Microvascular pressure distribution in skeletal muscle and the effect of vasodilation

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Fronek, K., and B. W. Zweifach. Microvascular pressure distribution in skeletal muscle and the effect of vasodilation. Am. J. Physiol. 228(3): 791-796. 1975.—In cats anesthetized with pentobarbital, 188 direct microvascular pressure and diameter measurements were made of the tenuissimus muscle. The microvascular pressure in arterioles of 70 μm in diameter or larger was proportional to the systemic arterial pressure (PA). The arterioles with diameters ranging from 35 to 20 μm have been shown to be the principal source of arteriolar resistance regulating micropressures down stream. Across the capillary bed proper, the drop in pressures was about 15% of PA. Micropressures in the smallest venules (8-15 μm) averaged 24 mmHg and reflect closely capillary blood pressure. With a background of basic microvascular data, the vasodilatory mechanism of papaverine (P) and isoproterenol (IPR) in the skeletal muscle was analyzed. Administration of IPR decreases both arteriolar and venular pressure, while P infusion decreases the pressure in arterioles wider than 20 μm in diameter; however, in smaller arterioles there was a substantial elevation in micropressure. The data establish two basically different vasodilatory effects on the terminal vasculature: one with increased capillary pressure and fluid filtration (P), a second with a decrease in capillary pressure enhancing absorption (IPR).

The relationship between changes in capillary pressure and the decrease in systemic blood pressure triggered by vasodilation has not been as well established, by direct means, as the importance of this relationship in the microvascular of skeletal muscle. Most of our current information has come from indirect studies of fluid exchange and pressure-flow relationships in whole limbs or in surgically isolated muscle preparations (14).

METHODS

Experiments were performed on 40 cats, each weighing about 2 kg, anesthetized with pentobarbital 30 mg/kg. No additional medication was used. The common carotid artery and jugular vein served as the site for systemic arterial and central venous pressure measurements. The m. tenuissimus was chosen because it is known to contain both fast and slow muscle fibers and can be taken to represent a typical skeletal muscle (8). Anatomically, it runs from the sacral and coccygeal bones down to fascia cruris of the hindlimb. It is about 0.5 cm wide, some three to six muscle-fiber layers thick, and approximately 10–12 cm long. The central artery representing the main blood supply is accompanied by a vein and nerve. The basic anatomical layout is shown in Fig. 1. Details of the dissection have been described by Brånemark and Eriksson (4) and here we will describe only modifications of their original approach.

Close to the fascia cruris is the thinnest portion of the muscle, which contains only two to four layers of muscle fibers and, therefore, offers the most suitable site for transillumination for microscopy. Special care was taken to remove the connective tissue from the surface to demude the muscle fibers and the blood vessels between them. The cat was placed on its side in a plastic mold of the body leaving only the hindlimb, bent at a 90° angle in the knee, fully exposed. A 12-cm-long light pipe with a prism fused to one end was used to direct the light and was slipped sidewise under the lateral edge of the muscle, so that the tissue rested loosely and flat on the surface prism, giving about a 5-mm² working area. A green filter was placed between the light source and light pipe for better optical resolution. Throughout the dissection, as well as during micropressure measurements, the muscle was kept moist with a continuous drip of isotonic Krebs solution containing 1/2: gelatin and maintained at 37°C.

The microscopic observations and micropressure measurements were made from the upper surface of the muscle, adjusted to the hydrostatic level of the heart. The light...
source was mounted on the same holder as the plaster body mold for the cat, so that it moved with the cross stage of the microscope. Magnifications of X300–400 were obtained with UM Leitz objectives having a long working distance. By changing the focus, microvessels at different depths of the muscle were available for observation and micropuncture. The pressures in microvessels (7–200 μm) were measured by using glass micropipettes with sharpened tips to 2–4 μm (OD) filled with 2 M NaCl and inserted into selected microvessels with the help of a micromanipulator. The micropipettes were connected with the servo-nulling pressure-pump system developed by Wiederhielm et al. (22) and modified by Intaglietta et al. (16). The diameter of the examined vessel was determined in two ways. Vessel dimensions on polaroid prints were compared with a calibration grid. The second diameter-measurement technique is based on the image-splitting technique described by Baez (2), and modified by Intaglietta and Tompkins (17), in which the optical image splitting was replaced by an electronic shearing system with repeatability within 0.5 %.

In the present experiments, microvascular pressures were evaluated in relation to the diameter of selected vessels and to the systemic arterial pressure. Infusion of papaverine (P) intravenously was administered in 54 runs in a dose from 100 μg/min per kg to 1 mg/min per kg body wt. Each infusion was maintained for several minutes to achieve a new steady state of the systemic arterial pressure. Isoproterenol (IPR) was administered intravenously in 48 check runs in a dose from 0.1 to 1.0 μg/min per kg body wt. Whenever a new steady-state level of systemic blood pressure was achieved, the infusion was discontinued. The effect of drugs was evaluated in relation to the dose, systemic blood pressure response, microvascular pressures, and to the size of given microvessels.

RESULTS

Steady-state conditions. Pressures in the central artery are within 95–90 % of the systemic blood pressure. The diameter of this artery ranges from 70–100 μm, depending on the size of the cat as well as of the muscle. The first order branches from the central artery which were readily accessible to micropuncture course perpendicularly across muscle fibers. Eriksson used Spalteholtz’s classification and denotes
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this first generation as transverse arterioles (Fig. 2). The
diameter of such arterioles varies from 70 to 20 μm. Direct
measurements show the blood pressure in these vessels
to average 70% of the systemic pressure (Fig. 4). The trans-
verse arterioles subdivide into a number of lateral off-
shoots—short precapillaries or metarterioles (4) with diam-
eters between 20 and 10 μm—or branch directly into five
to eight true capillaries which then course between the
muscle fibers (Fig. 3). Even when anatomically distinct
precapillary sphincters cannot be determined, the significant
site of precapillary resistance regulation in the skeletal
muscle is located in vessels larger than 20 μm in diameter,
as shown by the microvascular pressure drop. The true
capillaries, i.e., smaller than 10 μm in diameter, are accessible
for micropuncture only when they are located on the
surface of the muscle; otherwise, direct intubation was
difficult.

The pressure drop across the true capillaries proper is
approximately 15% of the systemic pressure. Several ve-
nous capillaries form small venules. The blood pressure in
these venules (<10–12 μm) is 24 mmHg and probably reflects
closely (within 2–3 mmHg) the hydrostatic capillary pres-
Sure. Venular pressures then decrease sharply to 20 mmHg
when confluent vessels 20 μm in diameter are formed.
Further distally, the gradual decrease in venular pressure is
proportional to the size of the vessel and in the central
vein (average diameter: 140 ± 20 μm) ranges from 8 to 14
mmHg (Fig. 4).

The micropressure distribution in two different tissues
(Fig. 4) indicates that in the mesentery, pressure falls within
the dichotomization of the larger feeding vessels (>35–40
μm) on the arterial side by almost 50% before the blood
enters the precapillaries and capillaries itself. On the other
hand, in the skeletal muscle, the blood pressure remains
above 60 mmHg in the terminal arterioles and precapillary
vessels. The next abrupt fall in microvascular pressure in
the muscle is the result of a splaying out of five to eight true
capillaries from a single terminal arteriole. Capillary pres-
sure in the cat mesentery is, on the average, less than 1
mmHg higher than the capillary pressure in skeletal muscle.
But the pressure in collecting venules of the mesentery is
higher (20.7 ± 1.5 vs. 11.5 ± 0.6 mmHg), presumably

because they drain into the portal vein. In the skeletal
muscle, the venular pressure falls gradually to the average
value of 11.43 ± 0.65 mmHg in the central vein.

Precapillary and postcapillary resistance comprises the
total resistance on the arteriolar and venular side, respec-
tively. For this calculation, pressure closest to the capillary
pressure were used, i.e., Pa and Pv. This approach is
applicable, especially in view of the fact that the resistance of
ture capillaries is constant. In spite of the fact that flow
was not measured, an attempt was made to express the pre-to-postcapillary resistance ratio in the following way:

\[ \frac{BP - Pa}{Q} = PrR \text{ or } BP - Pa = PrR \times Q \]  

(1)

and

\[ \frac{Pv - VP}{Q} = PsR \text{ or } Pv - VP = PsR \times Q \]  

(2)

where BP and VP are systemic arterial and central venous
pressures, Q is the flow through a given vascular region,
Pa = mean pressure in the smallest arterioles (10–12 μm),
Pv = mean pressure in the postcapillaries venules
(10–15 μm), PrR = precapillary resistance and PsR =
postcapillary resistance. If we assume that the inflow for
the terminal part of the arterioles and the venular outflow are
the same, dividing equation 1 by equation 2 results in the
following relationship:

\[ \frac{BP - Pa}{Pv - VP} = PrR/PsR \]  

(3)

Our findings suggest that the ratio of precapillary pressure
drop to postcapillary pressure drop is the same as the pre-
capillary-to-postcapillary resistance ratio (Table 1).

The pre-to-postcapillary resistance ratio calculated in this way
was, on the average, 3.37 ± 0.57, which is close to that
derived from indirect measurement by Folkow and Mel-
lander (9, 20), or from direct microvascular pressure-flow
determination established for the cat mesentery (12).

Effect of vasodilation. Two drugs were used to induce pe-
ripheral vasodilation, papaverine and isoproterenol. Papav-
erine was administered by intravenous infusion increasing
the dosage in steps from 100 μg to 1 mg/min per kg body
wt. Altogether 54 experimental runs were analyzed, and
the micropressure changes in the skeletal muscles were
compared with the systemic arterial pressure changes. As
expected, the decrease in systemic arterial blood pressure
due to vasodilatation was proportional to the administered
dose. The pressure drop in the larger arterioles (>20–25
μm) is dose dependent, but as shown in Fig. 5, the reduction in
pressure is proportionally smaller in the consecutively
smaller arteriolar segments until reaching the terminal
arterioles or precapillary vessels below 20 μm in diameter
in which the micropressures actually showed a significant

### TABLE 1. Pre-to postcapillary resistance ratios in tenuissimus muscle

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<thead>
<tr>
<th></th>
<th>Papaverine</th>
<th>Isoproterenol</th>
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<tbody>
<tr>
<td></td>
<td>100–1000 μg</td>
<td>0.1–0.4 μg</td>
</tr>
<tr>
<td></td>
<td>kg⁻¹ min⁻¹</td>
<td>kg⁻¹ min⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>3.37 ± 0.57</td>
<td>3.87 ± 0.65</td>
</tr>
<tr>
<td></td>
<td>±0.42</td>
<td>±0.46</td>
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<tr>
<td></td>
<td>±0.46</td>
<td>±0.46</td>
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<td></td>
<td>±0.31</td>
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Values are means with variations expressed as ± SE.
increase. This elevation of blood pressure in the precapillary vessels following systemic administration of papaverine is proportional to the dose and is transmitted to the venular side (Fig. 5). The effects of papaverine on blood pressure become less evident in the larger venules. In venules 80 μm in diameter and larger, no change in pressure was observed following papaverine.

The substantial difference in the effect of papaverine on arterioles smaller than 20 μm, as compared with that in larger vessels, suggests a considerable fall in the resistance in these large vessels since systemic arterial pressure dropped by approximately 12%, while the arteriolar micropressure in smaller vessels was increased by approximately 10%. In contrast to papaverine, the administration of isoproterenol in 48 experiments was associated with a reduction by approximately 12%, while the arteriolar micropressure in smaller vessels was increased by approximately 10%.

In the mesentery the feeding arterioles dichotomize into successively smaller terminal vessels (10) with relatively few abrupt side branchings as is the case in the m. tenuissimus. As a consequence, microvascular pressures are reduced in the mesentery more gradually with the subdivisions of the large arterioles.

**Discussion**

The servo-nulling micropressure technique is well established as a reliable procedure with regard to accuracy and reproducibility (24). Special care was taken to include only the results of those experiments in which the blood flow was not impeded by the microneedle. Despite these precautions in very small capillaries (6-8 μm), it was sometimes difficult to achieve ideal conditions. As long as the pipette was oriented along the midline of the vessel and our objectives were steady-state conditions or slow changes in blood pressure, the error of measurement was within 2.3% (16). On the basis of 188 micropressure measurements, conclusions can be drawn regarding the pressure distribution with the use of diameter to set up certain vessel categories in the skeletal muscle. Microvascular pressures were directly proportional to the systemic arterial pressure only in vessels with an average diameter of over 70 μm.

Since the major pressure drop in skeletal muscle is seen in arterioles with diameters ranging 35-20 μm, it can be concluded that vessels larger than 20 μm in diameter are the principal source of arteriolar resistance regulation in the m. tenuissimus. Micropressures in vessels smaller than 20 μm (metarterioles) depend primarily on the precapillary pressure. Bräncmark and Eriksson (4) have shown that skeletal muscle arterioles down to a diameter of 20 μm continue to have smooth muscle cells in the vessel wall.

From our data on micropressure distribution in relation to vessel diameter, it can be concluded that the term precapillary resistance is related anatomically to the transverse arterioles and their branches which usually terminate in five to eight capillaries. This anatomical arrangement of the terminal vasculature in skeletal muscles is quite different from that in the mesentery and from that in other muscle beds, such as the spinotrapezius and cremaster muscles in the rat. The feeding artery for m. tenuissimus is a direct branch from the femoral artery and, therefore, the pressure in this central arteriole is close to the systemic arterial pressure. This is not the case in the cremaster and this may explain why the arteriolar and venular micropressures are lower in the m. tenuissimus than in the m. tenuissimus (21). Furthermore, the average capillary length in the m. tenuissimus is 1,015 μm (8) creating a pressure drop of 15 mmHg, while in m. cremaster it is only 615 μm and the pressure drop is only 7 mmHg (21).

In the mesentery the feeding arterioles dichotomize into successively smaller terminal vessels (10) with relatively few abrupt side branchings as is the case in the m. tenuissimus. As a consequence, microvascular pressures are reduced in the mesentery more gradually with the subdivisions of the large arterioles.
The microvascular pressure in venules below 10 μm in diameter has been found to reflect closely (within 2–3 mmHg) the capillary pressure as determined directly in the skeletal muscle. The average of this pressure in venules smaller than 10 μm in our experiments was 24 ± 2.2 mmHg, which is in good agreement with the results obtained in cat mesentery experiments (12). In spite of the wide range of capillary pressures, various direct and indirect measurements of microvascular pressures performed recently on the dog hindlimb (11), or in the past on the wall of the cat intestine (18) or human skin around the nail fold (7), yielded values of capillary pressure essentially the same as in these experiments.

The vasodilatory effect of papaverine and isoproterenol on the peripheral circulation is well characterized. However, the effect of these substances on the terminal vascular bed is not well documented. A comparison of the mechanism of action of both drugs cannot be performed solely on the basis of systemic arterial blood pressure drop. Isoproterenol has, in addition to its dilatory effect on the peripheral circulation, an inotropic and chronotropic effect causing an increase in stroke volume, heart rate, and thus in cardiac output, which compensates to some extent the effect of a drop in peripheral arterial resistance (1, 5). In the case of papaverine, however, a direct effect on the heart muscle is far less pronounced (5). It is possible, due to this difference in central influence, that the decrease of systemic arterial blood pressure after administration of IPR may be accompanied by a greater decrease in precapillary resistance than that induced by papaverine. The present experiments indicate a significant difference in the mode of action on the terminal vasculature. During the administration of papaverine there was a decrease in microvascular pressure in the larger arterioles (>20 μm in diameter), while in smaller arterioles there was a consistent elevation in blood pressure, even when the administered dose was increased 10 times, which was transmitted through the capillary bed and was measurable on the venous side of the terminal vasculature. Thus, the pressure difference between the arteries and arterioles is, on the average, 22 mmHg after papaverine administration as compared with 35 mmHg during the control period. However, despite the reduced driving force, capillary pressure is elevated apparently because of the dilatation of the terminal arterioles or postcapillary vessels, while the postcapillary vessels are probably less influenced. These conditions would give rise to filtration in the tissue space.

The smallest dose of isoproterenol used, 0.1 μg/min per kg, had an effect on both arteriolar and venular micropressures and higher doses led to further arteriolar vasodilatation. Diana (6), in autoperfused-hindlimb experiments, using either constant flow or constant pressure during IPR administration, determined isogravimetrically a modest increase in capillary pressure. In our experiments with isoproterenol infusion, as the central arterial pressure decreases, both arteriolar and venular micropressures drop, therefore, the mean capillary pressure can be assumed to be lower. This evidence would tend to support Mellander’s (19) conclusion that IPR decreases precapillary as well as the postcapillary resistance. However, in contrast to Mellander’s contention, according to which filtration increases, it can be assumed that the resulting decrease of capillary pressure in skeletal micropressures leads to absorption to fluid from tissue into the blood. Such an explanation may account for the observations that some vasodilator agents do not increase lymphatic flow while others double or even triple lymphatic flow (18). Our results indicating differences in effects of papaverine and IPR would appear to be germane to these findings.

In conclusion, in spite of the fact that papaverine and isoproterenol are both considered to be potent vasodilators, their different actions on precapillaries determine the final effect on the capillary pressure and, therefore, the conditions for fluid transfer in skeletal muscle.

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