Theoretical model of metabolic blood flow regulation: roles of ATP release by red blood cells and conducted responses

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Arciero JC, Carlson BE, Secomb TW. Theoretical model of metabolic blood flow regulation: roles of ATP release by red blood cells and conducted responses. Am J Physiol Heart Circ Physiol 295: H1562–H1571, 2008. First published August 8, 2008; doi:10.1152/ajpheart.00261.2008.—A proposed mechanism for metabolic flow regulation involves the saturation-dependent release of ATP by red blood cells, which triggers an upstream conducted response signal and arteriolar vasodilation. To analyze this mechanism, a theoretical model is used to simulate the variation of oxygen and ATP levels along a flow pathway of seven representative segments, including two vasoactive arteriolar segments. The conducted response signal is defined by integrating the ATP concentration along the vascular pathway, assuming exponential decay of the signal in the upstream direction with a length constant of ~1 cm. Arteriolar tone depends on the conducted metabolic signal and on local wall shear stress and wall tension. Arteriolar diameters are calculated based on vascular smooth muscle mechanics. The model predicts that conducted responses stimulated by ATP release in venules and propagated to arterioles can account for increases in perfusion in response to increased oxygen demand that are consistent with experimental findings at low to moderate oxygen consumption rates. Myogenic and shear-dependent responses are found to act in opposition to this mechanism of metabolic flow regulation.

—The circulatory system is responsible for supplying every tissue in the body with sufficient oxygen and nutrients. Tissue demand varies according to factors such as metabolism, growth, injury, and infection. Small arteries and arterioles regulate the amount of blood flow supplied to tissue by changing their diameters. The capability of vascular supply to match demand implies the existence of mechanisms for information transfer within the vascular system (4, 56).

Studies of flow regulation have shown the presence of control mechanisms that act both locally and remotely in microvascular networks. Arterioles dilate or constrict in response to changing intravascular pressure (myogenic response) (31). Changes in luminal wall shear stress trigger endothelial release of nitric oxide (NO), which initiates coordinated dilation of local and feed arterioles (shear-dependent response) (43). Stimuli acting at a particular location in a network can elicit remote responses via cell-to-cell communication along the vessel wall (conducted response). For example, application of acetylcholine (ACh) to terminal arterioles in a tissue preparation leads to both local and ascending vasodilation of arterioles and feed arteries (13). Subsequent studies have shown that several different mechanisms are involved in conducted responses (6, 22, 61, 64) and that conducted responses are transmitted both upstream and downstream along vessel walls (3). These and other observations indicate that myogenic responses, flow-dependent vasodilation, local metabolic effects, and propagated effects all contribute to blood flow regulation.

Primarily responsible for carrying oxygen in blood, red blood cells (RBCs) may also act as oxygen sensors and thus play a role in communicating metabolic demand (16). RBCs respond to oxygen level by releasing ATP at a rate that depends on their oxyhemoglobin saturation level (5). This ATP release may initiate a conducted response that travels upstream and triggers arteriolar vasodilation (36). Ellsworth (17) established three points that support this proposed role of the RBC. First, RBCs released an increased amount of ATP when exposed to low PO2 (with pH and PCO2 held constant). Second, ATP applied intraluminally to collecting venules resulted in an increase in vessel diameter of upstream arterioles (11). Third, when arteriolar diameter and ATP levels from venule effluent were measured as PO2 was reduced, increases in diameter and ATP concentration occurred only in vessels containing RBCs. The conducted response occurred within seconds, supporting the physiological relevance of this possible regulatory mechanism. These observations imply that RBCs release ATP at higher rates when depleted of oxygen, initiating upstream conducted responses that increase flow (17).

Several studies have examined the mechanisms for release of ATP from the RBC in response to lowered oxygen saturation (7, 30). Jagger et al. (30) quantified the ATP release at low O2 levels in the presence and absence of CO to demonstrate that the release of ATP from RBCs may be linked to the conformational change of the hemoglobin molecule from its relaxed state (R state, fully liganded) to its deoxygenated state (T state). Once released from the RBC, ATP binds to P2Y purinergic receptors on the luminal surface of the endothelium, initiating the conducted response (26, 41, 49). Alternatively, ATP may be degraded into AMP or adenosine, which may bind to P1 receptors and initiate the vasodilatory response (15, 26). Conducted responses initiated by either of these mechanisms may contribute to metabolic regulation of blood flow.

The overall goal of the present study was to gain insight into the roles of several mechanisms contributing to metabolic blood flow regulation. A previous model for myogenic control of arteriolar diameter (9) was extended to include effects of...
metabolic and shear-dependent responses on blood flow as oxygen demand is varied. The model was used to test the hypothesis that saturation-dependent ATP release by RBCs, triggering a conducted response and upstream vasodilation, provides a mechanism for metabolic flow regulation. The effects of varying model parameters and input arterial pressure were assessed, and model predictions were compared with experimental data.

METHODS

Representative segment model. A flow pathway through the vascular system is represented by several compartments connected in series, each comprising a set of identical, parallel-arranged segments that are assumed to experience the same hemodynamic and metabolic conditions. The number of compartments is chosen according to the level of detail desired in the model and the amount of experimental data available. This model includes seven representative segments (Fig. 1): upstream artery (A), large arteriole (LA), small arteriole (SA), capillary (C), small venule (SV), large venule (LV), and downstream vein (V). Arterioles are divided into two compartments (LA and SA) according to diameter to permit different reactions to changes in pressure and shear stress (12, 60). LA and SA segments are assumed to be vasoactive, while the remaining segments are considered fixed resistances. Inclusion of vessel types spanning the entire circulatory pathway allows simulation of conducted responses involving a signal originating in the capillaries or venules and upstream effector sites located in the arterioles.

Geometric and hemodynamic parameters are defined for each compartment. The subscript i denotes compartment type, where i = A, LA, SA, C, SV, LV, or V. L_i is the length of segments, n_i is the number of segments, τ_i is the shear stress, D_i is the diameter of vessels, and Q_i is the flow in compartment i. Since total blood flow must be the same in each compartment, the following relationships hold:

\[ Q_{tot} = n_A Q_A = n_{LA} Q_{LA} = n_{SA} Q_{SA} = n_C Q_C = n_{SV} Q_{SV} = n_{LV} Q_{LV} = n_V Q_V \]

where Q_{tot} is the total flow. The pathway is assumed symmetrical with respect to the lengths and numbers of corresponding arterial and venous segments, i.e., n_A = n_C, L_A = L_C; n_{LA} = n_{SV}, L_{LA} = L_{SV}; and n_{SA} = n_{LV}, L_{SA} = L_{LV}. For convenience, n_A = 1. The flow resistance of each compartment is calculated with Poiseuille’s law: \( R_i = (128 L_i \mu_i)/(\pi D_i^4) \). Blood viscosity, \( \mu_i \), is assigned to each compartment according to an experimental in vivo relationship (48). The pressure drop across the entire pathway, \( \Delta P_{tot} \), is held constant.

The total flow is Q_{tot} = \Delta P_{tot}R_{tot}, where R_{tot} = \Sigma R_i, and the flow in an individual segment is Q_i = Q_{tot}/n_i. The wall shear stress and the pressure drop in each segment are \( \tau_i = (32 \mu_i Q_i)/(\pi D_i^2) \) and \( \Delta P_i = Q_i R_i \).

Oxygen saturation. The model assumes that oxygen is delivered to surrounding tissue by the upstream artery, large arterioles, small arterioles, and capillaries. Oxygen exchange by venules and veins is neglected. A Krogh-type cylinder model is used in which each oxygen-delivering vessel runs along the axis of a cylinder representing a tissue region to which it is exclusively responsible for supplying oxygen. The width of the tissue region, d, is assumed to be the same for each oxygen-delivering vessel, and so the radius of the tissue cylinder (r_j) and the radius of the vessel (r_j) satisfy \( r_j - r_j = d \), where j = A, LA, SA, and C. The oxygen demand is assumed to be constant, M_0.

By conservation of mass, the decline in oxygen flux must equal the rate of oxygen consumption, giving the following equation for the change in oxygen saturation, S(x), with distance, x, along each segment:

\[ \frac{d}{dx} [Q_c H_2 O S(x)] = -q \]

where Q is volume flow rate in an individual vessel, c_0 is the carrying capacity of RBCs at 100% saturation, H_2 O is the discharge hematocrit, and q = \pi M_0 (r_j^2 - r_j^2) is oxygen consumption per vessel length. Equation 2 is solved to give

\[ S(x) = S(0) - \frac{q}{Q_c H_2 O} x \]

Saturation at the start of the vascular pathway, S(0), is assumed to be 0.97, corresponding to an initial blood PO2 of 100 mmHg. The Hill equation \( S(P_0) = n H M / (n H M + P_0^4) \), where n_H is the Hill coefficient and P_0 is half-maximal Hb saturation, gives the relationship between saturation and blood PO2 (denoted as P_0). Values of the parameters are given in Table 1.

ATP concentration. The release rate of ATP from an RBC, R[S(x)], is defined by a decreasing linear function of oxyhemoglobin saturation based on experimental data. ATP release from human erythrocytes in response to normoxia and hypoxia was observed in in vitro experiments (5). Erythrocyte suspensions were exposed to 50 s of hypoxia and then assayed for ATP. The procedure was also conducted under control conditions (i.e., normoxia). At a saturation of 0.33, 0.985 nmol s^{-1} cm^{-3} of ATP was released. Under normoxic conditions (saturation of 0.97), 0.166 nmol s^{-1} cm^{-3} of ATP was released (5). A linear fit of these experimental values defines the ATP release function of saturation:

\[ R[S(x)] = R_0 [1 - R_1 S(x)] \]

Values of R_0 and R_1 are listed in Table 1. Ectonucleotidases on the endothelial cell surface of the vessel wall degrade ATP (14, 39). The rate of change in plasma ATP concentration, C(x), is given by the difference between the rates of ATP release and degradation:

\[ \frac{d}{dx} [(1 - H_2 O) Q C(x)] = \pi D^2 \eta_1 R[S(x)] - k_2 \pi DC(x) \]

where H_1 is tube hematocrit. The degradation reaction at the endothelial surface is described by Michaelis-Menten kinetics with maximum rate \( V_{max} = 22 \text{ nmol min}^{-1} \cdot 10^{-8} \text{ cells} \) and Michaelis constant \( K_m = 249 \mu M \) for cultured porcine aortic endothelial cells (14). Here, ATP degradation is assumed first order in plasma ATP concentration with rate constant k_2. The surface area of endothelial cells ranges from 400 to 900 \mu m^2 (2), giving a rate constant between 1.63 \times 10^{-4} and 3.68 \times 10^{-4} cm/s. Here, k_2 is assumed to be 2 \times 10^{-4} cm/s, yielding model predictions of venous ATP concentrations consistent with experimental data (25).

Equation 5 can be solved for ATP concentration.
THEORETICAL MODEL OF METABOLIC BLOOD FLOW REGULATION

Table 1. Parameter values describing oxygen transport and saturation-dependent ATP release by red blood cells

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Oxygen demand</td>
<td>$M_0$</td>
<td>1–25</td>
<td>cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$</td>
<td>37</td>
</tr>
<tr>
<td>Oxygen capacity of RBCs</td>
<td>$c_0$</td>
<td>0.5</td>
<td>cm$^3$ O$_2$/cm$^3$</td>
<td>37</td>
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<td>Tube hematocrit</td>
<td>$H_T$</td>
<td>0.3</td>
<td></td>
<td>45</td>
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<tr>
<td>Discharge hematocrit</td>
<td>$H_0$</td>
<td>0.4</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Maximal rate of ATP release</td>
<td>$R_0$</td>
<td>$1.4 \times 10^{-9}$</td>
<td>mol·s$^{-1}$·cm$^{-3}$</td>
<td>5</td>
</tr>
<tr>
<td>Effect of $S(x)$ on ATP release</td>
<td>$R_0$</td>
<td>1.4</td>
<td>$10^{-9}$</td>
<td>5</td>
</tr>
<tr>
<td>Hill equation exponent</td>
<td>$n_H$</td>
<td>2.7</td>
<td></td>
<td>37</td>
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<tr>
<td>Half-maximal Hb saturation</td>
<td>$P_{50}$</td>
<td>26</td>
<td>mmHg</td>
<td>37</td>
</tr>
<tr>
<td>Initial saturation</td>
<td>$S(0)$</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial ATP concentration</td>
<td>$C(0)$</td>
<td>0.5</td>
<td>μM</td>
<td>25</td>
</tr>
<tr>
<td>Rate of ATP degradation</td>
<td>$k_a$</td>
<td>$2 \times 10^{-4}$</td>
<td>cm/s</td>
<td>14</td>
</tr>
<tr>
<td>Time constant for diameter</td>
<td>$\tau_d$</td>
<td>1</td>
<td>s</td>
<td>31</td>
</tr>
<tr>
<td>Time constant for activation</td>
<td>$\tau_s$</td>
<td>60</td>
<td>s</td>
<td>20</td>
</tr>
<tr>
<td>Length constant for $S_{CR}$</td>
<td>$L_0$</td>
<td>1</td>
<td>cm</td>
<td></td>
</tr>
<tr>
<td>Upstream LA position for $S_{CR}$</td>
<td>$x_{mp,LA}$</td>
<td>0.90</td>
<td>cm</td>
<td></td>
</tr>
<tr>
<td>Upstream SA position for $S_{CR}$</td>
<td>$x_{mp,SA}$</td>
<td>1.38</td>
<td>cm</td>
<td></td>
</tr>
<tr>
<td>Downstream position for $S_{CR}$</td>
<td>$x_{end}$</td>
<td>2.57</td>
<td>cm</td>
<td></td>
</tr>
</tbody>
</table>

RBC, red blood cell; LA, large arteriole; SA, small arteriole; $S_{CR}$, conducted response signal; $x_{mp}$, midpoint; $x_{end}$, end point.

$$C(x) = \alpha + \beta x + e^{\alpha x_b - \alpha}(C_0 - \alpha - \beta x_b)$$  \hspace{1cm} (6)

where $\alpha$, $\beta$, and $\gamma$ are functions of diameter, hematocrit, oxygen consumption, flow, degradation rate, and initial conditions:

$$\alpha = \frac{H_T R_0}{4 k_0} \left[ D_c \left( 1 - R_i S(x_0) \right) - \frac{(1 - H_0) R_i q}{\pi c_0 H_k k_0} \right]$$  \hspace{1cm} (7)

$$\beta = \frac{D_c H_T R_i R_q q}{4 Q_c c_0 H_k k_0} \cdot \gamma = \frac{k_b \pi D_i}{(1 - H_0) Q_i}$$

Equation 5 is solved separately for each compartment to account for different diameters and flows. Therefore, in Eq. 6, $x_0$ denotes the initial position and $C_0$ refers to the initial ATP concentration in the compartment being considered. At the start of the vascular pathway (x0 = 0), $C_0$ = 0.5 μM for consistency with measured arterial ATP levels (25).

Conducted response signal. Metabolic control of LA and SA diameters is assumed to occur via a conducted response that is generated throughout the vascular pathway and transmitted upstream. Multiple mechanisms have been identified that contribute to conducted responses, which may decay with distance traveled (64) or travel without significant decay (23). For simplicity, exponential decay is assumed here with a length constant $L_0$. Effects of varying $L_0$ are examined. At each point in the network, a signal is generated at the vessel wall in proportion to the local concentration of ATP in the plasma. This signal is summed from the end of the LV to the midpoints of the LA and SA in order to obtain the conducted response signal, $S_{CR}(x)$, that reaches the large and small arterioles, respectively. The summation is represented by the integral of the ATP concentration along the vascular pathway, including exponential decay of the signal in the upstream direction:

$$S_{CR}(x_{mp,k}) = \int_{x_{end,k}}^{x_{mp,k}} e^{-dy} C(y)dy$$  \hspace{1cm} (8)

In Eq. 8, $x_{mp,k}$ is the midpoint of compartment $k$, for $k$ = LA or SA, and $x_{end}$ is the end point of the LV. Parameter values are given in Table 1.

Arteriolar activation and diameter. Circumferential wall tension (T) is related to pressure and diameter by the law of Laplace, T = P/2, assuming that vessel wall thickness is much less than vessel diameter. A theoretical model (8, 9) describes the vascular effects of the myogenic response based on active and passive length-tension characteristics of vascular smooth muscle (VSM) and defines the total tension in a vessel wall by:

$$T_{total} = T_{pass} + A_{pass}$$  \hspace{1cm} (9)

$T_{pass}$ represents the passive tension in a vessel wall and is given by an exponential function of diameter. The product of smooth muscle activation, A, and maximal active tension, $T_{act}^\text{max}$, defined by a Gaussian function of diameter, represents the contractile tension generated by VSM cells. Activation is given by a sigmoidal function that varies between 0 and 1:

$$A_{total} = \frac{1}{1 + \exp(-S_{tone})}$$  \hspace{1cm} (10)

$S_{tone}$ is defined as the stimulus that dictates the level of VSM tone:

$$S_{tone} = C_{myo} T - C_{shear} T_{wall} - C_{meta} S_{CR} + C_{tone}$$  \hspace{1cm} (11)

where $C_{myo}$ = 0.0101 cm/dyn (LA), 0.0359 cm/dyn (SA) and $C_{shear}$ = 0.0258 cm$^2$/dyn (LA and SA) (8). $C_{meta}$ is unknown, and a range of values is considered. In the model simulations presented here, $C_{meta}$ = 30 μM$^{-1}$·cm$^{-1}$·min$^{-1}$ in the LA and SA. The calculation of $C_{tone}$ = 0.0011 (LA). 0.066 (SA) is described below (Control state). The equation for $S_{tone}$ is analogous to the previous definition (9), with additional terms for metabolic and shear signals.

Determination of steady-state diameters and activation levels. If pressure is altered, a vessel shows a rapid passive change in diameter followed by an active smooth muscle contraction or dilation to a new equilibrium diameter. This behavior can be represented by the system of equations:

$$\frac{dD}{dt} = \frac{1}{\tau_D} \left( T - T_{total} \right)$$  \hspace{1cm} (12)

$$\frac{dA}{dt} = \frac{1}{\tau_A} \left( A_{total} - A \right)$$

Here, $D_{total}$ and $T_{total}$ are the values of diameter and tension in the control state (see below), $T_{total}$ and $A_{total}$ are the calculated steady-state values of vessel wall tension and smooth muscle activation for given levels of pressure and oxygen demand, and $\tau_D$ and $\tau_A$ are time constants governing the rates of passive diameter and VSM activation change, respectively. When arteriolar diameters were measured after step changes in arterial pressure in the range of 7.35–125 mmHg, the time to approach a new equilibrium was typically ~1 min (20). Therefore,
\( \tau_s = 60 \) s is used in this model. The initial passive response to changes in intraluminal pressure occurs within seconds (31), and thus \( \tau_d = 1 \) s is assumed. Steady-state values of \( D \) and \( \tau_s \) are determined by integrating Eq. 12 until equilibrium is reached. The assumed values of \( \tau_s \) and \( \tau_d \) do not affect the eventual steady-state condition.

Control state. A control (or reference) state is defined to represent conditions in skeletal muscle at a level of oxygen consumption corresponding to moderate exercise. Several experiments show that wall shear stress is approximately uniform in the arteriolar tree but has lower values in the venous circulation (27, 35, 45). Here, control values of \( \tau_A = \tau_{LA} = \tau_{SA} = \tau_C = 55 \) dyn/cm² and \( \tau_V = \tau_{LV} = \tau_{SV} = 10 \) dyn/cm² are assumed, consistent with experimental data (45). In addition, an input arterial pressure of 100 mmHg is assumed. Pressure drops of 10, 15, 40, and 15 mmHg are chosen in A, LA, SA, and C so that the midpoint control pressures of LA and SA, 82.5 and 55 mmHg, lie in the middle of the ranges of pressures observed in those vessel types (45). It is assumed that the level of activation of LA and SA in the control state is 50%, i.e., \( A_{LA} = 0.5 \) and \( A_{SA} = 0.5 \). Then, from Eq. 10, \( S_{\text{base}} = 0 \) in both segments.

From these assumptions and the symmetry of the vascular pathway, the remaining values of vessel diameter, flow, length, pressure drop, and number are calculated. Control diameters of the large and small arterioles, \( D_{LA} = 65.2 \) μm and \( D_{SA} = 14.8 \) μm, are obtained by solving Eq. 12 for its steady state. Capillary diameter is set to \( D_C = 6 \) μm, consistent with experimental values from rat skeletal muscle (32). \( D_A \) and \( D_V \) are not specified, and these segments are considered to act as fixed resistances. \( D_{LV} \) is computed from \( D_{LA} \):

\[
D_{LV} = \left( \frac{\mu_{LV} \tau_{LA}}{\mu_{LA} \tau_{LV}} \right)^{\frac{1}{6}} D_{LA}
\]  

and similarly for \( D_{SV} \). Given the control diameters, the control values of flow in each segment are calculated. Vessel lengths are deduced from the assumed pressure drops with Poiseuille’s law. Substituting these values into the length symmetry condition \((L_A = L_V, L_{LA} = L_{LV}, \text{and } L_{SA} = L_{SV})\) gives an equation for the remaining pressure drops along the pathway:

\[
\Delta P_L = \frac{\left( \frac{\mu_{LA}}{\mu_{LV}} \right)^{\frac{1}{3}} \frac{\tau_{LV}}{\tau_{LA}} \Delta P_{LA}}{6}
\]  

and similarly for \( \Delta P_V \) and \( \Delta P_{LV} \). Since \( n_{LA} = 1 \), the number of vessels in each compartment is \( n = Q_{LA}/Q_t \). The capillary density, \( N \), is given by

\[
N = \frac{n_i L_i}{\sum_{\text{all vessels}} \pi r_i^2 n_i L_i}
\]

where \( r_i = r_i + d \) in arterial vessels and capillaries, and \( r_i = r_i \) in venous vessels. The value \( N = 500 \) capillaries/mm² is chosen because it is the typical measured value of capillary density in human skeletal muscle (38). This choice for \( N \) corresponds to a tissue region of width \( d = 18.8 \) μm around each arteriole and capillary.

Perfusion in the control state depends on the total flow through the pathway and the volume of the tissue:

\[
\text{perfusion} = \frac{Q_{tot}}{\sum \pi r_i^2 n_i L_i} = \frac{Q N}{L_c}
\]

and is 70.9 cm³ O₂·100 cm⁻³·min⁻¹. The corresponding oxygen consumption rate, \( M_o = 8.28 \) cm³ O₂·100 cm⁻³·min⁻¹, is estimated by linear interpolation of experimental data (25). Control values of segment diameter, length, shear stress, pressure drop, resistance, number, velocity, transit time, viscosity, and volume fraction are listed in Table 2. \( C_{\text{base}} \) is chosen to satisfy the condition that \( S_{\text{base}} = 0 \) in the control state.

RESULTS

Conducted response signal. Figure 2 shows the changes in saturation, ATP concentration, and conducted response signal with distance along the vascular pathway for three levels of oxygen demand: 1, 8.28, and 20 cm³ O₂·100 cm⁻³·min⁻¹, representing rest, moderate exercise, and heavy exercise, respectively. Perfusion is held fixed at its control level. In each case, the greatest drop in oxygen saturation occurs across the capillaries. Saturation remains constant in the SV, LV, and V since oxygen exchange by these segments is neglected. ATP concentration declines slightly in the resistance vessels, where saturation is high and ATP degradation exceeds ATP release. The greatest ATP concentration occurs in the venules and veins, which are characterized by low oxygen saturation, decreased blood velocity, and long blood transit times. At rest, only slight changes in oxygen saturation and ATP concentration are predicted. Increasing oxygen demand to 20 cm³ O₂·100 cm⁻³·min⁻¹ at this perfusion level results in complete extraction of oxygen from the capillaries. ATP levels approach 2 μM at the venous end, resulting in the generation of a stronger vasodilatory conducted response signal. ATP levels return to lower levels in arterial blood after traveling through the lungs, where a significant amount of ATP is taken up (24). In Fig. 2C, the conducted response signal is plotted as a function of distance along the vascular pathway. The majority of the signal originates in the venules. Arrows at the midpoints of the small and large arterioles indicate the locations at which the conducted response signal is evaluated in Eq. 8.

Metabolic regulation of flow. Figure 3 shows model results for levels of oxygen demand ranging from 1 to 25 cm³ O₂·100

Table 2. Control state values for representative segments

<table>
<thead>
<tr>
<th>Description</th>
<th>Artery</th>
<th>Large Arteriole</th>
<th>Small Arteriole</th>
<th>Capillary</th>
<th>Small Venule</th>
<th>Large Venule</th>
<th>Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter, ( D ), μm</td>
<td>65.2</td>
<td>14.8</td>
<td>6</td>
<td>23.5</td>
<td>119.1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Wall shear stress, ( \tau ), dyn/cm²</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Pressure drop, ( \Delta P ), mmHg</td>
<td>10</td>
<td>15</td>
<td>40</td>
<td>15</td>
<td>4.60</td>
<td>1.49</td>
<td>1.00</td>
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<tr>
<td>Segment resistance, ( R ), mmHg·cm⁻³·s⁻¹·(×10⁶)</td>
<td>1.88</td>
<td>2.81</td>
<td>7.50</td>
<td>2.81</td>
<td>0.86</td>
<td>0.28</td>
<td>0.19</td>
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<td>Number of segments, ( n )</td>
<td>1.00</td>
<td>143</td>
<td>5515</td>
<td>143</td>
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<tr>
<td>Segment length, ( L ), cm</td>
<td>0.61</td>
<td>0.59</td>
<td>0.36</td>
<td>0.05</td>
<td>0.36</td>
<td>0.59</td>
<td>0.61</td>
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<td>Velocity, ( V ), cm/s</td>
<td>2.13</td>
<td>0.29</td>
<td>0.05</td>
<td>0.11</td>
<td>0.11</td>
<td>0.64</td>
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<tr>
<td>Transit time, ( T_c ), s</td>
<td>0.28</td>
<td>1.25</td>
<td>1.20</td>
<td>3.14</td>
<td>3.14</td>
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<td>Viscosity, ( \mu ), cP</td>
<td>2.26</td>
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<td>3.55</td>
<td>9.05</td>
<td>2.56</td>
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<td>Vascular volume, % of tissue</td>
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<td>0.33</td>
<td>1.48</td>
<td>1.41</td>
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<td>Values in bold are specified, and the remaining values are calculated.</td>
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THEORETICAL MODEL OF METABOLIC BLOOD FLOW REGULATION

Fig. 2. Model predictions along flow pathway for 3 levels of exercise (in cm$^3$ O$_2$/100 min$^{-1}$cm$^{-3}$) at fixed perfusion: oxygen demand $M_0 = 1$ (rest), $M_0 = 8.28$ (control, moderate exercise), and $M_0 = 20$ (heavy exercise). A: saturation. B: ATP concentration. C: conducted response signal ($S_{CR}$). Dots indicate ends of segments. A, artery; LA, large arteriole; SA, small arteriole; C, capillary; SV, small venule; LV, large venule; V, vein.

Fig. 3. A: model predictions of perfusion as a function of oxygen consumption rate at an input arterial pressure of 100 mmHg. Effects of deactivating myogenic (myo), shear-dependent (shear), and metabolic (meta) response mechanisms are shown. Data from canine studies (▲, Ref. 29; ■, Ref. 57; ●, Ref. 40) are included. The maximum perfusion possible in this model, with arterioles fully dilated, is shown by top horizontal line [activation ($A = 0$)]. The bottom horizontal line ($A = 0.5$) indicates no metabolic response active and corresponds to the control state. The diagonal dashed line indicates the perfusion corresponding to 100% oxygen extraction. B: oxygen extraction as a function of oxygen consumption rate in the presence or absence of the 3 regulatory mechanisms, and for $A = 0$ and $A = 0.5$. Thin solid line, metabolic response only; dashed line, shear and metabolic responses; dashed-dotted line, myogenic and metabolic responses; thick solid line: myogenic, shear, and metabolic responses.

Fig. 3A: model predictions of perfusion as a function of oxygen consumption rate at an input arterial pressure of 100 mmHg. Effects of deactivating myogenic (myo), shear-dependent (shear), and metabolic (meta) response mechanisms are shown. Data from canine studies (▲, Ref. 29; ■, Ref. 57; ●, Ref. 40) are included. The maximum perfusion possible in this model, with arterioles fully dilated, is shown by top horizontal line [activation ($A = 0$)]. The bottom horizontal line ($A = 0.5$) indicates no metabolic response active and corresponds to the control state. The diagonal dashed line indicates the perfusion corresponding to 100% oxygen extraction. B: oxygen extraction as a function of oxygen consumption rate in the presence or absence of the 3 regulatory mechanisms, and for $A = 0$ and $A = 0.5$. Thin solid line, metabolic response only; dashed line, shear and metabolic responses; dashed-dotted line, myogenic and metabolic responses; thick solid line: myogenic, shear, and metabolic responses.

cm$^{-3}$ min$^{-1}$, with the various regulatory mechanisms activated or deactivated. The predicted tissue perfusion and oxygen extraction are plotted as functions of oxygen consumption rate, which may be lower than demand. With all mechanisms activated, the model predicts a strong increase in perfusion with increasing consumption (Fig. 3A, heavy line). Myogenic and shear stress responses are deactivated by holding values of wall tension and shear stress, respectively, constant at control levels for the purpose of calculating $S_{CR}$. For low and moderate levels of oxygen consumption (0–10 cm$^3$ O$_2$/100 cm$^{-3}$-min$^{-1}$), deactivation of the myogenic or shear stress responses has little effect on the predicted perfusion. At higher rates of oxygen consumption, deactivating the myogenic and/or shear-dependent responses leads to increased perfusion, implying that these responses tend to weaken metabolic regulation. The upper horizontal line in Fig. 3A shows the maximum supply of blood available when both arterioles are fully dilated. Figure 3B shows the predicted oxygen extraction under corresponding conditions. In the presence of all three mechanisms, extraction varies from ~25% under resting conditions to 90% under heavy exercise.

Figure 4, A and B, show the dependence of activation and diameter of the large and small arterioles on oxygen consumption rate when all three responses are activated. Diameters increase with increasing consumption. Figure 4, C and D, show the dependence of the components of $S_{CR}$ on oxygen consumption rate when all three responses are activated. Diameters increase with increasing consumption.
consumption rate. The metabolic term ($C_{meta}S_{CR}$) increases with consumption, causing vasodilation. The myogenic term ($C_{myoT}$) increases with consumption, because wall tension increases with diameter. The resulting myogenic constriction tends to oppose the metabolic dilation. The shear-dependent response term ($C_{shear\tau}$) increases very slightly in the large arteriole and decreases in the small arteriole. Thus the shear-dependent response also tends to oppose the dilation induced by the metabolic response.

The effects on perfusion of the assumed conducted response length constant, $L_0$, and metabolic sensitivity parameter, $C_{meta}$, are examined in Fig. 5. With $C_{meta} = 30 \mu M^{-1}cm^{-1}$, a length constant of 1 cm yields an increase in perfusion for low to moderate exercise levels consistent with experiment (Fig. 5A). Increasing $L_0$ above 1 cm has little effect on perfusion. Decreasing $L_0$ to 0.2 or 0.5 cm reduces the amount of perfusion attained for $M_0 = 25 \text{cm}^3 \text{O}_2 \cdot 100 \text{cm}^3 \text{min}^{-1}$. This effect can be reversed by increasing $C_{meta}$ to much larger values (data not shown). In this case, only the SA would participate significantly in flow regulation since very little metabolic signal would reach the LA. If a smaller value of $C_{meta}$ is assumed, perfusion is decreased for a given value of $L_0$ (Fig. 5B). In this case, large increases in $L_0$ yield only slight changes in perfusion. The available data do not uniquely determine the values of $C_{meta}$ and $L_0$. In the following, it is assumed that $L_0 = 1 \text{cm}$ and $C_{meta} = 30 \mu M^{-1}cm^{-1}$.

In Fig. 6, the effect of varying input arterial pressure (70, 100, and 130 mmHg) on model predictions of perfusion is examined. The assumed mechanism of metabolic flow regulation operates effectively at all three pressure levels, but the maximum consumption rate that can be achieved decreases with decreasing pressure. Higher perfusion values are obtained as input arterial pressure increases. The effect of the myogenic response is evident in that perfusion does not increase linearly with pressure.

Figure 7 compares the model predictions with data collected from both canine and human studies (1, 25, 29, 33, 40, 42, 50–53, 57) over a wide range of exercise levels. With the present assumptions and parameter values, particularly the assumed capillary density of 500 mm$^{-2}$, the model does not predict the very high rates of oxygen consumption and perfusion observed in some human studies. This apparent discrepancy is discussed below.

**DISCUSSION**

**Model predictions.** The results of this model support the concept that the saturation-dependent ATP release by RBCs can act as a mechanism for metabolic flow regulation by triggering a conducted response and upstream vasodilation. In Fig. 2, the effects of increasing $M_0$ are examined in the absence of the conducted response.
of flow regulation, i.e., at constant blood flow. With increasing \( M_0 \), venous saturation declines and ATP concentration increases significantly in the venules but not in the arterioles or capillaries. The ATP levels predicted by the model lie within a physiologically realistic range and are obtained from independent data on ATP degradation and release rates (5, 14). Ellsworth et al. (11, 16, 36) showed that these ATP levels are sufficient to cause arteriolar vasodilation. The model assumes that the conducted response signal is generated along the vascular pathway in proportion to ATP level. For a conducted response with \( L_0 = 1 \text{ cm} \), the signal reaching large and small arterioles varies significantly with \( M_0 \) (Fig. 2C). Together, these model predictions confirm the potential of this mechanism to provide metabolic flow regulation.

As shown in Fig. 3A, the model predicts an increase in flow consistent with experimental observations (29, 40, 57) as oxygen demand increases from low to moderate levels in the presence of the metabolic, myogenic, and shear-dependent response mechanisms. The shear-dependent response has been considered an important contributor to flow regulation (43) since it provides a potential mechanism for vessel diameters to increase in response to increased flow rate through a vascular network (56). However, the present model predicts that the shear-dependent response has limited effect on metabolic flow regulation. Moreover, the shear-dependent response is predicted to act in opposition to the metabolic mechanism, contrary to previous concepts. This unexpected behavior can be explained as follows. With increasing oxygen consumption rate, the metabolic response triggers vasodilation of the small and large arterioles, such that wall shear stress decreases despite the increase in flow (Fig. 4D). This decrease in wall shear stress reduces the overall vasodilatory stimulus. The myogenic response causes vasoconstriction due to increased

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Fig. 6. Predicted perfusion as a function of oxygen consumption rate for input arterial pressures of 70, 100, and 130 mmHg. Data from canine studies as in Fig. 3.

Fig. 7. Predicted and observed perfusion as a function of oxygen consumption rate. Data from canine studies (29, 40, 57) as in Fig. 3 and from human studies (1, 25, 33, 42, 50–53). Horizontal line, maximum possible perfusion with assumed constant capillary density.
wall tension as vessels dilate (Fig. 4, C and D). This increase in wall tension also reduces the vasodilatory stimulus. According to this model, both the myogenic and shear-dependent mechanisms cause a reduction in perfusion from the levels that would be attained at high consumption rates with only the metabolic response active.

These effects are shown schematically in Fig. 8, with the primary effect in the system highlighted by bold lines and arrows. Increased metabolic demand yields an increased metabolic signal, which decreases vascular tone (pathway a). This decrease in tone, resulting in increased diameter, is represented schematically by (−). The increase in diameter causes both decreased shear stress and increased wall tension, yielding an increase in vascular tone, represented by (+), according to the shear-dependent and myogenic responses (pathways b and c). Thus myogenic and shear-dependent responses act in opposition to metabolic flow regulation.

Figure 5 shows the effect of the conducted response length constant on predicted perfusion levels. These results imply that a length constant of ~1 cm is required to trigger arteriolar vasodilation consistent with experimental values. The distance the signal must travel from the venule to the arterioles is ~1 cm. Increasing L0 above this value does not lead to a significant increase in perfusion. Some studies have suggested that conducted responses travel only 0.5–2 mm (11, 36), although these values may be more indicative of limitations on the field of view in intravital microscopy than of actual conduction lengths (4). More importantly, experimental studies have shown that applying ATP to venules leads to a significant increase in diameter of upstream arterioles (17). In Ref. 18, segments were observed to dilate when ACh was applied 750 μm downstream, and the conduction through the segment was not attenuated. Pries et al. (44) used a length constant of 1.73 cm in a model that simulates structural diameter changes in response to shear stress, intravascular pressure, and a conducted metabolic response. The conducted response is assumed to decay in the upstream direction with a single L0. As mentioned above, multiple mechanisms may contribute to the conducted response. The assumed length constant represents an effective decay rate taking into account the combined effects of the mechanisms involved.

The model predicts that metabolic flow regulation is achieved over a range of pressures. An approximately fourfold range of perfusion is predicted at each pressure level considered (Fig. 6). The predictions of the model with regard to autoregulation of blood flow are considered in a separate study (8).

Other regulatory mechanisms. In the present model, the metabolic signal is assumed to result only from ATP release by RBCs, which occurs mainly in the venules. The effects of ATP from other sources, such as nerves and muscles, and of other vasoactive substances, such as adenosine, NO, and potassium, that are produced in response to muscle contraction are not included in the present model. These substances may diffuse into and relax the smooth muscle cells of arterioles, leading to local vasodilation. Stamler et al. (59) described a mechanism that involves the binding of NO to hemoglobin and the release of NO from S-nitrosohemoglobin after a change in oxygenation state. It was hypothesized that the released NO may then act on the endothelium to cause vasodilation. However, theoretical models (34) show that strictly local responses of arterioles in skeletal muscle provide poor matching of blood supply with local demand. At high perfusion rates, the extraction from arterioles is small, and therefore arteriolar oxygen level does not provide a sensitive indication of tissue oxygen levels. Mechanisms based on local responses do not appear capable of accounting for local metabolic regulation of blood flow over a wide range of consumption rates.

Diffusion of vasoactive substances between paired venules and arterioles can cause arteriolar vasodilation (28). Known as the countercurrent exchange of metabolites or venular-arteriolar communication, this diffusion typically occurs between larger arterioles and venules since vessels of these sizes often exist in close alignment (in pairs) in vivo. Increased venular levels of ATP were found to cause an endothelium-dependent dilatation of adjacent arterioles that could be blocked by disrupting the venular endothelium (28).

The effects of the autonomic nervous system should also be considered when modeling the control of blood flow. Increased muscle activity is accompanied by recruitment of motor units and vasodilation. Simultaneously, the sympathetic nervous system is stimulated and causes smooth muscle contraction...
primarily through the release of norepinephrine (62). However, blood flow increases with exercise despite activation of sympathetic nerve activity (63). Several explanations for the decreased sensitivity of active muscles to nerve activity compared with inactive muscles have been offered and may play a role in blood flow regulation (62). These regulatory mechanisms could in principle be integrated into the present model by including additional terms in $S_{\text{tone}}$.

**Limitations of the model.** The present model includes several simplifications. Oxygen and ATP concentration levels are estimated in a flow pathway consisting of seven representative segments. This highly simplified network system excludes some characteristics of real networks. For example, it neglects the role of diffusive exchange between capillaries and arterioles in oxygen delivery (54), the effects of heterogeneity in pathway length and transit time (47), and the effects of arcading structures of arterioles (19). A Krogh-type model is used to simulate oxygen transport from vessels to tissue, leading to the possibility of 100% extraction of oxygen from blood. In reality, oxygen extraction is restricted by several factors including diffusive and convective limitations of oxygen transport, as evidenced by substantial oxygen saturation (15–30%) remaining in venous blood (37). The present approach could be extended to overcome these limitations by introducing dependence of oxygen consumption on the partial pressure of oxygen with Michaelis-Menten kinetics, and, further, by introducing detailed three-dimensional simulations of the oxygen field (55).

As shown in Fig. 7, perfusion levels attained in some studies on humans exceed the maximum level that this model can predict (1, 25, 33, 42, 50–53). The present model assumes a constant capillary density, 500 capillaries/mm², although actual capillary density has been shown to be higher (38). Increased exercise rates are accompanied by capillary recruitment, which is not considered in this model. Capillary recruitment may occur independently of arteriolar dilation (10). The present results support the established concept that capillary recruitment, working in conjunction with arteriolar dilation, is necessary to generate the very wide range of perfusion levels between rest and maximal exercise (58).

In the present model, parameter values and comparisons with experimental data are based on observations of skeletal muscle. The model could in principle be applied to other tissues in which ATP release by RBCs is a major mechanism of metabolic flow regulation. For example, Farias et al. (21) have provided evidence for a role of plasma ATP in regulation of cardiac blood flow.

**Conclusion.** This study supports the concept that upstream conducted responses stimulated by ATP release from RBCs can account for increases in perfusion observed for moderate increases in oxygen consumption rates. It provides a quantitative assessment of the roles of myogenic, shear-dependent, and metabolic responses in flow regulation and confirms that the metabolic response is the primary mechanism contributing to the increase in perfusion with increasing demand, overcoming the opposing effects of the myogenic and shear-dependent responses.

**REFERENCES**


**GRANTS**

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