ARTICLES ORIGINAUX

CAPILLARIES AND FLOW REDISTRIBUTION PLAY AN IMPORTANT ROLE IN MUSCLE BLOOD FLOW RESERVE CAPACITY

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ABSTRACT:

Capillaries and flow redistribution play an important role in muscle blood flow reserve capacity.

Perfusion of skeletal muscle varies considerably during rest, exercise, or when arteries are occluded. The extent that a muscle can adapt to changes in flow demand is often expressed as the ratio of the highest inducible flow and control flow, the microvascular blood flow reserve capacity (MBFRC). However, perfusion of the nutritive capillaries of skeletal muscle may not only be improved by the increase in blood flow proportional to the increase in arterial flow, but also by diverting originally shunted flow towards the muscle proper. Consequently, MBFRC is not a good measure of capillary flow reserve, unless the assessed flow in both conditions is purely nutritive in nature. Therefore, in critical conditions, flow measurements in large vessels are not appropriate to assess MBFRC.

In muscle, capillaries are compliant, i.e., with varying transmural pressure capillary diameter varies. During high perfusion states, when capillary transmural pressure is increased, capillary compliance results in increased capillary diameter and, hence, in reduced resistance and increased exchange surface area. This results in improved perfusion and enlarged capillary exchange surface area. In low perfusion states, capillary diameter is reduced. This augments the detrimental effects of the low perfusion status. Operative restoration of perfusion pressure not only increases the driving force for perfusion, but also leads to (passive) dilatation of the capillary bed and an extra reduction in resistance to flow, and, hence, a disproportional increase in flow. (J Mal Vasc 2002; 27: 63-67)


RÉSUMÉ:

Les capillaires et la redistribution sanguine du flux jouent un rôle important dans la réserve microcirculatoire du muscle strié.

La perfusion capillaire du muscle strié varie considérablement entre l’état de repos et celui d’exercice ou lorsque les artères d’amont sont occluses. La capacité de cette adaptation aux besoins est exprimée comme le quotient entre le débit maximum sur le débit basal. C’est ce que l’on appelle la réserve microcirculatoire. Toutefois, la perfusion nutritive des capillaires du muscle strié n’est pas seulement améliorée par l’augmentation du flux proportionnelle à l’augmentation du flux artériel, mais aussi par une redistribution du flux des shunts vers le flux nutritif. Ainsi, la réserve microcirculatoire telle que définie plus haut ne représente-t-elle qu’une partie de la réserve réelle capillaire sauf si les conditions de mesure sont dans des situations nutritives analogues. C’est pourquoi, dans certaines situations critiques, la mesure du flux macrocirculatoire n’est pas représentative de la mesure microcirculatoire et ne doit pas être utilisée pour cette mesure.

Le capillaire du muscle strié est compliant, i.e., son diamètre varie en fonction de la pression transmurale.

En situation de haut débit, quand la pression transmurale est augmentée, la compliance artérielle induit une augmentation du diamètre capillaire et donc une diminution des résistances et une augmentation de la surface capillaire d’échanges.

Ceci provoque une amélioration de la perfusion et une augmentation de la filtration.

A l’inverse et en situation de bas débit, le diamètre capillaire est diminué ce qui aggrave comme un cercle vicieux les effets de cette mauvaise perfusion.

La restauration thérapeutique de cette pression de perfusion augmente non seulement les forces de perfusion, mais aussi entraîne une dilatation passive du lit capillaire et donc une réduction supplémentaire des résistances au flux, conduisant à une augmentation supplémentaire du flux. (J Mal Vasc 2002 ; 27 : 63-67)

The state of activity of skeletal muscle largely determines its metabolic needs, which will be attended by changes in [effectiveness of] capillary perfusion and metabolic efficiency. Perfusion of muscle capillaries is regulated by diameter changes of the pre-capillary resistance vessels (1). This may lead to a generalized increased capillary perfusion or in redistribution of capillary flow. In case the muscle vascular bed is not capable of increasing perfusion to the required level [as in peripheral vascular disease] and metabolism becomes inadequate, the muscle becomes at risk. A variable often used to quantify the level of possible vascular flow improvement is the microvascular blood flow reserve capacity (MBRFC). Usually, it is defined as the ratio of maximal inducible flow [by exercise or other means] and control flow.

Whether MBFCR is a good descriptor of the actual capacity of a muscle to maintain tissue metabolism, perfusion, and nutrition depends on whether flow is only nutritive in nature and the metabolic process remains the same under the various conditions.

**VASCULAR ARRANGEMENT IN SKELETAL MUSCLE**

The arrangement of the vasculature within a skeletal muscle determines the effectiveness of its capillary perfusion. The number of large blood vessels entering the muscle depends on the actual size and thickness of the muscle. Large flat muscles, such as the musculus pectoralis, and some non-flat muscles, contain several input vessels and an extensive meshwork of anastomosing large vessels (2). This built-in system of collateral blood vessels is capable of maintaining appropriate capillary perfusion when flow through one of the input vessels is impaired. Moreover, local flow disturbances may be compensated for through preexisting collateral pathways. In other muscles, such as the musculus gastrocnemius, anastomosing interconnections are usually limited to the largest intramuscular vessels.

Branches from the major arteries distribute the blood to the various sub-units of the muscle. These secondary arteries run parallel to the muscle fibers in the thickest part of the muscle sub-unit. The architecture of the vasculature of the tenuissimus muscle of rabbit and cat may be considered as representative of the vascular units of larger muscles (3). In this muscle, the central artery is equivalent to the secondary artery in larger muscles. In thin, flat muscles, such as tenuissimus muscle, the terminal arterioles and venules branch into a two-dimensional pattern. In thick muscle, this pattern is three-dimensional. Transverse arterioles branch from the central artery and run perpendicular or oblique to the muscle fibers. Their branches are the terminal arterioles that end in a dichotomizing vascular network ending in numerous capillaries, which run in between the muscle fibers and may form interconnections. Finally, the capillaries drain into venules that collect into a network of veins. In muscle, shunting of flow may occur through two pathways. As in tenuissimus muscle, in all other muscles arteriovenous “bridges” may be found in the connective tissue septa, forming a natural shunt for non-nutritive flow. Capillaries with a larger diameter may also function as shunts and are often called thoroughfare channels. In rabbit tenuissimus muscle, the arteriovenous “bridges” in the connective tissue provide a mechanism to prevent complete cessation of flow during low perfusion states; they still carry flow when capillary flow ceases in the muscle proper. This also means that some flow is still carried by the transverse arterioles, which avoids complete flow cessation in the muscle. As a result, yield stress (4) between vessel wall and blood has to be overcome in a much smaller portion of the muscle vasculature and flow is much easier resumed.

The balance between flow through the muscle proper, the “true” nutritive flow, and shunt flow is regulated by diameter changes of the arterioles. Lindbom (5) measured in rabbit tenuissimus muscle blood flow in transverse arterioles at the orifice and at the site where they leave the muscle to enter the connective tissue. While flow into the transverse arteriole changed considerably during functional hyperemia (resulting in almost 3-fold flow), shunt flow changed only 1.75-fold. Exposure to a high oxygen environment virtually shuts down the perfusion of the muscle capillaries, while shunt flow is hardly changed. Consequently, changes in muscle perfusion obtained through measurements performed at the input of the muscle under varying conditions do not necessarily reflect changes in nutritive muscle perfusion.

**DYNAMIC PERFUSION PATTERNS**

In skeletal muscle at rest, perfusion is not always stationary. More or less rhythmic variations in flow velocity [flowmotion, (6)] may be observed, that originate from more or less rhythmic contractions and dilatations of arterioles [vasomotion, (7)]. Often vasomotion and flowmotion patterns are observed that have two rhythms superimposed that originate from different arterial branching levels. At rest, about 70-80% of capillaries is perfused. In exercising muscle, most capillaries are perfused after or in between contractions. With a transition from rest to exercise, two ways of capillary recruitment may be discerned; temporal recruitment, i.e., flowmotion disappears and perfusion becomes continuous, and spatial recruitment, i.e., non-perfused capillaries become perfused by opening of previously closed arterioles. When perfusion pressure is reduced and flow has to be maintained, dilatation of the arterioles will occur. This results in a change in the vasomotion pattern. Ultimately, vasomotion will disappear due to progressive arteriolar vasodilatation (8).

**CAPILLARIES**

Capillary diameter is determined by a balance between the extending force of the transmural pressure (difference between pressure inside the capillary and tissue pressure) and the counteracting force exerted by the capillary wall itself (tube in a liquid model) or that of the surrounding tissue (tunnel in a gel). Usually, capillaries are considered to be like a tunnel in a gel and to have an invariant
diameter (9). In skeletal muscle several reports (10-13) have demonstrated that capillary diameter actually varies with changes in transmural pressure. In muscle in which hyperperfusion was induced by dilatation of the arterioles with a high dose adenosine in the suffusion solution, capillary diameter increased on the average by as much as 26%, as compared to the resting state (11). Maximal capillary diameter increased on the average by as much as 60% and, according to Poiseuille’s law, capillary conductance to flow velocities and shear rates, and an enlarged capillary surface area available for exchange of nutrients and metabolites.

During experiments with (partial) aortic occlusion to a level that resulted in almost complete cessation of flow through the capillary bed, capillary diameter was reduced by about 6% (10). Such a minor diameter change would still result in a decrease in conductance and, hence, flow by 22% in case capillary perfusion pressure would not change. Lee and Schmid-Schönbein (12) demonstrated that in the extreme case of zero transmural pressure, capillaries virtually close for perfusion. Such dramatic changes, however, were not observed in rabbit tenuissimus muscle, even during complete aortic occlusion.

Whether the changes in capillary diameter as a result of changes in transmural pressure are caused by the compliance of the capillary wall or low tissue stiffness is still not known.

FACTORS DETERMINING MUSCLE PERFUSION (DURING EXERCISE)

Skeletal muscle perfusion is not only influenced by perfusion pressure and mean arteriolar diameter, but also by the vasomotion pattern, which determines effective diameter (14). During exercise, capillary flow may be enhanced by several causes: 1. Temporal recruitment: disappearance of vasomotion and, hence, flow, 2. Spatial recruitment: capillaries without flow become perfused by opening of previously closed arterioles, and 3. Compliance of capillary wall: capillary diameter increases due to elevated transmural pressure. Or in other words, arteriolar vasomotion and capillary distensibility contribute to the characteristics of skeletal muscle perfusion. To illustrate this, we consider a skeletal muscle at rest with a certain perfusion pressure of $\Delta P_0$. Assume that capillaries are only effectively perfused for 50% of the time, either due to vasomotion or due to spatial heterogeneity in which case 50% of the capillaries is excluded from flow for extended periods. Let volume flow be $F_0$ and flow velocity be $v_0$ for each of the perfused capillaries (open circles in table I) and be zero for the non-perfused ones (closed circle). Mid-capillary pressure of a muscle at rest is in the order of 25 mmHg and pressure difference over the capillary bed about 5mmHg (15). Hence, post-capillary venous pressure is about 22.5mmHg. We also assume that this pressure is invariant. With all capillaries recruited [no vasomotion or preferential closing of (terminal) arterioles] the same perfusion pressure, $\Delta P_0$, would lead to a flow of $F_0$ and a flow velocity of $v_0$ in all capillaries, resulting in doubling of muscle perfusion without affecting perfusion pressure. During heavy exercise, volume flow through the muscle may increase up to twenty-fold. All capillaries will then be perfused and volume flow through each of the capillaries will be 10$F_0$. In case of an invariant capillary diameter, this ten-fold capillary flow would result in a ten-fold pressure difference over the capillary bed, i.e., 50 mmHg. As a result, mid-capillary pressure would be as high as 22.5+25=47.5 mmHg. Pre-capillary transmural pressure would be as high as 22.5+50=72.5 mmHg. Let us now assume that this condition of heavy exercise is comparable to that during adenosine suffusion. Bosman and colleagues (10) demonstrated that, under those conditions, capillary compliance results in a capillary diameter increase of 26%. Or in other words, capillary diameter increases to 1.26 $D_0$, with $D_0$ being capillary diameter at rest. Resistance would drop to $[1.26]^{-2}$, or 40%, and the pressure difference over the capillary bed would only be 20mmHg, resulting in a mid-capillary pressure of only 32.5 mmHg and a pre-capillary pressure of 42.5 mmHg. Such values seem much more realistic than values of 47.5 and 72.5 mmHg for mid- and pre-capillary pressure in the absence of capillary adaptation.

Given the fact that for a compliant capillary velocity during exercise is decreased to 60% and diameter increased by 26% when compared to the situation in a rigid capillary, wall shear rate is decreased to 48% when the parabolic flow conditions may be applied.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Each circle represents 50% of capillaries. Open indicates perfused. Filled indicates non-perfused. Pairs of data refer to the pairs of circles. Pressure drop over capillary bed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Vasomotion</td>
<td>No vasomotion</td>
</tr>
<tr>
<td>Capillary Diameter</td>
<td>$D_0$</td>
</tr>
<tr>
<td>Volume flow</td>
<td>$F_0$; $0$</td>
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<tr>
<td>Flow velocity</td>
<td>$v_0$; $0$</td>
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<tr>
<td>Pressure drop</td>
<td>$\Delta P_0$; $\Delta P_0$</td>
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</table>

MUSCLE IN PERIPHERAL VASCULAR OCCLUSIVE DISEASE

Measurements by Clark and colleagues (16, 17) during rest and exercises in man suggest a tight regulation of the proportion of nutritive and non-nutritive flow. As a result, it influences muscle metabolism and contraction by regulating delivery and removal of products. The non-nutritive shunt flow may be considered as flow reserve, by rerouting non-nutritive flow towards nutritive flow. Inadequate recruitment of this shunt-flow may result in reduced perfusion efficacy.

When perfusion pressure is low, as in peripheral vascular disease, capillary recruitment in human skin is very limited. To accommodate flow demand under these conditions, even at rest all capillaries are always perfused. Since the arterioles are already [almost] maximally dilated at rest, reactive hyperemia does not induce an increase in diameter (18) and, hence, flow and therefore transmural pressure remains low. Let us assume that in peripheral vascular disease the conditions in muscle are comparable with those in the skin. In that case, an increased flow demand will not change perfusion or transmural pressure. Therefore, capillary diameter will hardly change. This indicates that the resistance lowering effect of capillary diameter increase during exercise is absent. Nutritional flow and exchange capacity remains low. Restoration of perfusion pressure will affect perfusion more than proportionally; the resulting increased transmural pressure will induce an increase in capillary diameter and, hence, increase in conductance.

CAPILLARY WALLS ARE INVESTED WITH A GLYCOCALIX

Capillary perfusion is not just determined by its geometry. Surface charge of the capillary wall modulates capillary red blood cell velocity-flux relationships in hamster cremaster muscle (19). Moreover, the physical capillary cross-section available for perfusion is not the same for red blood cells, white blood cells, and plasma because capillary diameter is not just determined by the distance between the endothelial cells at opposing walls (anatomical capillary cross-section). The presence on the endothelial cells of a glyocalix of considerable thickness (20) actually considerably limits the area available for perfusion. Plasma and white blood cells actually occupy the anatomical capillary cross-section, whereas red blood cells occupy less. This indicates that the wall of skeletal muscle capillaries is decorated with an endothelial surface coat of about 0.5 µm thick. During routine microscopy observations, the apparent position of the vessel wall reflects the position of the lining of the endothelial cells. Vink and colleagues (21, 22) demonstrated that oxidized LDL degrades the endothelial surface layer. The various conditions that may influence the thickness of the glyocalix are still under investigation. It would not be surprising if vascular diseases influence the endothelial surface layer. In that case, it may become a target for treatment.

EXERCISE TRAINING OF PATIENTS

Training is often used to improve perfusion of muscles of patients with intermittent claudication in order to ameliorate their usually poor physical aspect and quality of life. Although after exercise training in general an improvement of the physical aspect of the patient is observed, flow measurements seldom demonstrate improvement of blood delivery to the affected muscle. Redistribution of blood flow within the muscle is probably the cause of the observed improvement, as well as changes in oxidative capacity of the skeletal muscle, and better utilization of oxygen (23). The associated dysfunction of the muscles is rectified by these alterations.

CONCLUSIONS

Blood flow through a muscle is not only influenced by the dilatation of the feeding arterioles, but also by the compliant nature of capillaries within the muscle. Muscle blood flow reserve capacity [MBFRC] is only a good measure of the capability of the muscle vascular bed to improve skeletal muscle perfusion, provided that actual nutritional flow is measured. The normally used ratio of peak perfusion and rest perfusion usually does not take into account the diversion of shunt flow to nutritional flow that may occur. The perfusion status of a patient, therefore, does not necessarily reflect the nutritional status of the patient’s muscle. The metabolic condition of the patient has to be taken into account as well.

RÉFÉRENCES

10. BOSSMAN J, TANGELDER GJ, OUE EGEBRINK MGA, REINEMAN RS, SLAAF DW. Red blood cell flow cessation and diameter


