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

Vito Starc

University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia

Abstract

Increased metabolic rate (MR) and arterial hypoxemia are independent stimuli to increase blood flow and delivery of oxygen (O2) 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 O2 (pO2) that lead to O2 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 O2 saturation of the arterial blood, suggesting that the increased radial O2 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 (O2) 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. O2 consumption by the tissue

Metabolic activity of the tissue (A) in the normoxemic conditions is covered by the tissue O2 consumption (A02). In the hypoxemic conditions with insufficient O2 delivery, a part of the metabolic activity is covered by anaerobic metabolism with the lactate production, resulting in O2 deficit (defO2). Then, A equals

\[ A = A_{O2} + \text{def}O_2. \]  \hspace{1cm} (1)

O2 is delivered to the tissues via convective transport by blood flow (Q), followed by diffusion of O2 into the tissue, with O2 uptake equal to A02,

\[ A_{O2} = Q \cdot (c_{aO2} - c_{vO2}), \]  \hspace{1cm} (2)

where both Q and A02 expressed per unit mass of the tissue [3], and c_{aO2} and c_{vO2} are the arterial and venous O2 concentrations, respectively. Neglecting low solubility of O2 in the blood, blood O2 concentration (cO2) is proportional to blood hemoglobin concentration ([Hb]) and O2 saturation of Hb (sO2), which further depends on the partial pressure of O2 (pO2), \[ sO2 = s(pO2), \]  \hspace{1cm} (3)

with the constant \( \kappa = 1.34 \) ml O2/g Hb.

2.2. Radial O2 diffusion gradient

Diffusion of O2 from the capillary into the tissue is described using Krogh cylinder model, consisting of a tissue cylinder with radius rK and with uniform uptake of O2 delivered by an axial blood-perfused capillary with radius rc (Fig. 1). Assuming only radial O2 diffusion, this steady state model allows interactions of O2 requirements, diffusion and blood flow [3]. In our study we extended the model for non-uniform consumption of O2 at low pO2 resulting in O2 deficit.

Figure 1. Krogh cylinder with an axially located capillary and corresponding axial distributions of caO2 and pO2.
Figure 2. Spatial distribution of paO\textsubscript{2} in the axial cross-section of the Krogh cylinder through the central capillary, showing area of tissue not supplied by O\textsubscript{2}.

At radius \( r \), radial \( p_\text{O}_2 \) gradient (\( dp_\text{O}_2/dr \)) develops due to O\textsubscript{2} diffusion and O\textsubscript{2} uptake, proportional to \( A_\text{O}_2/K \),

\[
dp_\text{O}_2/dr = \frac{A_\text{O}_2}{2K} (r - r_k^2 / r),
\]

where \( K \) is Krogh diffusion constant for O\textsubscript{2} (e.g., for the muscle tissue, \( K = 3 \ \mu\text{m}^2/\text{mmHg/min} \)). This gradient generates O\textsubscript{2} pressure difference (\( \Delta p_\text{O}_2 \)) between blood and the periphery to the distance \( r_{\text{lim}} \),

\[
\Delta p_\text{O}_2 (r_{\text{lim}}) = \frac{A_\text{O}_2}{4K} \left[ r_c^2 - r_{\text{lim}}^2 + 2r_{\text{lim}}^2 \ln(r_{\text{lim}} / r_c) \right].
\]

When capillary \( p_\text{O}_2 \) (\( p_{\text{cO}_2} \)) is big enough, exceeding some threshold value \( p_{\text{O}_2}^* \), it allows complete O\textsubscript{2} supply of the cylinder and diffusion of O\textsubscript{2} to the radius \( r_K \). In this case \( r_{\text{lim}} = r_K \), and \( \Delta p_\text{O}_2 = \Delta p_\text{O}_2(r_K) \).

This threshold \( p_{\text{O}_2} \) is called a critical \( p_{\text{O}_2} \) (\( p_{\text{O}_2}^* \)), since \( p_{\text{O}_2}^* \) is the smallest \( p_{\text{O}_2} \) that allows complete O\textsubscript{2} supply of the whole cross-section area of the cylinder, with \( p_{\text{O}_2} \) at \( r=r_K \) reaching zero value, \( p_{\text{O}_2}(r_K) = 0 \) (Fig. 2). It occurs at \( p_{\text{O}_2} = p_{\text{O}_2}^* = \Delta p_\text{O}_2(r_K) \) as derived from (5).

When \( p_{\text{O}_2} \) is below \( p_{\text{O}_2}^* \), \( p_{\text{O}_2} < \Delta p_\text{O}_2(r_K) \), it allows penetration of O\textsubscript{2} only to the distance \( r_{\text{lim}} < r_K \). The region beyond \( r_{\text{lim}} \) becomes anoxic, leading to hypoxemic conditions. By applying (5), \( p_{\text{O}_2} \) is determined by

\[
p_{\text{cO}_2} = \Delta p_{\text{O}_2} (r_{\text{lim}}).
\]

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

2.3. Axial O\textsubscript{2} concentration gradient

In the axial direction, \( z \) (0 < \( z < 1 \), from the beginning to the end of the capillary), blood O\textsubscript{2} concentration falls with increasing \( z \) due to radial diffusion of O\textsubscript{2} into the tissue, creating thus axial concentration gradient, \( dc_{\text{O}_2}/dz \), proportional to the O\textsubscript{2} uptake,

\[
dc_{\text{O}_2}/dz = -A_{\text{O}_2}/Q.
\]

with \( A_{\text{O}_2} \) proportional to the relative volume of O\textsubscript{2} consuming tissue,

\[
A_{\text{O}_2} = A \cdot \left( r_{\text{lim}}^2 - r_c^2 \right) / \left( r_K^2 - r_c^2 \right).
\]

For describing O\textsubscript{2} consumption in the hypoxemic conditions at low \( p_{\text{O}_2} \), two regions of the Krogh cylinder are considered. Being separated at \( z = z^* \) with \( p_{\text{O}_2}^* \), the normoxemic region exits with \( p_{\text{O}_2} \) above, and the hypoxemic one below \( p_{\text{O}_2}^* \).

In the normoxemic region, when capillary \( p_{\text{O}_2} \geq p_{\text{O}_2}^* \), \( A_{\text{O}_2} = A \), the axial gradient is linear. Below \( p_{\text{O}_2}^* \), diffusion is limited to the radius \( r_{\text{lim}} \), provided by the inverse value of (6) and \( A_{\text{O}_2} \leq A \) is obtained from (8). As \( r_{\text{lim}} \) 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 \( c_{\text{aO}_2} \) results in the capillary profile of \( c_{\text{O}_2} \), reaching a normoxemic value of venous \( c_{\text{vO}_2} \). Being equal to \( c_{\text{cO}_2} \), provided by (2) means, that O\textsubscript{2} extraction by the tissue does not depend on diffusion unless it reaches the critical value of \( c_{\text{cO}_2} \) (\( c_{\text{cO}_2}^* \)) at \( p_{\text{O}_2}^* \), and hypoxemic conditions occur. If the critical \( c_{\text{cO}_2}^* \) is reached, integration is affected by (8), as \( A_{\text{O}_2} \leq A \), finally providing a hypoxemic value of venous \( c_{\text{vO}_2} \) (Fig. 3), being higher than the normoxemic one. The difference between the two, normoxemic and hypoxemic \( c_{\text{cO}_2} \), is proportional to \( \Delta \text{cO}_2 \).

\[
\text{Figure 3. The axial gradient of } c_{\text{cO}_2} \text{ with the critical } c_{\text{cO}_2}^* \text{ value (green, dashed), normoxemic (red) and hypoxemic (blue, dashed) } c_{\text{cO}_2} \text{ profiles.}
\]

2.4. O\textsubscript{2} carriage by blood

In order to relate \( c_{\text{cO}_2} \) in (7) to \( p_{\text{O}_2} \) in (5) using (3), \( s(p_{\text{O}_2}) \) dependence on \( p_{\text{O}_2} \) is necessary to know. \( s(p_{\text{O}_2}) \) is a complex function of \( p_{\text{O}_2} \), depending also on the partial pressure of CO\textsubscript{2} (\( p_{\text{CO}_2} \)), temperature, pH and 2,3 DPG erythrocyte concentration [4]. Hence, it also depends on CO\textsubscript{2} metabolism and acid-base status of the blood,
requiring thus the appropriate expressions for CO₂ carriage and plasma pH.

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

Hence, sO₂ was determined as proposed by Lodbell [4],

\[ sO₂ = f(pO₂, pCO₂, pH, temperature, [2,3 DPG]), \]  

(10)

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

\[ [H^+] = f(pCO₂, SID, [Phosphate], [Alb], sO₂), \]  

(11)

and cCO₂ was determined as reported by Douglas et al. [6],

\[ cCO₂ = f(pCO₂, sO₂, [Hb], pH). \]  

(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 sO₂, cCO₂ and the product \( \kappa \cdot [Hb]=0.23 \) mL O₂/L of blood, neglecting thus the solved O₂. For simplify, CO₂ diffusion was not calculated independently of O₂ diffusion, but assumed that CO₂ release by tissue and its uptake by blood is equal to O₂ uptake by the tissue, corrected for the respiratory quotient RQ=0.9 for the mixed food, so that \( \Delta cCO₂ = \Delta cO₂/ RQ \). Then, for obtaining cCO₂ profile, cCO₂ was integrated from the value caCO₂ with the arterial pCO₂=40 mmHg.

2.5. Calculations

The above set of equations enables to calculate O₂ deficit for a given metabolic rate, A, blood flow, Q, and Krogh radius, rK. Namely, integration of (7) from the initial value of caO₂ provides venous cvO₂, and O₂ deficit using (1-2). When measured def O₂ is given to find unknown rK, the latter can be found using the same procedure, but varying rK until finding an acceptably small difference between measured and calculated def O₂. Using data of Goodman et al. [8] we calculated how the apparent capillary density (nₐ) is related to the level of metabolic activity, A, at different sₐO₂, where nₐ was related to radius of Krogh cylinder by \( nₐ = 1/ \pi rK^2 \).

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 O₂ deficit. Their study provided data on Q and defO₂, obtained at different levels of metabolic activity, A₀₂, and at different exposure to breathing gas O₂ mixture, resulted in different sₐO₂.

3. Results

The apparent density of capillaries, nₐ, as calculated from the apparent radius of Krogh cylinder, rK, changed proportionally to MR, nearly independently of sₐO₂ of the arterial blood. It also exhibited slight dependence on the blood flow, being slightly reduced with increasing Q after the initial sₐO₂ lowering sO₂ and again increased at higher Q.

![Figure 4](image-url)  

Figure 4. Density of the recruited capillaries as calculated for each metabolic activity (MR) at different arterial sO₂. It is nearly independent of the arterial sO₂, 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](image-url)  

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 normoxic 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 hypoxic conditions: though providing higher $O_2$ flow into the tissue by higher $Q$ at lower $s_aO_2$, 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 $pO_2^*$ at the end of the normoxic region. In the normoxic 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 $O_2$ 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 $A_O_2$ 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, $A_O_2$ might not be uniform even in the normoxic 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 $dpO_2/dr$, similarly as described by eq. (4). Thus, at low local $O_2$ consumption following ATP refilling due to previously increased $O2$ delivery, $dpO_2/dr$ would flatten, enabling deeper penetration of $O2$ into the tissue. $O2$ 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 normoxic region.

In conclusion we summarize the following.

1. The apparent density of capillaries, connected with characteristic diffusion distance in the normoxic tissue, is proportional the total metabolic activity of the tissue.
2. It does not depend on the arterial blood $sO_2$.
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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References


Address for correspondence.

Vito Starc, MD, PhD
Ljubljana University, Faculty of Medicine
Zaloska 4
SI 1104 Ljubljana, Slovenia
vito.starc@mf.uni-lj.si.