THE INFLUENCE OF FLOW REDISTRIBUTION ON WORKING RAT MUSCLE OXYGENATION

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Abstract: We applied a theoretical model of muscle tissue O_2 transport to investigate the effects of flow redistribution on rat soleus muscle oxygenation. The situation chosen was the anaerobic threshold where redistribution of flow is expected to have the largest impact. In the basic situation all capillaries received an equal proportion of the total flow through the tissue, resulting in 4.7% anoxic tissue and a mean tissue PO_2 = 3.62 kPa. Both a redistribution of flow where 1) capillaries in blocks of tissue receiving 50% of the basic flow alternated with tissue blocks with capillaries receiving 150% of the basic flow (6.8% anoxic tissue; mean tissue PO_2 = 3.32 kPa) and 2) matching flow to O_2 consumption (3.3% anoxic tissue; mean tissue PO_2 = 3.60 kPa) had little effect. When overall flow was decreased by 20%, the anoxic tissue increased to 7.6% and the mean tissue PO_2 decreased to 3.22 kPa. The conclusion from these model calculations is, that flow redistribution has little impact on skeletal muscle oxygenation, which is in line with earlier findings for rat heart.

1. INTRODUCTION

Tissue oxygenation is the result of a balance between O_2 supply, by the capillary blood, and O_2 consumption, in the tissue cells. In between, there is an important role for O_2 diffusion. For a muscle with a varying O_2 consumption depending on the work it performs, the question arises how blood flow and O_2 consumption are related and, in particular, if flow can be matched to consumption to maintain adequate oxygenation. To maintain an adequate oxygenation, the muscle has two mechanisms available; capillary recruitment and increasing blood flow. During maximal recruitment all, that is 100%, of the capillaries are open and available for O_2 exchange with the surrounding tissue. It is unlikely, however, that each individual capillary receives an equal proportion of the total

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blood flow through the muscle, since capillaries are distributed inhomogeneously in the tissue. Indeed, the flow distribution over capillaries may vary with varying (working) conditions. Yet, in an earlier investigation on rat heart[1], we found that flow redistribution has little influence on tissue oxygenation. It should be noted that this does not automatically apply to skeletal muscle, as skeletal muscle differs from heart in a number of ways, in particular in the much wider range of working states including lactate production at maximum work.

Heterogeneity of capillary spacing is the most important factor in muscle tissue oxygenation[2]. Consequently, reliable data of capillary localisation must be available. Average tissue values of capillary density and heterogeneity of capillary spacing allow to select a representative tissue portion where calculations can be based on. Here we use data of rat soleus muscles that were obtained in a previous study[3].

2. MATERIALS AND METHODS

The muscle tissue considered here is rat soleus skeletal muscle. Since muscle working state can be very different, from rest to maximum work, we had to select a state where the relation between flow and consumption will be the most relevant. At rest, only few capillaries will be open. At maximum work, the muscle produces a significant amount of lactate from anaerobic energy production strongly suggesting inadequate O_2 supply at least locally. Thus, the anaerobic threshold, at the verge of lactate production, seemed the most relevant state for our investigation. According to textbooks on work physiology, we assumed this threshold to be at ⅔ of the maximum oxygen consumption and ⅔ of the maximum flow.

2.1. Mathematical model

The mathematical treatment is based on oxygen diffusion from a number of point-source capillaries into a surrounding plane, coordinate $\vec{r}$[4]:

$$PO_2 + P_F S_{MbO_2} = \frac{Q}{4\wp}\left[\Phi(\vec{r}) - \sum_{i=1}^{N}\frac{A_i}{\pi}\ln\left(\frac{|\vec{r}-\vec{r}_i|^2}{r_{ci}^{\,2}}\right)\right]$$

where PO_2 is oxygen partial pressure, P_F is facilitation pressure[5] of the tissue myoglobin, Mb, with saturation S_{MbO_2}, Q and $\wp$ are the tissue's oxygen consumption and oxygen permeability respectively, N is the number of capillaries, and A_i, $\vec{r}_i$ and r_{ci} are supply area, location and radius of the ith capillary respectively. The term $\Phi(\vec{r})$ accounts for the distribution of oxygen consumption and can be calculated according to the cited paper; here, the solution for a homogeneous rectangle was taken r_4. The N supply areas can be calculated from the N capillary rim pressures P_{ri} which in turn were calculated from the capillary O_2 pressures P_{ci} by the method of the Extraction Pressure EP[6, 7]:

$$P_{ri} = P_{ci} - \frac{A_i}{A}EP$$

where A is the average supply area. The EP is the PO_2 gradient in and near the capillary for the average capillary and depends on a variety of local capillary data, the most important being blood velocity and hematocrit. Values were calculated by the approximate method of Bos[8]. The above equation is equivalent to a flux-dependent PO_2 difference as used by other authors[9].

The consecutive planes are coupled by subtracting the amount of oxygen delivered for each capillary k[10]:

$$\frac{d}{dz}(c_{tk}O_2) = -\frac{Q}{F_k}\left(A_k - \pi r_{ck}^{\;2}\right)$$

where z is the coordinate perpendicular to the planes, and $c_{tk}O_2$, F_k are the capillary's total O_2 content and blood flow, respectively. The $c_{tk}O_2$ incorporates both free oxygen and oxygen bound to hemoglobin, Hb. Contrary to the other equations, which are all analytical, this latter equation has to be solved numerically which was done by taking a non-infinitesimal step Δz equal to the distance between the planes instead of the infinitesimal dz.

2.2. Input data

The overall tissue and blood data were: Q = 0.092 mM, i.e., ⅔ of maximal consumption[11] assuming that the soleus contains 90% type I and 10% type II fibers[3]; Permeability = Krogh's diffusion coefficient[12] $\wp = 1.18\ 10^{-11}$ $mol \cdot m^{-1} \cdot kPa^{-1} \cdot sec^{-1}$; Mb $P_{50} = 0.7$ kPa and $D_{Mb}/D_{O2} = 0.075$[13] and cMb = 0.28 mM[3, 11] leading to $P_F = 2$ kPa; blood O_2 solubility $\alpha O_2 = 0.024$ $L \cdot L^{-1} \cdot atm^{-1}$[14] and Hb content[15] 17 $g \cdot dL^{-1}$; ⅔ of maximum flow[16] of 276 $mL \cdot min^{-1} \cdot (100\ g)^{-1}$; $r_c = 2.65$ µm from capillary luminal diameter of 5.3 µm[17]. Hb saturation was described by the Hill equation with $P_{50} = 4.93$ kPa and n = 2.69. For these data, EP = 0.79 kPa[8].

A representative tissue cross-section of 400 × 400 µm was selected (rat 14A[3]) containing 91 capillaries and extended to a block of 800 µm capillary length. At z = 0, capillary PO_2 was set at 13 kPa.

2.3. Situations calculated

A basic situation (BASIC) was calculated where all capillary data were identical, in particular, capillary flow. A border zone of 45 µm was excluded from the calculations to avoid border effects. Other situations were compared with this basic situation. These were: 16 adjacent regions of 80 × 80 µm with alternating 150% and 50% of the average flow in a checkerboard pattern (4 × 4); 4 adjacent regions of 160 × 160 µm alike (2 × 2); flow relative to O_2 delivery for each capillary (MATCHED); and 20% less flow uniformly distributed (80%).

3. RESULTS

For each of the situations, tissue PO_2 was calculated at equidistant points in the tissue block with a spacing of 10 µm, except when within a capillary. The resulting 73 224 points were gathered into a histogram of class width 0.5 kPa. A region where the calculated PO_2 was below zero was considered an anoxic region where in fact $PO_2 = 0$. These regions are indicated in the leftmost bar of the histograms. Figure 1 shows the results for four of the situations; the 4 × 4 case was only slightly different from the 2 × 2 case and not shown.

As expected, the basic situation (upper left panel in Figure 1) showed some anoxic tissue, i.e. 4.7%, consistent with the emergence of lactate around the anaerobic threshold. Most of the tissue PO_2 was not low, a mean PO_2 of 3.62 kPa with a standard deviation (SD) of 2.46 kPa indicating quite a heterogeneous tissue PO_2 distribution.

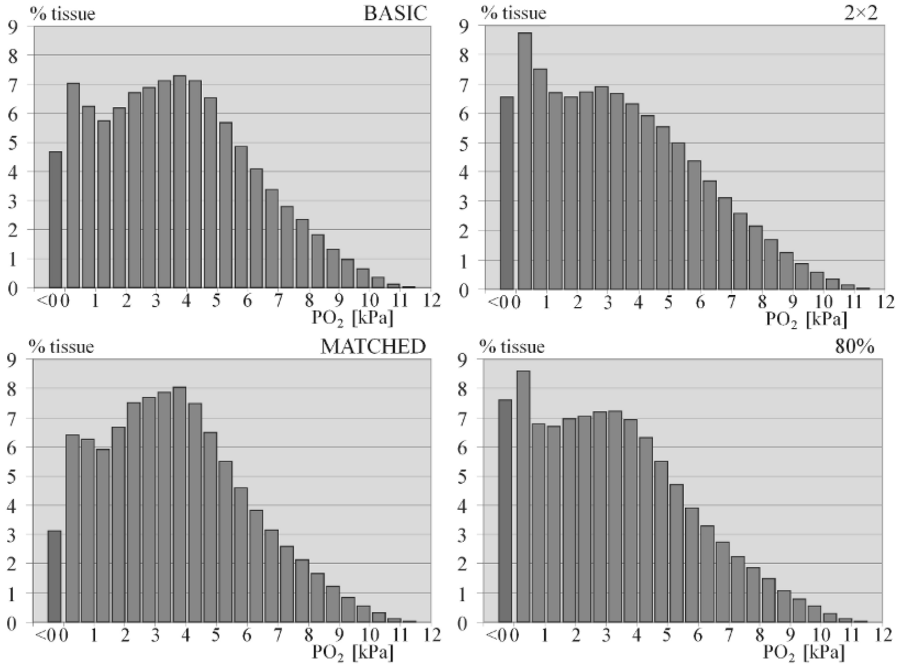

Figure 1. PO_2 histograms, %tissue with PO_2 within the class boundaries of 0.5 kPa, calculated for the basic situation (upper left), the 4 flow regions (upper right), matched capillary flow (lower left), and 20% overall decreased flow (lower right).

During the conditions of a heterogeneous flow distribution, regions of high (150%) and low (50%) flow, there was no large change in the tissue PO_2 distribution. For the 2 × 2 case (upper right panel in Figure 1), where two large regions of 160 × 160 μm suffer from halved flow, the anoxic tissue increased with only 1.9% to 6.6%, and mean PO_2 decreased no further than to 3.33 kPa. For the 4 × 4 case, these figures were 6.8% and 3.32 kPa. The standard deviation was virtually unaltered in both situations; 2.51 and 2.46 kPa, respectively vs. 2.46 kPa in the BASIC situation

As expected, matched flow (lower left panel in Figure 1) resulted in a marginally better oxygenation; there remained anoxic regions, now 3.1%, whereas mean PO_2 was unchanged, 3.60 kPa and the histogram became slightly narrower, SD = 2.35 kPa.

Also as expected, decreased overall flow (lower right panel in Figure 1) worsened oxygenation, but only moderately. The anoxic tissue portion increased to 7.6% and mean tissue PO_2 decreased to 3.22 kPa; histogram SD was unchanged, 2.44 kPa.

4. DISCUSSION

Tissue is supplied with oxygen by the blood in the capillary network and consequently capillary distribution within the tissue is a major determinant of tissue PO_2. Beside capillarisation also the blood flow through the capillaries is important for tissue oxygenation. Here we addressed the question how the distribution of blood flow over the various capillaries affects the oxygenation of the tissue. To do so, it is important, that the capillary geometry is adequately accounted for. Since the mathematical model allows for individually independent capillary data[6], it is suitable for theoretical predictions of the impact of alterations of flow distribution on tissue oxygenation.

The most remarkable finding is, that flow redistribution only marginally affects tissue oxygenation. This is best appreciated when comparing this outcome with the impact of, for instance, a homogeneous distribution of capillaries on tissue oxygenation. We calculated a case where all capillaries were equidistant in a rectangular grid of 42 μm spacing, a capillary density identical to the current situation. Then, the mean tissue PO_2 becomes 4.45 kPa vs. 3.62 kPa in the basic situation, the histogram narrows and there are no PO_2s below 1.2 kPa. The flow redistributions we considered here have much less effect. This is in line with earlier findings, that heterogeneity of capillary spacing is by far the most important factor in tissue oxygenation[2, 5, 18].

We also calculated situations where the redistribution of flow was more marked than presented here. A 40% overall flow decrease gave 13% anoxic tissue and a 190% – 10% flow redistribution in the checkerboard cases resulted in 10% anoxic tissue. These calculations, however, were considered less reliable; the model will overestimate the anoxic portion, because the term $\Phi(\vec{r})$ was applied for uniform O_2 consumption and anoxic regions do not consume oxygen. So in fact, the anoxic portion in the present calculations will also be somewhat too high. Thus, considering that the amount of anoxic tissue is overestimated with our model it is even more remarkable that the 190% – 10% 2 × 2 case, making a region of 160 × 160 μm virtually devoid of blood flow, had such a limited effect on tissue PO_2.

The current calculations can only be compared with results also for a heterogeneous tissue layout. Recently, Goldman et al.[18] considered a situation of 24 capillaries in a 165 × 155 μm rectangular field in a numerical calculation. Because of their different objective, results are not well comparable. They found only a moderate PO_2 decrease for a flow reduction of baseline to 75%, but a sudden and significant increase in anoxic tissue for a reduction from 50% to 40%. The current model is not numerical but semi-analytical. Both methods have their advantages and disadvantages. The current semi-analytical model runs very fast (a few seconds on a standard PC) even for the 91 capillaries and it has no trouble with boundary conditions, as numerical models do. However, the term $\Phi(\vec{r})$ in the model will have to be adapted for anoxic regions if a better analysis of such situations is to be done.

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