Metabolic but not Hypoxemic Stimuli are Related to the Apparent Recruitment of Capillaries in the Muscle

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Abstract

Increased metabolic rate (MR) and arterial hypoxemia are independent stimuli to increase blood flow and delivery of oxygen (O_2) into the active muscle tissue and may differ in location of their action. We speculated that blood gas analysis could provide the answer whether a given stimulus acts on the recruitment of capillaries, manifested by the apparent density of capillaries. We used the Krogh cylinder model, modified for the description at low partial pressure of O_2 (p_{O2}) that lead to O_2 deficit. Using data of Goodman et al. (Circ Res 43: 769-76, 1978) we calculated the apparent density of capillaries, which changed proportionally to MR, but was independent of O_2 saturation of the arterial blood, suggesting that the increased radial O_2 diffusion gradient at higher MR might be responsible for it.

1. Introduction

Increased metabolic rate (MR) and arterial hypoxemia are independent stimuli to increase blood flow and delivery of oxygen (O_2) into the active muscle tissue [1, 2]. Whereas both stimuli tend to reduce vascular resistance, they might differ in the location, either at the conduit arterioles or at the terminal arteriole. As the later might be connected with the capillary recruitment, and hence the diffusion distance, we speculated that the blood gas analysis could provide the answer whether a given stimulus acts by changing the density of blood perfused capillaries, if O2 consumption is diffusion limited.

2. Methods

2.1. O_2 consumption by the tissue

Metabolic activity of the tissue (A) in the normoxemic conditions is covered by the tissue O_2 consumption (A_{O2}). In the hypoxemic conditions with insufficient O_2 delivery, a part of the metabolic activity is covered by anaerobic metabolism with the lactate production, resulting in O_2 deficit ($defO_2$). Then, A equals

$$A = A_{O2} + defO_2 . \quad (1)$$

O_2 is delivered to the tissues via convective transport by blood flow (Q), followed by diffusion of O_2 into the tissue, with O_2 uptake equal to A_{O2},

$$A_{O2} = Q \cdot (c_{aO2} - c_{vO2}), \quad (2)$$

where both Q and A_{O2} expressed per unit mass of the tissue [3], and c_{aO2} and c_{vO2} are the arterial and venous O_2 concentrations, respectively. Neglecting low solubility of O_2 in the blood, blood O_2 concentration (c_{O2}) is proportional to blood hemoglobin concentration ([Hb]) and O_2 saturation of Hb (s_{O2}), which further depends on the partial pressure of O_2 (p_{O2}), $s_{O2}=s(p_{O2})$,

$$c_{O2} = \kappa [Hb] \cdot s(p_{O2}), \quad (3)$$

with the constant κ, κ=1.34 ml O_2/g Hb.

2.2. Radial O_2 diffusion gradient

Diffusion of O_2 from the capillary into the tissue is described using Krogh cylinder model, consisting of a tissue cylinder with radius r_K and with uniform uptake of O_2 delivered by an axial blood-perfused capillary with radius r_c (Fig. 1) Assuming only radial O_2 diffusion, this steady state model allows interactions of O_2 requirements, diffusion and blood flow [3]. In our study we extended the model for non-uniform consumption of O_2 at low p_{O2} resulting in O_2 deficit.

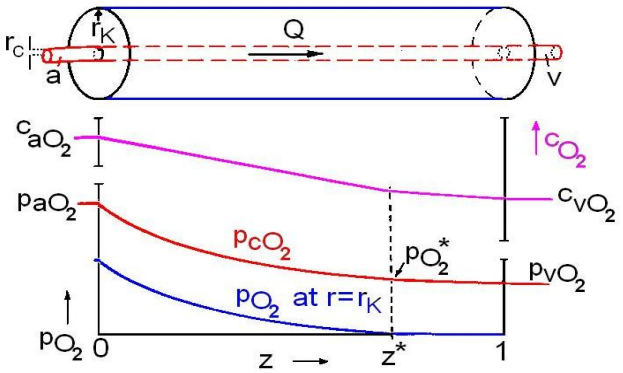

Figure 1. Krogh cylinder with an axially located capillary and corresponding axial distributions of c_{aO2} and p_{aO2}.

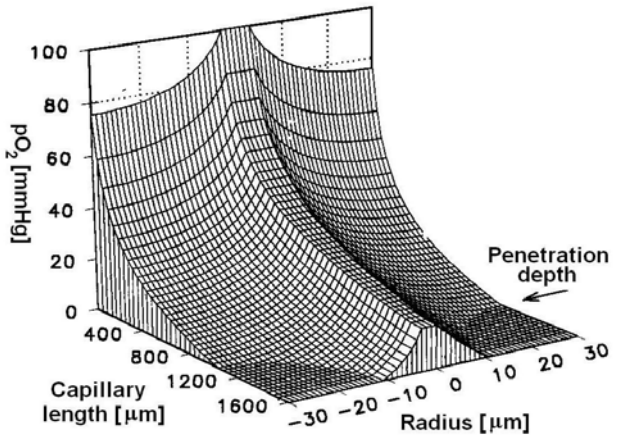

Figure 2. Spatial distribution of paO2 in the axial cross-section of the Krogh cylinder through the central capillary, showing area of tissue not supplied by O_2.

At radius r, radial p_{O2} gradient (dp_{O2}/dr) develops due to O_2 diffusion and O_2 uptake, proportional to A_{O2}/K,

$$dp_{O2}/dr = \frac{A_{O2}}{2K}\left(r - r_K^2/r\right), \quad (4)$$

where K is Krogh diffusion constant for O_2 (e.g., for the muscle tissue, K=3 μm²/mmHg/min). This gradient generates O_2 pressure difference (Δp_{O2}) between blood and the periphery to the distance r_{lim},

$$\Delta p_{O2}\left(r_{\lim}\right) = \frac{A_{O2}}{4K}\left[r_c^2 - r_{\lim}^2 + 2r_{\lim}^2 \ln(r_{\lim}/r_c)\right] \quad (5)$$

When capillary p_{O2} (p_{cO2}) is big enough, exceeding some threshold value p_{O2}*, it allows complete O_2 supply of the cylinder and diffusion of O2 to the radius rK. In this case $r_{lim}= r_K$, and $\Delta p_{O2}= \Delta p_{O2}(r_K)$.

This threshold p_{O2} is called a critical p_{O2} (p_{O2}*), since p_{O2}* is the smallest p_{O2} that allows complete O_2 supply of the whole cross-section area of the cylinder, with p_{O2} at $r=r_K$ reaching zero valu, $p_{O2}(r_K)=0$ (Fig. 2). It occurs at p_{cO2} and is equal to $p_{O2}^* = \Delta p_{O2}(r_K)$ as derived from (5).

When p_{cO2} is below p_{O2}*, $p_{cO2} < \Delta p_{O2}(r_K)$, it allows penetration of O_2 only to the distance $r_{lim}<r_K$. The region beyond r_{lim} becomes anoxic, leading to hypoxemic conditions. By applying (5), p_{cO2} is determined by

$$p_{cO2} = \Delta p_{O2}\left(r_{\lim}\right). \quad (6)$$

from which the penetration distance r_{lim} can be determined as its inverse value.

2.3. Axial O_2 concentration gradient

In the axial direction, z (0<z <1, from the beginning to the end of the capillary), blood O_2 concentration falls with increasing z due to radial diffusion of O_2 into the tissue, creating thus axial concentration gradient, dc_{O2}/dz, proportional to the O2 uptake,

$$dc_{O2}/dz = -A_{O2}/Q. \quad (7)$$

with A_{O2} proportional to the relative volume of O_2 consuming tissue,

$$A_{O2} = A\cdot\left(r_{\lim}^2 - r_c^2\right)/\left(r_K^2 - r_c^2\right). \quad (8)$$

For describing O_2 consumption in the hypoxemic conditions at low p_{O2}, two regions of the Krogh cylinder are considered. Being separated at z = z* with pO2*, the normoxemic region exits with p_{O2} above, and the hypoxemic one below pO2*.

In the normoxemic region, when capillary $p_{O2}>=p_{O2}$*, $A_{O2}=A$, the axial gradient is linear. Below p_{O2}*, diffusion is limited to the radius r_{lim}, provided by the inverse value of (6) and $A_{O2}<A$ is obtained from (8). As r_{lim} is being reduced toward the end of the capillary, diffusion occurs at a slower rate and is non-linear.

Integration of (7) from the initial arterial c_{aO2} results in the capillary profile of c_{O2}, reaching a normoxemic value of venous c_{vO2}. Being equal to c_{vO2}, provided by (2) means, that O_2 extraction by the tissue does not depend on diffusion unless it reaches the critical value of c_{O2} (c_{O2}*) at p_{O2}*, and hypoxemic conditions occur. If the critical c_{O2}* is reached, integration is affected by (8), as $A_{O2}<A$, finally providing a hypoxemic value of venous c_{vO2} (Fig. 3), being higher than the normoxemic one. The difference between the two, normoxemic and hypoxemic c_{vO2}, is proportional to $defO_2$.

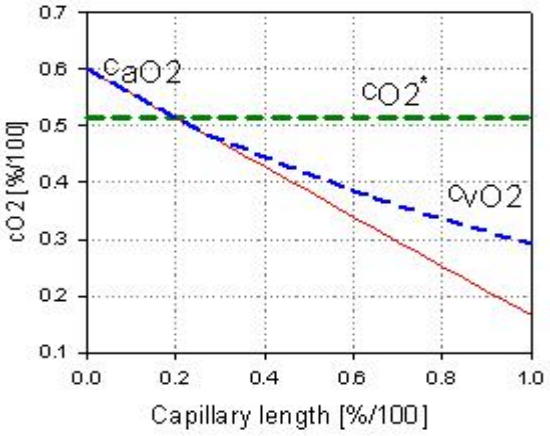

Figure 3. The axial gradient of c_{O2} with the critical c_{O2}* value (green, dashed), normoxemic.(red) and hypoxemic (blue, dashed) c_{O2} profiles.

2.4. O_2 carriage by blood

In order to relate c_{O2} in (7) to p_{O2} in (5) using (3), $s(p_{O2})$ dependence on p_{O2} is necessary to know. $s(p_{O2})$ is a complex function of p_{O2}, depending also on the partial pressure of CO_2 (p_{CO2}), temperature, pH and 2,3 DPG erythrocyte concentration [4]. Hence, it also depends on CO_2 metabolism and acid-base status of the blood,

requiring thus the appropriate expressions for CO_2 carriage and plasma pH.

To avoid a detailed description, we provide here only functional dependences with references to the original papers.

Hence, s_{O2} was determined as proposed by Lodbell [4],

$$s_{O2} = f\,(p_{O2}, p_{CO2}, pH, temperature, [2,3\ DPG]), \quad (10)$$

plasma free hydrogen ion concentration $[H^+]$ and pH was determined as proposed by Watson [5],

$$[H^+] = f\,(p_{CO2}, SID, [Phosphate], [Alb], s_{O2}), \quad (11)$$

and c_{CO2} was determined as reported by Douglas et al. [6],

$$c_{CO2} = f\,(p_{CO2}, s_{O2}, [Hb], pH). \quad (12)$$

Here SID is strong ion difference [7], [Phosphate] is phosphate concentration, and [Alb] is plasma albumin concentration, all in arterial blood. As there were no reported data on them, default values for SID=38 mM/L, [Phosphate]= 2.2 mM/L, and [Alb]= 72g/L were used. Three nonlinear sets of equations (10-12) were solved at each particular position in the capillary providing the input variables s_{O2}, c_{CO2} and the product $\kappa\cdot[Hb]$=0.23 mL O2/L of blood, neglecting thus the solved O_2. For simplify, CO_2 diffusion was not calculated independently of O_2 diffusion, but assumed that CO_2 release by tissue and its uptake by blood is equal to O_2 uptake by the tissue, corrected for the respiratory quotient RQ=0.9 for the mixed food, so that $\Delta c_{CO2} = \Delta c_{O2}/$ RQ. Then, for obtaining c_{CO2} profile, c_{CO2} was integrated from the value c_{aCO2} with the arterial p_{aCO2} =40 mmHg.

2.5. Calculations

The above set of equations enables to calculate O_2 deficit for a given metabolic rate, A, blood flow, Q, and Krogh radius, rK. Namely, integration of (7) from the initial value of c_{aO2} provides venous c_{vO2}, and O_2 deficit using (1-2). When measured def O_2 is given to find unknown r_K, the latter can be found using the same procedure, but varying rK until finding an acceptably small difference between measured and calculated def O_2. Using data of Goodman et al. [8] we calculated how the apparent capillary density (n_c) is related to the level of metabolic activity, A, at different s_{aO2}, where n_c was related to radius of Krogh cylinder by $n_c = 1/\pi r_K^2$.

2.6. Description of the measured data

Goodman et al. [8] studied the effect of changing hind limb metabolic rate (MR) on hind limb blood flow control in anesthetized dogs. The hyperemias were induced by graded levels of arterial hypoxemia and the degree of steady state autoregulation evoked by changes in the mean arterial pressure (MAP). MR was increased above the resting value by direct electrical stimulation of hind limb muscles at rates from 0.5 to 1.5 pulses per second. In response to 6 minutes of arterial hypoxemia, hind limb steadily increased to provide final instantaneous values of relative O_2 deficit. Their study provided data on Q and defO_2, obtained at different levels of metabolic activity, A_{O2}, and at different exposure to breathing gas O_2 mixture, resulted in different s_{aO2}.

3. Results

The apparent density of capillaries, n_c, as calculated from the apparent radius of Krogh cylinder, rK, changed proportionally to MR, nearly independently of s_{O2} of the arterial blood. It also exhibited slight dependence on the blood flow, being slightly reduced with increasing Q after the initial s_{O2} lowering s_{O2} and again increased at higher Q.

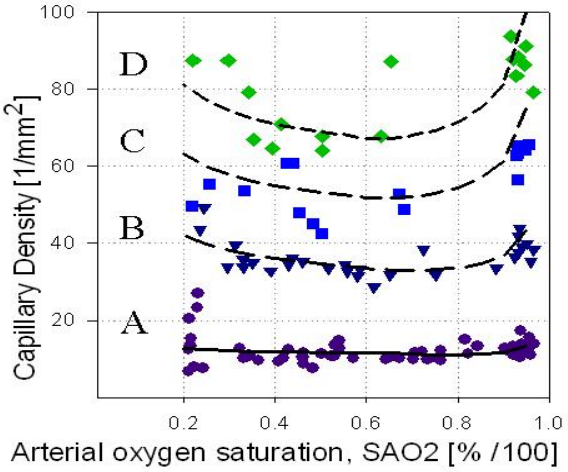

Figure 4. Density of the recruited capillaries as calculated for each metabolic activity (MR) at different arterial s_{O2}. It is nearly independent of the arterial s_{O2}, but increases with the MR (A – resting, B, C, and D – muscle electrical stimulation of 0.5, 1 and 1.5 pulses/s, respectively).

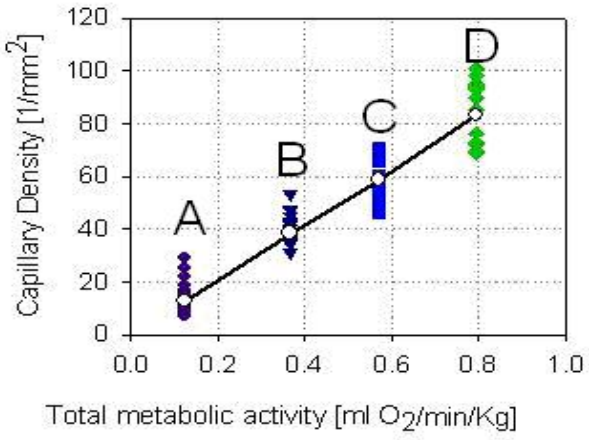

Figure 5. The apparent capillary density increases proportionally to the total MR that includes O2 deficit, defined by (1). MR is denoted by letters A-D as in Fig. 4.

4. Discussion and conclusion

Our finding that the apparent density of capillaries (n_c) follow the increased MR in the normoxemic conditions is not surprising, but only confirms that in order to extract more O_2 at higher MR, the diffusion of O_2 should adapt exactly to the increased MR by increasing n_c. Less expected is our finding that n_c does virtually not change in hypoxemic conditions: though providing higher O_2 flow into the tissue by higher Q at lower sa_{O2}, it does not influence the apparent density of capillaries.

Here n_c is related to a characteristic diffusion distance, equal to the radius r_K, derived from the critical p_{O2}* at the end of the normoxemic region. In the normoxemic conditions it just enables sufficient uptake of O_2 by the tissue to cover metabolic activity. In case of insufficient O_2 supply, n_c does not change, resulting in O_2 deficit. If n_c increased in the hypoxia, it might have prevent O2 deficit

Regarding the control of microvascular perfusion of the tissue there are two opposing views that there is/ is not capillary recruitment in active skeletal muscle during exercise. The first view [9] considers that there exist unperfused capillaries that are recruited during the increased metabolic activity, and the second one [10] that all capillary are perfused in the resting state.

Though our model is consistent with the first view, it may not provide inconsistent results to the second one for the following reason. When assuming that all capillary are perfused in the resting state, it should be considered that hemoglobin is not continuously distributed along the capillary, but concentrated discretely in the erythrocytes that enter capillaries randomly. Also, O_2 uptake as expressed by A_{O2} may not be steady, since the cellular respiration rate changes depending on the cellular concentration of ADP, being higher when ATP resources are low [11]. Hence, A_{O2} might not be uniform even in the normoxemic conditions, but depending on the local, current cellular ATP/ADP state. Then, local O_2 uptake might not be steady but would rather fluctuate from low to high values, influencing local radial gradient dp_{O2}/dr, similarly as described by eq. (4). Thus, at low local O_2 consumption following ATP refilling due to previously increased O2 delivery, dp_{O2}/dr would flatten, enabling deeper penetration of O2 into the tissue. O_2 could pass many currently unperfused capillaries and even reach the diffusion distance equal to r_K of the resting tissue; the assumption that still needs to be proved

With respect to the mechanism responsible for the apparent recruitment of the capillaries, two possibilities are foreseen. First, an active substance might be released from the active muscle proportionally to MR acting on the precapillary sphincters that control the number of open capillaries. Second, if all capillaries are perfused all the time and the tissue extract as much O2 as necessary, then at the increased MR the radial diffusion gradient (eq. 4) is increased proportionally allowing for proportional supply of O2 with diffusion in the normoxemic region.

In conclusion we summarize the following.

1. The apparent density of capillaries, connected with characteristic diffusion distance in the normoxemic tissue, is proportional the total metabolic activity of the tissue,
2. It does not depend on the arterial blood s_{O2},
3. Though it can not provide answer to the capillary recruitment dilemma, it does not exclude any of the two suggested views. The view pro provides the consistent solution for the recruitment that still needs a control mechanism, whereas the counter view only suggests the solution, requiring no mechanism to control the recruitment.

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