.5</td>
<td>34.2 ± 8.5</td>
<td>19.5 ± 2.8</td>
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</table>

*p values are for paired comparison of observed with each of predicted parameters (Student’s *t*-test).

### Discussion

**Time Course of Vascular Response to a Brief Tetanus.**—The time courses of the resistance changes following a brief tetanus (Fig. 2) are quite similar under conditions of high constant-flow or constant-pressure perfusion when flow varies over a fivefold range during the response. If a factor responsible for this metabolic vasodilation is removed from the interstitial space by flow washout, the time course for resistance changes under these two conditions should be different unless (1) the factor is diffusion limited so that its removal is not greatly affected by varying flow rate or (2) its washout is so rapid that, in both cases, the return to control is determined by some other factor such as the maximum contraction rate of vascular smooth muscle. Both of these possibilities can be eliminated, since the rate constant for return of resistance to control (k = 0.1/sec) is considerably more rapid than the maximum possible rate of flow removal of a highly diffusible substance from this tissue. The rate constant of flow removal (or replenishment) of substances which are infinitely diffusible, distributed within the entire tissue space, and equally soluble in blood and tissue is 0.017/sec (1/min) at the maximum flow rate in this tissue of 100 ml/100 g min⁻¹. Any diffusion limitation at the capillary wall would cause the maximum possible washout rate to be even slower. Thus, we concluded that it was not possible to explain the rate of return to control of the resistance response to a brief tetanus solely on the basis of flow washout of a vasodilator which is equally soluble in blood and tissue. This conclusion concerning the mediator of the vascular response to a brief tetanus may not be applicable to other situations in which some investigators have observed considerably slower resistance recoveries following cessation of exercise (7, 21).

If a substance is more soluble in blood than it is in tissue, it can be replenished or removed more rapidly than is indicated by the above rate constant (0.017/sec). At a flow rate of 30 ml/100 g min⁻¹, it is possible for washout to match the rate constant of the observed resistance return (0.1/sec) with a highly diffusible substance roughly 20 times more soluble in blood than in tissue. Because of hemoglobin binding, O₂ easily meets this criterion in all but very low and very high P₀₂ ranges. Thus, tissue O₂ could theoretically be replenished by flow rapidly enough to account for the return of resistance to normal following the brief tetanus. However, the possibility that P₀₂ is the sole controller of the response to a brief tetanus is at
issue because of the time course of decreased venous O₂ content observed following 1 second of tetanus at high flow. During high constant-flow perfusion, observed venous O₂ saturation returned to control slower than was predicted from the assumption that vascular wall Po₂ follows the same time course as the resistance response. This finding means, given our assumptions (see below), that vascular wall Po₂ does not recover as rapidly as resistance and therefore could not be involved in the control of resistance at high flow.

There are several assumptions which have been made in the prediction of venous O₂ saturation from a particular time course of arterial wall Po₂ or tissue oxidative metabolism. Some of these assumptions could represent sources of considerable error and might invalidate our conclusions and so should be dealt with in some detail. Our conclusion that oxidative metabolism is probably not involved in the control of the vascular response to a brief tetanus at high flow is based on the observation that the observed time course for venous O₂ content is more prolonged than the time course predicted for venous O₂ content assuming that either vascular wall Po₂ or muscle oxidative metabolism follows a time course at least as fast as the observed vascular response (Fig. 5 top).

The attempt to predict venous O₂ changes from the test assumption that arterial wall Po₂ changes with the time course of the resistance response proceeds from the following assumptions. (1) The vascular response is linearly related to vessel wall Po₂. (2) End-capillary blood gives an adequate estimate of average arteriolar wall Po₂ exposure. (3) There is little heterogeneity of the time courses of O₂ change in various parts of the tissue so that the time course of the change in O₂ can be viewed as a function with a single value at any given time. (4) The distribution of intravascular transit times given by the intravascular dye transit through the entire bed adequately indicates dispersion of transit times on the venous side of the circulation.

There are few experimental data to bring to bear on the first assumption. Most responses are considered to be linearly related to the log of the effector concentration. However, it is difficult to predict how resistance, which is related to a power of vascular smooth muscle shortening, would be related to Po₂. Calculations from the data of Guyton et al. (22) on minute muscle arteries indicate that the relationship between resistance and Po₂ may be quite linear between a Po₂ of 20 and 100 mm Hg.

The second assumption is based on the time course of arterial wall Po₂ changes from a particular time course of arterial wall Po₂ or tissue oxidative metabolism. Some of these assumptions could represent sources of considerable error and might invalidate our conclusions and so should be dealt with in some detail. Our conclusion that oxidative metabolism is probably not involved in the control of the vascular response to a brief tetanus at high flow is based on the observation that the observed time course for venous O₂ content is more prolonged than the time course predicted for venous O₂ content assuming that either vascular wall Po₂ or muscle oxidative metabolism follows a time course at least as fast as the observed vascular response (Fig. 5 top).

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venous O$_2$ curve would be shifted to the left (Fig. 5), which would strengthen our conclusion that tissue O$_2$ does not change rapidly enough to be a controller of resistance changes.

Several investigators have presented evidence for a dual circulation in skeletal muscle (24, 25) with two sets of vascular pathways, one nutrient and the other nonnutrient. If such a concept is correct, our prediction of the time course of venous O$_2$ changes should involve only the distribution of venous transit times involving nutrient channels, whereas our estimate of vascular transit times derived from arterial injections necessarily includes transit times for both nutrient and nonnutrient channels. If the longest transit times represent nutrient pathways and if there is a large shift in flow to these channels following a brief tetanus, the discrepancy between the predicted and the observed venous O$_2$ curves might be explained on this basis. We do not believe this possibility is likely, however, because the distribution of transit times as measured by intrarterial dye injection does not show more dispersion when the muscle is exercising at a rate of 4/sec than it does when it is at rest if the flow is the same. This result indicates that (1) the dispersion of transit times in nutrient and nonnutrient channels is the same, (2) no shift to nutrient channels occurs with exercise, or (3) dual flow channels do not exist in our preparation. In any case we have not been able to explain the differences between the predicted and the observed venous O$_2$ curves (Fig. 5 top) in terms of dual circulation.

The prediction of venous O$_2$ response from the assumption that resistance is controlled by some factor other than P$_O_2$ related to the rate of oxidative metabolism proceeds from the third and fourth assumptions discussed previously as well as from the following additional assumptions. (5) The process linking oxidative metabolism to the resistance response operates linearly on the resistance response and does so with no time delay. (6) The major effect causing differences between the dynamics of mitochondrial O$_2$ use in oxidative phosphorylation and blood-to-tissue O$_2$ transfer is tissue capacitance due to O$_2$ dissolved in tissue water and oxymyoglobin stores. (7) The diffusional transport of O$_2$ is complete by the end of exchange vessels so that end-capillary blood P$_O_2$ is equal to some "average" muscle cell P$_O_2$.

The assumption of linearity between vascular response and oxidative metabolism cannot be based on any particular rationale or experimental logic. Any other assumed relationship would be equally hard to defend, however, and more difficult to work with. The assumption that there is no delay between changes in the rate of oxidative metabolism and changes in resistance was used to determine the slowest possible time course for change in oxidative metabolism that is compatible with it controlling resistance. Otherwise we would have to pick a faster time course for oxidative metabolism to allow time for transport of some agent from skeletal muscle cells to the vascular wall and further time for the agent to exert its effect. Thus we have attempted to predict the slowest possible time course for venous O$_2$ saturation that would indicate changes in mitochondrial oxidative metabolism rapid enough to control the vascular system.

The sixth and seventh assumptions are intertwined and are fundamental to the mathematical statement of the model used to make these predictions. Therefore, detailed consideration of them has been placed in the Appendix. The major capacitive effects are almost certainly exerted by dissolved O$_2$ and oxymyoglobin, but the importance of the nonlinear capacitance of oxymyoglobin depends on tissue P$_O_2$, since it exerts greater damping effects with lower tissue P$_O_2$. We assumed end-capillary diffusion equilibrium based on the work of Stainsby and Otis (10) indicating that the end-capillary diffusion gradient during exercise must be 5 mm Hg or less and on the similarity of O$_2$ to inert gases which appear to come into diffusion equilibrium by the end of capillaries of many organs (26). We have attempted to use assumptions which would favor the outcome that the vascular resistance response to a brief tetanus at high flow could be controlled by the rate of mitochondrial oxidative metabolism. Our conclusion that such control is not likely, however, is based on less discrepancy from the observed venous O$_2$ response than is the case for the prediction based on vascular wall P$_O_2$ as a controller of the vascular response. In addition, more assumptions are involved in the venous O$_2$ prediction from the rate of oxidative metabolism. We view our conclusion concerning the role of muscle cell oxidative metabolism as more tentative than that concerning the role of vessel wall P$_O_2$ and therefore more contingent on new information concerning the validity of our assumptions.

Biphasic Vascular Response at Low Flow.—The biphasic vascular response which follows a brief tetanus during low constant-flow perfusion suggests that at least two influences on vascular smooth
muscle tone may be involved in this response. High constant-flow rates appear to abolish only the slow phase of the vascular response to a brief tetanus, leaving the rapid phase (Fig. 3). In addition, twin stimulation increases the magnitude of the slow but not of the rapid phase of the biphasic response. This finding suggests that the relative influence of the factor responsible for the slow phase of the vascular response could increase during exercise of longer duration.

We attempted to examine the possible role of decreased vessel wall Po2 in the biphasic vascular response with the same approach used for the high-flow studies. When we asked this question for either the entire biphasic response or the rapid phase only, we reached the same conclusion as we did in the high-flow studies, i.e., vessel wall Po2 does not change rapidly enough to control the entire vascular response or its rapid phase. In contrast, the observed venous O2 response was at least as fast as that predicted by assuming that end-capillary Po2 follows a time course which could control only the slow phase of the biphasic vascular response. We concluded that vascular wall Po2 (and therefore oxidative metabolism also) changes with a time course which is fast enough to control the second phase of the vascular response to a brief tetanus at low flow. This conclusion is, of course, subject to the assumptions outlined above for the high-flow situation.

Our observations of the time course of the change in O2 content of venous blood following a brief tetanus indicate that, whereas the vascular wall Po2 and muscle oxidative metabolism may change rapidly enough to be factors controlling the second phase of the vascular response at low flow, the vascular events are probably too rapid during free-flow and high constant-flow perfusion to be explained by changes in tissue O2. Several other pieces of evidence from these studies seem to fit with these conclusions. The similar time course for the vascular conductance response during free-flow and high constant-flow perfusion implies that the control is not likely to be mediated by a factor whose delivery or removal depends on flow. A mediator with the same rapid dynamics appears to cause the first phase of the biphasic vascular response at low constant-flow perfusion. The magnitude of this rapid phase increases very little with added stimulation. The magnitude of the slow phase of the biphasic response, however, does appear to increase markedly with additional brief tetani as might be expected if oxidative metabolism were involved and more energy were expended. Moreover, the slow phase is only present at low constant-flow perfusion, which is the situation in which the lowest values for vascular wall Po2 would occur. There is strong evidence supporting a role for at least three factors in the production of metabolic vasodilation. These factors are the potassium ion (27), osmolarity (28), and a substance related to oxidative metabolism (29, 30). The concept that two or more factors are involved in the control of vascular resistance during active hyperemia has received considerable experimental support. Skinner and Powell (30) have shown that potassium ions and decreased Po2 have an additive effect in the production of decreased vascular resistance. It now appears that there is a similar relationship between elevated osmolarity and lowered Po2 (31). The biphasic responses at low constant-flow perfusion in the current study support the idea that two or more agents participate in the control of vascular resistance. Furthermore, this study demonstrates that different factors may exert different relative influences on vascular smooth muscle tone depending on the particular type of exercise.

Appendix

Two models were used to predict venous O2 saturation responses from particular time courses of tissue Po2 or muscle oxidative metabolism.

**Tissue Po2**—We predicted a venous O2 saturation response from an assumed time course of change in tissue Po2 equal to that of the vascular response to a brief tetanus as follows:

\[
\Delta \text{Po2}_c(t) = K \Delta \text{R}(t),
\]

\[
\text{Po2}_c(t) = \text{Po2}_c(\text{rest}) + \Delta \text{Po2}_c(t),
\]

\[
\text{Po2}_c(t) = \text{Po2}_c(t),
\]

\[
\text{O2}_c(t) = f(\text{Po2}_c(t)),
\]

\[
\text{O2}_c(t) = \int_0^T \text{O2}_c(T) h(t - T) dt,
\]

where \(\Delta \text{R}(t) = \) change in vascular resistance as a function of time, \(\Delta \text{Po2}_c(t) = \) change in tissue Po2, \(\text{Po2}_c(\text{rest}) = \) resting tissue Po2, \(\text{Po2}_c(t) = \) end-capillary Po2, \(\text{O2}_c(t) = \) end-capillary O2 saturation, \(\text{O2}_c(t) = \) venous O2 saturation, \(K = \) constant relating resistance change to tissue Po2 change, \(f(\text{Po2}) = \) oxyhemoglobin dissociation curve, and \(h(t) = \) estimate of the distribution of vascular transit delays between end-capillaries and the venous measuring site.

\(\text{Po2}_c(\text{rest})\) was determined by the resting venous O2 content and the oxyhemoglobin dissociation curve. The
constant, \( K \), was selected in every experiment so that the total extra \( O_2 \) consumption was equal to that observed experimentally. The convolution integral (Eq. 5) and the assumptions implicit in this set of equations are fully discussed in the text.

**Rate of Oxidative Metabolism.**—The model used to predict venous \( O_2 \) saturation responses from a time course of increased muscle oxidative metabolism assumed to be equal to the time course of decreased vascular resistance is defined by the following set of equations:

\[
M_f(t) = K\Delta R(t),
\]

\[
O_2r(t) = \hat{Q} \cdot (O_2A - O_2v(t)) - M_N - M_f(t),
\]

\[
PO_2(t) = g(O_2r),
\]

plus Eqs. 3, 4, and 5 above, where \( O_2r \) = total tissue \( O_2 \) content (ml/100 g), \( O_2v = \) arterial oxygen content (ml/100 g min\(^{-1}\)), \( O_2A = arterial \) oxygen content (ml/ml), \( O_2e = end-capillary \) blood oxygen content (ml/ml), \( M_N = \) resting mitochondrial \( O_2 \) use rate (ml/100 g min\(^{-1}\)), \( M_f = \) additional rate of \( O_2 \) use in response to exercise (ml/100 g min\(^{-1}\)), \( PO_2 = \) partial pressure of \( O_2 \) in tissue (mm Hg), \( g(O_2r) = \) oxymyoglobin dissociation curve, and \( K = \) constant.

The nonlinear myoglobin and hemoglobin dissociation curves prevented direct solution of these equations. Particular solutions for our experiments were obtained by simulation on an IBM 360/67 digital computer using the IBM continuous systems modeling program. The function \( g \) was obtained from the oxymyoglobin dissociation curve (18) and the assumption that 100 g of muscle contains 0.7 g of myoglobin (32). This function accounts for the small capacity of dissolved \( O_2 \). Similarly, the function in Eq. 3 was defined from the oxyhemoglobin dissociation curve for dog (10) and the assumption that each 100 ml of blood contains 15 g of hemoglobin. In the simulation of particular experiments, the measured values of \( \hat{Q} \) and \( M_N \) were used in the model. The intent was to predict the time course of blood-tissue \( O_2 \) transfer, \( F(O_2A - O_2v) \), resulting from a time course of extra oxidative phosphorylation, \( M_f \), identical to the time course of the vascular response to a brief tetanus. Therefore, we set the shape of the \( M_f \)-time curve equal to the change in the vascular resistance-time curve for each experiment and then adjusted the amplitude so that the area under the \( M_f \)-time curve matched the total extra \( O_2 \) consumption measured in each experiment. The simulation allowed prediction of the time course of change in end-capillary \( O_2 \) content. This value, then, was convoluted with the dye transit curve to obtain the corresponding prediction of the time course of venous \( O_2 \) saturation changes at the measuring site.

This model attempts to deal with the problem arising in relating blood-tissue \( O_2 \) transfer rate to the rate of oxidative phosphorylation (mitochondrial \( O_2 \) use) in dynamic states because of the capacitive effect of tissue \( O_2 \) stores. In general, tissue \( O_2 \) capacitance will cause blood-tissue \( O_2 \) transfer to lag behind the actual time course of \( O_2 \) use in oxidative phosphorylation. For example, a sudden increase in oxidative phosphorylation may not be fully reflected by blood-tissue \( O_2 \) transfer, since stores may transiently supply \( O_2 \). The reverse can occur at the offset of exercise.

Muscle oxymyoglobin is the major contributor to tissue \( O_2 \) capacity. It may be estimated that, at a \( PO_2 \) of 100 mm Hg, 100 g of muscle (70 ml of \( H_2O \)) contains 0.21 ml of dissolved \( O_2 \) and roughly four times that amount of oxymyoglobin, assuming 0.7 g myoglobin/100 g muscle (32). The percent of total \( O_2 \) in the form of oxymyoglobin increases greatly at lower values of \( PO_2 \) owing to the shape of the oxymyoglobin dissociation curve. This curve makes tissue \( O_2 \) capacitance a nonlinear function of \( PO_2 \). The highest effective tissue capacitance values occur at very low values of \( PO_2 \) where the oxymyoglobin dissociation curve is steepest. The lag between the time course of \( O_2 \) use in phosphorylation and blood-tissue \( O_2 \) transfer due to fluctuations in tissue \( O_2 \) stores is most significant at low values of \( PO_2 \) where tissue \( O_2 \) capacitance is the highest. Thus, any consideration of the effects of tissue \( O_2 \) capacitance on \( O_2 \) dynamics depends critically on what range of tissue \( PO_2 \) is involved. The actual situation is considerably more complex with many unknown factors such as geometry, homogeneity of the distribution of myoglobin and mitochondria, and the possibility of significant diffusion barriers for \( O_2 \). For example, it seems likely that, at any one time, different portions of tissue myoglobin are exposed to different levels of \( PO_2 \) since the \( PO_2 \) near the arterial end of a capillary is almost certainly higher than that at the venous end. In addition, a point far from exchange vessels may have a \( PO_2 \) significantly lower than that of blood as it leaves the exchange vessels. There are few data bearing directly on the former point, and there seems to be some dispute as to the magnitude of end-capillary-mitochondrial \( PO_2 \) gradients. Stainsby and Otis (10) reported no drop in steady-state \( O_2 \) consumption of exercising canine gastrocnemius muscle until venous \( PO_2 \) reached values less than 10 mm Hg. Thus the maximum venous blood-mitochondrial \( PO_2 \) gradient during exercise in that study would appear to be 10 mm Hg. Landis and Pappenheimer (5), on the other hand, presented data for cat hind limb which were interpreted to indicate much larger \( PO_2 \) gradients. Both Landis and Pappenheimer (5) and Stainsby and Otis (10) compared their results with those predicted by the simple Krogh cylinder analysis. Landis and Pappenheimer (5) concluded that observed \( PO_2 \) gradients from the end-capillary to the outer tissue radius were larger than those expected from the mathematical analysis, whereas Stainsby and Otis (10) found good agreement between theory and experiment with the muscle exercising. The low values of muscle tissue \( PO_2 \) found with direct microelectrode measurements (33) and inferred from the rapid desaturation of myoglobin during brief exercise reported by Millikan (32, 34) are often viewed as evidence for large \( PO_2 \) gradients from end-capillary blood to mitochondria (5) despite the fact that venous \( PO_2 \) was not measured in these studies. Recently, Whalen et al. (35) have presented data which suggest that, in vivo, cat muscle oxygen con-
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Assumption may be influenced by values of Po₂ considerably higher than those previously assumed to be limiting. Thus, at least in cat muscle, limitation of muscle oxygen consumption when venous Po₂ is high may not be viewed as evidence that blood-tissue equilibrium for O₂ does not exist. There are undoubtedly substantial gradients in Po₂ from the arterial end of exchange vessels to mitochondria, but the existence of such gradients at the venous end is in question.

We have not attempted to use the distributed parameter model which would be necessary to accurately describe muscle O₂ transport. We have used instead a lumped parameter model in an attempt to set limits on the influence of tissue O₂ stores on the dynamics of tissue O₂ delivery.

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References


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