Blood flow, blood oxygen tension, oxygen uptake, and oxygen transport in skeletal muscle

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STAINSBY, WENDELL N., AND ARTHUR B. OTIS. Blood flow, blood oxygen tension, oxygen uptake, and oxygen transport in skeletal muscle. Am. J. Physiol. 206(4): 858-866. 1964.—The effect of changes in blood flow and of blood oxygen tension on oxygen uptake of the in situ gastrocnemius-plantaris muscle group of the dog was examined. Oxygen uptake by resting muscle was not altered by changes in blood flow or blood oxygen tension except when these parameters were reduced below critical values. When the muscle group was contracting once per second, changes in blood oxygen tension were similarly without effect until a critically low value was reached. Although the contracting muscle used eight times as much oxygen per minute as resting muscle, the critical oxygen tension was lower than that for resting muscle. In an attempt to explain this observation the blood-tissue oxygen tension difference was estimated and used in the Krogh equation to calculate capillary density. The capillary density in contracting muscle was found to be much greater than in resting muscle and was about the same as the capillary density measured by others by histological techniques.

METHODS

Sixty-two mongrel dogs weighing from 9 to 41 kg were used in these experiments. They were anesthetized with either sodium pentobarbital, 30 mg/kg, or Dial with urethan (Ciba), 1 ml/2.0 kg, given either intravenously or intraperitoneally. Additional doses of the same anesthetic were given when needed. The trachea was cannulated. The animals were warmed by a low-heat heating pad and radiant heat from a lamp directed at the animals' legs and abdomen so that rectal temperature and muscle surface temperature were maintained between 35.5 and 37.5 C. Blood coagulation was prevented by intravenous Mepesulfate (Hoffmann-LaRoche), 100 mg/kg, initial dose, and 200 mg each hour thereafter.

The muscle preparation used was the in situ left gastrocnemius-plantaris muscle group (Fig. 1). The arterial and venous circulations were isolated surgically by ligating all branches of the popliteal artery and vein which did not go directly to or come directly from the muscle group (25, 26). All other vascular connections to the muscle not associated with the popliteal artery and vein were also ligated. The sciatic nerve was exposed close to the muscle and cleaned of connective tissue. In all experiments the popliteal vein was cannulated and the venous outflow was metered by a recording rotameter (23) and returned to the animal via the left jugular vein. The animals were tilted with the head 5 cm below the popliteal

Received for publication 15 October 1963.

1 This study was supported by National Institutes of Health Research Grant GM 06264 and School of Aviation Medicine, USAF, Contract AF 41 (657)-102.
vein to counterbalance the 5 cm H$_2$O pressure drop across the rotameter and thus to maintain the venous pressure of the muscle at approximately 5 cm H$_2$O. After dissection and cannulation the muscle was covered with saline-soaked gauze and a piece of plastic film to prevent drying and cooling by evaporation. At the end of each experiment, the rotameter was calibrated with the animal's own blood and the muscle was removed for weighing.

Arterial blood samples were taken from the contralateral femoral artery. Venous blood samples were drawn through a small plastic tube threaded through the wall of the venous outflow tubing to the tip of the venous cannula in the popliteal vein. Samples of 0.6 ml were drawn into tuberculin syringes and analyzed spectrophotometrically for oxygen content and per cent saturation (24). In each experiment four larger blood samples were analyzed both spectrophotometrically and manometrically (30) to confirm the calibration of the spectrophotometric method. Oxygen uptake by the muscle group was calculated from the Fick relationship.

In some experiments blood flow was reduced by cannulating the popliteal artery and connecting the tubing to a small Starling resistance bypass device inserted between the femoral artery and vein of the contralateral leg (Fig. 1). This device made it possible, without use of a pump, to perfuse the muscle at any desired pressure at or below the animal's systemic blood pressure (26).

In another series of experiments progressive hypoxia was produced by connecting the tracheal cannula via breathing valves to a 9-liter spirometer half filled with room air and containing a CO$_2$ absorption canister. End-tidal gas was sampled continuously (15) and its Po$_2$ measured by a direct-reading oxygen analyzer (Beckman, model C2). During rebreathing the end-tidal Po$_2$ generally fell at a rate of 2-5 mm Hg/min, but this rate of fall was reduced by 50% in some of the experiments by slowly adding oxygen to the spirometer.

In about one-half of the progressive hypoxia experiments on resting muscle the blood Po$_2$ values were estimated from in vivo dissociation curve. Arterial Po$_2$ was assumed equal to end-tidal Po$_2$ without regard for the probable 10 mm Hg alveolar-arterial Po$_2$ difference which has been reported for the dog (27) and seen by us in more recent experiments. Oxygen saturations determined by the spectrophotometric analysis of arterial samples were plotted against the end-tidal Po$_2$ observed at the time the samples were drawn. The resulting dissociation curve for each experiment, of which Fig. 2 is an example, was used to estimate the Po$_2$ of venous samples from the corresponding spectrophotometrically determined saturation values.

In the remaining progressive hypoxia studies on resting muscle and in all the experiments on contracting muscle the oxygen tensions of both arterial and venous blood samples were measured directly by a Clark electrode in a constant-temperature (37°C) water bath (21). In spite of the probable errors of the in vivo dissociation curve method, the data from comparable experiments using the two different methods did not reveal any noticeable differences in the results.

**RESULTS**

**Control values.** Each experiment began with a 15- to 45-min period during which blood flow and oxygen uptake were measured to obtain base line or control data. The oxygen consumption during this period averaged 6.0 µl O$_2$/g wet wt. of muscle per minute and ranged in different animals from 2.0 to 14.3 µl/g min. Thirty-nine of these muscles were innervated during the control period. The average control blood flow in these experiments was 0.11 ml/g min and ranged in the different experiments from 0.03 to 0.25. The values obtained during these control periods for oxygen uptake and blood flow are presented in Fig. 3. Although there is considerable scatter of the data there is, in general, a direct relationship between oxygen uptake and blood flow. In the denervated experiments the blood flow was higher on the average and much more variable, ranging from .05 ml/g min to 1.0 ml/g min. Since the blood flow de-

![Fig. 2. In vivo blood oxygen dissociation curve constructed by plotting arterial blood oxygen saturation (Sao2) against the end-tidal PaO2 at the time the sample was drawn.](http://ajplegacy.physiology.org/Downloaded fromhttp://ajplegacy.physiology.org/)
creased with time following denervation and because the time between denervation and measurement of control values was not constant, no further analysis of these data was made.

All of the muscles studied showed good isometric autoregulation (26), large changes in perfusion pressure of the muscle being associated with relatively smaller changes in blood flow. The muscles also showed brisk reactive hyperemia following a test period of arterial occlusion.

**Effects of changes in blood flow on oxygen uptake.** In the first series of experiments blood flow through the muscle was reduced by lowering the perfusion pressure of the muscle by means of the bypass device. All of the muscles were innervated. Oxygen uptake was measured at approximately 5-min intervals during the period of reduced flow. An exemplary experiment of this type is shown in Fig. 4A. When the perfusion pressure was reduced, the flow was decreased. The reduction in blood flow was matched by an equivalent increase in the arteriovenous oxygen difference. As a result, the calculated oxygen uptake was unchanged. Representative data from each experiment are presented in Table 1. Some remarkably low levels of venous oxygen content are evident during the period of reduced flow. Even though the venous blood oxygen saturation fell as low as 10% (corresponding to a venous P0₂ of about 10 mm Hg), in no experiment was there a decrease in oxygen uptake.

In four experiments of this series both common carotid arteries were clamped to produce reflex vasoconstriction. An experiment of this type is shown in Fig. 4B. When the carotids were clamped, the resistance to flow through the muscle increased to exactly balance the rise in arterial blood pressure. There was, therefore, no change in blood flow through the muscle. The effects of reducing the perfusion pressure of the muscle during the period of carotid clamping were identical to those obtained when the carotids were not clamped. Oxygen uptake remained unchanged, as observed during reduced flow without carotid clamping.

In a second series of experiments the muscle was perfused without the use of the bypass device. The perfusion pressure of the muscle was reduced by bleeding the animal rapidly until the arterial blood pressure was approximately 50 mm Hg. Presumably, reflex vasoconstriction must have occurred during the period of hypotension. Data from each experiment are presented in Table 1. In all of the experiments except two, the data are essentially the same as in the preceding series of experiments. The blood flow fell along with the blood pressure while the increase in arteriovenous oxygen difference was sufficient to maintain the oxygen uptake. In the two exceptional experiments oxygen uptake was reduced during the hypotensive period. One of these experiments is shown in Fig. 4C. Both are included in Table 1, P-29 and P-31. Experimental dog P-31 was somewhat anemic as evidenced by the low Cao₂, but P-29 was not obviously different from the other dogs in the series. The oxygen uptake deficit was small in both experiments and appeared to be completely repaid by extra consumption of oxygen after the hypotensive period when the bled blood was returned to the animal. The estimated venous oxygen saturation and P0₂ values were low, but not noticeably lower than in other experiments of the group. Apparently the minimal or critical blood P0₂ values below which oxygen uptake is decreased were approached in all the experiments in this series, but in only these two was it actually attained.

The third series of experiments examining the relationship between blood flow and oxygen uptake put to test the effect of increasing blood flow by suddenly removing neurogenic vasoconstrictor tone.

The first method tried has been reported previously (6). Donor dog blood drawn 10 min previously was rapidly infused by gravity into the jugular vein of the dog. Although this transfusion of about 600 ml of blood sometimes increased blood pressure and muscle blood flow temporarily, it just as often caused immediate hypotension and reduced muscle blood flow, probably because of a transfusion reaction. The effect on oxygen uptake in the five experiments on innervated muscle was variable. Three of the five experiments showed an increase in oxygen uptake after the transfusion. The increase in oxygen uptake was not necessarily associated with an increase in blood flow and it was not abolished sometimes even if the transfused volume was bled from the animal. It persisted until the end of the experiment and was always associated with some sign of transfusion reaction, hypotension, urticaria, or both (1, 28). In the other two animals there was a transient increase in blood flow through the muscle but O₂ uptake was unchanged.

Nerve block by cooling was attempted by circulating iced saline through a small brass coil placed around the sciatic nerve. Cooling the nerve produced a sharp increase in blood flow which was accompanied by an increase in oxygen uptake by the muscle. However, visual inspection showed the muscle to be fasciculating. The increase in oxygen uptake was considered to be due to the contractions of the muscle and the cooling procedure was abandoned.

Conduction through the nerve to the muscle was blocked either by injection of 1 ml of 1% procaine into the sheath of the nerve or by double ligation and section of the nerve between the ligatures. These procedures produced a brisk elevation in blood flow to an average of 3 times the control values. The largest increase in flow observed was to 4.6 times the control value. These high flows were transient and decreased gradually, becoming
FIG. 4. Sample experiments. A: blood flow reduced by decreasing perfusion pressure with the bypass apparatus. B: blood flow reduced before and during clamping of the carotid arteries (the carotids were clamped at CC and released at CR). C: blood flow reduced by decreasing the animal's blood pressure (B = bleeding, I = infusion of bled blood). D: blood flow increased by nerve section. E: effect of rebreathing (begun at RB) in an innervated resting muscle (at O₂, oxygen was added slowly to the spirometer to reduce the rate of fall of PaO₂). F: the effect of progressive hypoxia on a denervated muscle contracting once per second. (At the arrow rebreathing and contractions were begun.)
When the relationship between oxygen uptake and spontaneous blood flow for all of the resting innervated muscles is examined (Fig. 3) it appears that a direct relationship exists; the higher blood flows are associated with the higher oxygen uptakes. However, the blood flow through any individual muscle preparation could be experimentally varied over a wide range without causing any change in oxygen uptake. Although each preparation was studied at only one or two experimentally altered flows, the range of flows covered by the different preparations extended from 0.26 to 4.6 times the spontaneous resting value. In only two of the experiments was there any alteration of oxygen uptake. In these a decrease in oxygen uptake occurred when the blood flow was reduced. The general relationship between oxygen uptake and experimentally altered blood flow is shown graphically in Fig. 5.

Effects of changes in arterial blood oxygen tension on oxygen uptake. In these experiments the arterial inflow to the muscle was intact and venous outflow was measured as described above. The animal rebreathed room air to progressively reduce the oxygen tension of the arterial blood. Both innervated and denervated muscles were studied. An exemplary experiment on a resting innervated muscle is shown in Fig. 4E. As end-tidal PO$_2$ fell, the arterial oxygen content decreased. The blood flow generally remained fairly steady as pictured. The oxygen consumption remained steady until a critical PO$_2$ was reached, then decreased progressively with further decreases in blood PO$_2$. The data from denervated muscles were similar except for a sharp rise in blood flow when the critical PO$_2$ was reached. Figure 6 shows the relationship between end-tidal or arterial blood PO$_2$ and oxygen uptake for a few of the experiments in this series. Figure 7 shows the averaged relationship in the 16 experiments in the series for arterial and venous PO$_2$ and oxygen uptake. Oxygen uptake remained constant as the blood PO$_2$ fell until a minimal critical PO$_2$ was reached. On the average the minimum arterial PO$_2$ consistent with the normal oxygen uptake was 60 mm Hg. The corresponding venous PO$_2$ was 25 mm Hg. This critical venous PO$_2$ value appeared to be significantly higher than that obtained in the reduced blood flow experiments. We believe this difference stems from the progressive nature of the experiment and the relatively slow vascular responses of resting muscle. In an effort to make steady state measurements several dogs were made to breathe gas mixtures low in oxygen. Unfortunately, gas mixtures sufficiently

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TABLE 1. Data from reduced flow experiments

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Muscle Wt. g</th>
<th>V0$_2$, ml O$_2$/min</th>
<th>Perf. press., mm Hg</th>
<th>CA0$_2$, V%</th>
<th>CV0$_2$, V%</th>
<th>Q, ml/min</th>
<th>Q, ml/min</th>
</tr>
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<tr>
<td>Bypass Experiments</td>
<td></td>
<td></td>
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<tr>
<td>P9</td>
<td>60.0</td>
<td>3.8</td>
<td>40</td>
<td>20.0</td>
<td>6.0</td>
<td>1.7</td>
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<td>P16</td>
<td>54.5</td>
<td>7.5</td>
<td>50</td>
<td>22.5</td>
<td>4.5</td>
<td>2.0</td>
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<td>P23</td>
<td>46.4</td>
<td>8.2</td>
<td>50</td>
<td>18.0</td>
<td>3.5</td>
<td>4.7</td>
<td>0.71</td>
</tr>
<tr>
<td>P27</td>
<td>45.5</td>
<td>5.5</td>
<td>25</td>
<td>17.5</td>
<td>3.5</td>
<td>2.0</td>
<td>0.37</td>
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<tr>
<td>P28</td>
<td>45.5</td>
<td>5.5</td>
<td>45</td>
<td>16.0</td>
<td>2.0</td>
<td>3.0</td>
<td>0.71</td>
</tr>
<tr>
<td>P30</td>
<td>45.5</td>
<td>5.5</td>
<td>50</td>
<td>15.0</td>
<td>1.9</td>
<td>3.0</td>
<td>0.71</td>
</tr>
<tr>
<td>P31</td>
<td>45.5</td>
<td>5.5</td>
<td>45</td>
<td>19.0</td>
<td>3.5</td>
<td>2.0</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* Acutely denervated. † Carotids clamped.

steady slightly above control values in about 30 min. The experiment shown in Fig. 3D was unique in this series inasmuch as the increase in blood flow occurred gradually. Nevertheless, the increase in blood flow was not associated with an increase in oxygen uptake in this experiment or in any of the experiments in this series. There was, in fact, a small decrease in oxygen uptake, similar to that shown in Fig. 3D, in five of the seven experiments in the series. This could be explained by the existence of a small degree of spontaneous motor nerve activity which was removed when nerve transmission was blocked.

In view of the lack of effect of nerve section on oxygen uptake and of the importance of a possible metabolic effect of transfused blood, the experiments in which donor blood was infused to raise the blood flow were repeated with the muscles acutely denervated. Two of the ten dogs showed a severe transfusion reaction with hypotension. Two dogs developed hypertension after the infusion and maintained mean blood pressures between 150 and 200 mm Hg for the remainder of the experiment. The other dogs showed no significant hemodynamic response to the infusion except for a transient increase in blood pressure and muscle flow during the infusion. None of the dogs showed any changes in oxygen uptake during or after the infusion of blood. We concluded that the increase in oxygen uptake after donor blood infusions in previous experiments was due to an increase in motor nerve activity associated with the transfusion reaction.
low in oxygen to reduce the arterial and venous \( P_{O_2} \) values to critical levels produced such rapid deterioration of the animal that we were not able to obtain valid measurements.

The effects of progressive hypoxia were also studied while the muscle was contracting at a frequency of 1 twitch/sec. The twitches were produced by supramaximal stimulation (10–20 v, 1 msec duration) of the distal stump of the cut sciatic nerve. In the absence of hypoxia the contractions caused an immediate rise in oxygen uptake which then decreased slightly during the next 15 min, at which time it became steady and remained so until the contractions were stopped at the end of an additional 15 min. When the contractions and progressive hypoxia began simultaneously, as shown in Fig. 4F, the oxygen uptake followed the same pattern as just described in the absence of hypoxia until a critical arterial \( P_{O_2} \) was reached. Then the oxygen uptake decreased rapidly with further decreases in arterial \( P_{O_2} \). The critical arterial \( P_{O_2} \) for the contracting muscle averaged 40 mm Hg. The corresponding venous \( P_{O_2} \) was 10 mm Hg. Some exemplary experiments showing the relationship between arterial \( P_{O_2} \) and oxygen uptake are shown in Fig. 8, while the average relationship between arterial and venous \( P_{O_2} \) values and oxygen uptake is shown in Fig. 9.

In contracting muscle as in resting muscle the oxygen consumption remained constant over a wide range of blood oxygen content and \( P_{O_2} \) values. Only when the blood oxygen tension fell below a critical value was oxygen uptake reduced. The critical values for the contracting muscle were remarkably low. Although the oxygen uptake in these contracting hypoxic muscles was eight times that of the resting hypoxic muscles, both the arterial and venous critical \( P_{O_2} \) values were lower in the contracting muscle.

**Discussion**

In these experiments oxygen uptake by resting muscle was not altered by changes in blood flow except when the blood flow was reduced below a minimal or critical value. Similarly, when the blood oxygen tension was reduced, the oxygen uptake was not altered until the \( P_{O_2} \) of the blood dropped below a critical value. Otherwise, the rate of oxygen uptake by resting skeletal muscle in these experiments was regulated by some factor other than the amount and partial pressure of oxygen supplied by the blood.

The present studies disagree with most other reports as to the degree to which the oxygen supply to resting skeletal muscle may be reduced before oxygen uptake becomes supply dependent. The critical blood flows and blood \( P_{O_2} \) values are lower than those reported previously for similar experiments (13, 16, 31). They are, however, similar to other reports of critical values in other vascular beds and in contracting skeletal muscle (7, 8, 10, 22). Not seen in our experiments was any decrease in oxygen uptake associated with reflex vasoconstriction (3, 11, 14, 16). No certain explanation for these differences comes to mind. However, we believe that they may arise from differences in the preparations; our preparations, which avoid the use of pump perfusion and which show vigorous autoregulation, are better able to distribute their blood flow uniformly through nutritional capillaries and are, therefore, able to extract more of the oxygen from the blood.

In the transfusion experiments on innervated muscles and during nerve cooling, increases in oxygen uptake were observed in muscles that were supposed to be resting. These changes in oxygen uptake were sometimes associated with increases in blood flow. However, since nerve cooling produced visible muscle contractions and nerve section abolished the oxygen uptake increase associated with blood transfusions, these increases in oxygen uptake must have been due to activity of the muscle. The transfusion experiments emphasize that the absence of visible contractions is not adequate proof of the resting state. The possible presence of microscopic contractions must always be considered in metabolic studies of resting muscle.

These experiments do not explain the change in oxygen uptake with passive stretch (25). They would seem to lend further credence to the notion that change in blood flow per se is not the cause of this change in oxygen uptake. The same may be said regarding the observation of a decrease in oxygen uptake by muscle during partial venous occlusion (5). Neither do these experiments help...
explain the decrease in oxygen uptake during vasodilator nerve stimulation (29).

When contracting once per second, this muscle group had an oxygen uptake eight times that of resting muscle. During progressive hypoxia this rate of oxygen uptake was maintained undiminished even when the blood PO\textsubscript{2} values were lower than the critical PO\textsubscript{2} values for resting muscle exposed to the same conditions. The critical PO\textsubscript{2} values for the contracting muscles were 40 mm Hg for arterial blood and 10 mm Hg for venous blood. The corresponding values for resting muscle were 60 mm Hg and 25 mm Hg, respectively.

This ability to extract an increased amount of oxygen from the blood despite the lower blood oxygen tensions can only be accounted for by a change in the ability of the tissue to use oxygen at reduced oxygen tensions or by a change in the ability of the circulation to supply oxygen to the tissue. There is no evidence for such a change in tissue metabolism; there is good evidence that activity increases the effective capillary circulation in muscle (9, 17). The magnitude of such changes in this muscle group can be estimated using Krogh's classical equation for the transport of gas from one cylinder, the capillary, to a second cylinder around that capillary (9).

\[
\Delta PO_2 = \frac{\dot{V}_{O_2}}{dO_2} \left( \frac{R}{2} \ln \frac{R}{r} - \frac{R^2 - r^2}{4} \right)
\]

where \( \Delta PO_2 = PO_2 \) gradient from capillary to site of utilization, \( \dot{V}_{O_2} = rate \) of metabolism of oxygen, \( dO_2 \) - diffusion coefficient of the muscle tissue for oxygen, \( r \) - radius of the capillary, and \( R \) = radius of the cylinder supplied oxygen by the capillary, one-half the intercapillary distance.

This equation can be solved graphically for \( R \) and the effective capillary density in the muscle can then be calculated. Oxygen uptake was measured directly. The capillary radius, \( r \), was estimated to be about one-half the diameter of a dog red cell, i.e., 3.5 \( \mu \). Krogh's value for the diffusion coefficient, \( dO_2 \), was used. There remains the \( PO_2 \) gradient for the diffusion of oxygen from the capillary to the sites of utilization, which are presumed to be mainly in the mitochondria.

Oxygen uptake by mitochondria is steady until the extramitochondrial \( PO_2 \) is reduced below 5 mm Hg (4).

The oxygen uptake by the muscle group in the present experiments remained steady until the blood \( PO_2 \) fell to a critical point. Presumably this fall in \( PO_2 \) uptake by the muscle is determined by a reduction in oxygen uptake by the mitochondria. Thus, at the critical point the \( PO_2 \) in the immediate vicinity of the mitochondria is of the order of 5 mm Hg and the gradient for oxygen diffusion will be the difference between the critical \( PO_2 \) of the blood and this value of 5 mm Hg. The question arises as to what value represents the blood \( PO_2 \) for calculation of the gradient. In the Krogh model the mitochondria exposed to the lowest \( PO_2 \) would be at the venous end of the surface of the tissue cylinder. Oxygen will diffuse to this site mainly from the venous end of the capillary. Hence venous \( PO_2 \) at the critical point is a measure of the blood \( PO_2 \) gradient rather than mean capillary \( PO_2 \) which is more traditional and used by us previously (12).

In resting muscles exposed to progressive hypoxia the critical venous \( PO_2 \) was 25 mm Hg. If the critical mitochondrial \( PO_2 \) is 5 mm Hg then the gradient would be 25 - 5, or 20 mm Hg. For the contracting muscles and the resting muscles with reduced flow the critical venous \( PO_2 \) was 10 mm Hg and the corresponding gradient would be 10 - 5, or 5 mm Hg.

Figure 10 is a graphical solution of the Krogh equation for the rates of oxygen consumption observed at rest and during contractions. For the resting hypoxic muscle in which the \( PO_2 \) gradient was estimated to be 20 mm Hg, the observed oxygen uptake of 5 ml/min requires a capillary density of 40/mm². The resting muscle with reduced flow also had an oxygen uptake of 5 ml/g min; the estimated \( PO_2 \) gradient was only 5 mm Hg, indicating a considerable increase in capillary density, to about 150/mm². Contracting muscles during progressive hypoxia also had a \( PO_2 \) gradient of 5 mm Hg, but the oxygen uptake was 40 ml/g min signifying a capillary density of about 700 capillaries/mm².

The capillary density at the critical \( PO_2 \) of the resting muscles exposed to progressive hypoxia appears to be lower than in the resting muscles exposed to reduced flow. This difference may be due to the progressive nature of the hypoxia experiments which does not permit a steady states to be achieved. In the absence of a steady
Muscle Oxygen Supply

The effective capillary bed in this muscle group is altered in response to changes in oxygen supply or metabolic rate. Since the response occurs in the absence of extrinsic innervation, it must be autonomous or, in present terminology, autoregulated. The mechanism is unknown.

We thank Drs. S. M. Cain and N. Joels for their advice and assistance during some of these experiments. We also thank Patricia Bodiford for her excellent technical assistance, and D. Logadou, E. Clarke, and S. Sanders who participated in some of these experiments while they were medical students.

The number of capillaries in this muscle group has previously been measured histologically (19) and found to be about 750/mm². The close agreement of this figure with our calculations from contracting muscles is better than expected, and may be fortuitous. All the known experimental errors would result in overestimation of the calculated capillary density greater than that measured histologically. Regarding such a discrepancy one might consider several likely sources of error in the Krogh relationship. Krogh measured the diffusion coefficient in tissue which did not contain myoglobin. Myoglobin in solution has been shown to enhance diffusion of oxygen in sintered-glass disks (20). The myoglobin in mammalian skeletal muscle might increase the rate of oxygen transfer in the tissue. The value for do₂ used in the Krogh equation may be too low. Mechanical stirring within contracting muscle could also contribute to the transport of oxygen.

There is also the possibility that the Krogh model is anatomically too gross an oversimplification. Although skeletal muscle shows the parallel arrangement of the capillaries required for the Krogh model, flow through adjacent capillaries is not necessarily in the same direction. If counterflow occurs to a significant degree the Krogh analysis would not be valid. Furthermore, the Krogh analysis makes no allowance for longitudinal diffusion of oxygen in the tissue around the capillary (6).

It is certain that these muscles do not use all of their potential capillary beds when at rest. It is not yet known why there is no flow through such a large proportion of these vessels, but it is easy to speculate that this indicates regulation of oxygen tension in the tissue. For some reason it may be desirable to keep tissue PO₂ at a low level. This seems to us to be an interesting possibility worthy of further investigation.

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