Structural response of microcirculatory networks to changes in demand: information transfer by shear stress

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Pries, A. R., B. Reglin, and T. W. Secomb. Structural response of microcirculatory networks to changes in demand: information transfer by shear stress. Am J Physiol Heart Circ Physiol 284: H2204–H2212, 2003.—Matching blood flow to metabolic demand in terminal vascular beds involves coordinated changes in diameters of vessels along flow pathways, requiring upstream and downstream transfer of information on local conditions. Here, the role of information transfer mechanisms in structural adaptation of microvascular networks after a small change in capillary oxygen demand was studied using a theoretical model. The model includes diameter adaptation and information transfer via vascular reactions to wall shear stress, transmural pressure, and oxygen levels. Information transfer is additionally effected by conduction along vessel walls and by convection of metabolites. The model permits selective blocking of information transfer mechanisms. Six networks, based on in vivo data, were considered. With information transfer, increases in network conductance and capillary oxygen supply were amplified by factors of 4.9 ± 0.2 and 9.4 ± 1.1 (means ± SE), relative to increases when information transfer was blocked. Information transfer by flow coupling alone, in which increased shear stress triggers vascular enlargement, gave amplifications of 4.0 ± 0.3 and 4.9 ± 0.5. Other information transfer mechanisms acting alone gave amplifications below 1.6. Thus shear-stress-mediated flow coupling is the main mechanism for the structural adjustment of feeding and draining vessel diameters to small changes in capillary oxygen demand.

vascular adaptation; hemodynamics; model simulation; blood flow; blood pressure

The ability of the vascular system to adapt to changing demands is essential for normal growth and maturation, for wound healing, and for maintenance of tissue function. According to Poiseuille’s law, the resistance of a vascular segment to blood flow is proportional to the inverse fourth power of its diameter. Therefore, vessel diameters must be controlled within relatively narrow limits to achieve adequate tissue perfusion, without inefficient oversupply. Such control requires structural adaptation of vessel diameters according to demand (25, 26). For vessels that are capable of active diameter changes by modulating smooth muscle tone, the structural diameter determines the operating range of the vessel. Deficiencies or alterations in the structural regulation of the vascular system are associated with several diseases, including hypertension and cancer.

In a network of microvessels, the flow rate of any given segment depends not only on the flow resistance of that segment but also on the flow resistance of all the segments upstream and downstream, forming a flow pathway through the given segment. Consequently, modulation of blood flow over a wide range can be achieved only if diameter changes in multiple segments along a flow pathway are coordinated. For example, suppose that some terminal microvessels (including precapillary arterioles, capillaries, and post-capillary venules) supply a region that experiences increased oxygen demand. The increase in capillary flow that can be achieved solely by a structural increase in diameter of terminal vessels is limited by the resistance of the series coupled arteries, arterioles, venules, and veins. To achieve a substantial increase in flow, information about the metabolic needs must be transmitted to upstream and downstream segments, so that they are also enlarged. Information transfer is therefore an essential aspect of the ability of the vascular network to meet functional demands. This reasoning applies to both acute blood flow regulation and long-term structural adaptation (32).

A number of mechanisms for information transfer in microvascular networks have been identified or proposed (32). The mechanisms include hemodynamic coupling involving vascular responses to wall shear stress and intravascular pressure, convective information transfer involving vascular responses to oxygen and other vasoactive metabolites, and electrotonic conduction of vasoactive stimuli along vessel walls, as described in the following paragraphs and Fig. 1.

The acute response of blood vessels to wall shear stress, with increased stress causing dilation, has long been known (31). Recent studies have linked this response to the shear-induced production of dilatory autacoids by endothelial cells (4, 7, 29, 35). Chronic alterations in wall shear stress have been shown to lead to structural changes that parallel the acute responses (17, 18, 36, 37). This behavior provides a mechanism

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Active transmission of stimuli along vessel walls provides yet another mechanism of information transfer. Local application of a number of vasoactive substances (e.g., acetylcholine and bradykinin) has been found to stimulate signals that are transmitted along the vessel wall and evoke vasodilation or constriction at locations remote from the application site (2, 3, 30, 33). This process involves electrotonic transmission of changes in intracellular potential through gap junctions generated by vascular connexins (5, 12) and is therefore called “conduction.” Use of this term in the present context does exclude the possibility of active regeneration of the transmitted signal, as occurs in the propagation of action potentials.

Given this multiplicity of information transfer mechanisms, the following question arises: What role does each mechanism play in the response of a vascular network to an alteration in functional demands? This question is difficult to address using biological experiments. In vitro approaches allow investigation of individual mechanisms at vascular, cellular, and molecular levels but lack the complexity and mutual interactions that determine the quantitative impact of such mechanisms in real vascular networks. Conversely, such interactions make in vivo experiments difficult to interpret, particularly because the underlying biological mechanisms involved are incompletely understood, and experimental methods to suppress specific mechanisms are lacking. Theoretical models provide a framework for integrating available information on vascular responses and testing hypotheses on their interactions in a network context. They permit quantitative assessment of the effects of suppressing specific mechanisms of information transfer, in a mathematical “knockout” approach.

A theoretical model for structural adaptation of vascular diameters in microvascular networks was developed by Pries et al. (24, 26). This model includes all of the vascular responses and information transfer mechanisms referred to in the preceding paragraphs, along with detailed simulation of network hemodynamics. The development of the model was based on a consideration of the responses that are needed to ensure stable, functionally adequate network properties. The initial concept that vessel diameters adapt so as to maintain a set level of wall shear stress (16) was shown to be inadequate because it leads to unstable network structures (11). Vascular responses to wall shear stress, intravascular pressure, and the local metabolic state, as reflected, for example, by the oxygen partial pressure (PO2), were found to be necessary to achieve stable network structures, in which arterioles are smaller in diameter than the corresponding venules as seen experimentally. Inclusion of responses to wall shear stress and pressure ensured that information transfer by hemodynamic coupling was present. However, to achieve realistic hemodynamic properties and to prevent the formation of short large-diameter “shunt” pathways through the network, additional mechanisms for information transfer had to be included. These mechanisms ensure that vessels supply-
ing or draining many dependent segments (capillaries) with strong metabolic demand are stimulated to increase in diameter relative to those with few (or low demand) dependent segments. When all these mechanisms were included, the model was found to lead to stable network structures, with predicted vascular diameters and flow velocities in good agreement with in vivo observations in rat mesenteric networks.

The aim of the present study was to use this theoretical model to assess the quantitative relevance of the previously stated mechanisms of information transfer in the structural response of vascular networks to an incremental increase in oxygen demand at the capillary level.

METHODS

Experiments. After approval from the university and state authorities for animal welfare was obtained, male Wistar rats (250–350 g body wt) were prepared for intravital microscopy and monitoring of heart rate, arterial pressure anaesthetic level, and fluid balance (23). The small bowel was exteriorized, and fat-free portions of the mesentery were selected for investigation. Papaverine (10−4 M) was continuously applied to suppress active vessel tone. Microvascular networks (n = 6) were scanned and video recorded. From the video recordings and photomontages, diameter, length, hematocrit, and flow velocity were measured in all segments between branch points using a digital image-analysis system (21). Network area ranged between 25 and 80 mm² supplied between branch points using a digital image-analysis system.

Feeding arterioles and draining venules exhibited diameters of 33 ± 15 and 52 ± 24 μm, respectively. The topological arrangement of segments and the length, diameter, blood flow velocity, and hematocrit of each segment were measured (26).

Model simulation: network hemodynamics and oxygen distribution. The input to the model consists of data on the arrangement of segments and the length, diameter, blood flow velocity and hematocrit of each segment were measured (26). Hemodynamics and oxygen distribution was performed based on experimentally determined vessel diameters and volume flow values for boundary segments (27). For each boundary segment, three internal reference segments were selected, which exhibited the highest values of a composite similarity parameter (S).

\[
\text{Similarity} = S_{\text{sim}}^4 \cdot S_{\text{pre}}^2 \cdot S_{\text{flow}} \cdot S_{\text{main}} \cdot S_{\text{topol}}^{0.5}
\]  

(1)

where the individual similarity values for diameter (S_{\text{diam}}), flow (S_{\text{flow}}), and pressure (S_{\text{pre}}) are

\[
S_r = 1 - \left( \frac{|X_{\text{bound}} - X_{\text{seg}}|}{|X_{\text{bound}} + X_{\text{seg}}|} \right)
\]  

(2)

Here, X_{\text{bound}} and X_{\text{seg}} are the values for the parameter considered in the respective boundary segment and a given internal segment. S_{\text{main}} refers to the share of flow in the given internal segment, which is drained by the main venule (for input boundaries) or is supplied by the main arteriole (for output boundaries). S_{\text{topol}} refers to the number of branch points between the internal segment and its boundary feeding or draining vessel for arteriolar and venular segments, respectively. The exponents in Eq. 1 were chosen to assign different weights to the individual similarity values. For all subsequent runs of the model simulation, the necessary parameters for secondary boundaries were estimated as the weighted average of the corresponding values in its internal reference segments obtained in the preceding calculation. Although the criterion for selecting these reference segments was arbitrary to some extent, it was found to be adequate to avoid artifactual effects, in the sense that the changes in diameter exhibited by boundary segments were comparable to those of the internal segments after manipulation of oxygen demand as described below. Simpler procedures, such as assigning fixed flows or pressures to boundary segments, were found to be inadequate in this regard.

Rheological phenomena are represented as parametric descriptions of experimental findings in vitro and in vivo: the Fahraeus effect (27), Eq. 1; and blood viscosity (28), Eqs. 5, 9, and 10. The distribution of red blood cells and plasma at microvascular bifurcations (phase separation) was represented according to the approach described earlier (27) with small modifications to render predictions more robust for extreme combinations of input hematocrit and diameter distribution. The fractional flow of erythrocytes into one daughter branch (F_{Qe}) was calculated from the respective fractional blood flow (F_{Qb})

\[
\logit F_{Qe} = A + B \logit \left[ \frac{(F_{Qb} - X_0)(1 - X_0)}{X_0} \right]
\]  

(3)

where A, B, and X_0 define the phase separation characteristics of the bifurcation and \logit x = ln(x/(1 − x)). A, B, and X_0 for each bifurcation were obtained from linear fits to experimental data obtained in the rat mesentery (22)

\[
A = -13.29 \left[ (D_2^4 - D_1^4)/(D_2^4 + D_1^4) \right] (1 - H_{v})/D_{p}
\]  

(4)

\[
B = 1 + 6.98(1 - H_{v})/D_{p}
\]  

(5)

\[
X_0 = 0.964(1 - H_{v})/D_{p}
\]  

(6)

where D_2, D_1, and D_{p} are the diameters of the daughter branches and the mother vessel and H_{v} is the discharge hematocrit in the mother vessel.

SO_2 in the main feeding segment was assumed to be 0.94. Oxygen supply to each vessel segment was calculated from its blood flow (Q), H_{v}, and SO_2 of the blood flowing into the segment (SO_2^{in}) as Q/O_2/2 H_{v} SO_2^{in}, assuming an oxygen carrying capacity of 0.5 (vol/vol) for red blood cells. Oxygen loss for the segment was assumed to be the product of segment length and the oxygen demand of the tissue fed by the segment per unit vessel length. According to literature values for connective tissues, the oxygen consumption rate was set to 0.01 liters of O_2/liter of tissue·min (6). On the basis of the total tissue area supplied by the vascular networks and the summed length of all vessels, vessel segments were estimated to supply a tissue volume of 4,000 μm³/μm vessel length (100 μm to each side of the segment, thickness 20 μm). From SO_2^{in} and the oxygen loss, the average SO_2 (SO_2^{av}) was calculated by conservation of mass and used to calculate the midpoint PO_2 (in mmHg) for each vessel segment using Hill’s equation as \text{PO}_2 = \text{PO}_2^{50}(\text{SO}_2^{av}/(1 - \text{SO}_2^{av}))^{1/NOX}, where the half-saturation pressure (P_{O2}^{50}) was set to 38 mmHg and the exponent N_{OX} was set to 3 according to experimental data for rat blood (10).
The computational method for simulation of network hemodynamics and oxygen distribution involves two nested loops that are each iterated until a preset level of convergence is achieved (24). In the linear analysis (inner loop), the nodal pressures are calculated, given the hematocrit, viscosity, and diameter for each segment. The nodal pressures are then used to update the volume flow rate, hematocrit, and viscosity in each segment (outer loop), and the procedure is repeated.

Model simulation: structural adaptation. The mathematical approach to simulate structural adaptation of vessel diameters to hemodynamic and metabolic conditions including information transfer has been described in detail earlier (24). The observed vessel diameters were used as initial conditions for a simulated adaptive process. All vessels in the network (arterioles, capillaries, and venules) were assumed to be capable of structural changes in diameter. For each segment in the network, the diameter \( D \) was assumed to vary with time \( t \) according to

\[
\frac{dD}{dt} = D - S_{\text{tot}} = S_i + k_i S_0 + k_{\text{wall}}[S_m + k_i S_i] - k_i \quad (7)
\]

where the terms on the right side represent responses to hemodynamic stimuli, namely, wall shear stress and transmural pressure \((S_i + k_i S_0)\), responses to a metabolic signal substance and a conducted signal \([k_m(S_m + k_m S_i)]\), and a basal tendency of vessels to shrink in the absence of positive growth stimuli \((k_i)\). For \( S_i \), the signal derived from wall shear stress \((\tau_w)\) was calculated as \( \log(\tau_w + \tau_{\text{ref}}) \), where \( \tau_{\text{ref}} \) is a small constant included to ensure that \( S_i \) remains bounded for very low shear stress values. The impact of transmural pressure \( P \) is given by \( k_p S_p \), where \( k_p \) is the vascular sensitivity to pressure and \( S_p \) is \(-\log(\tau(P))\). The expected shear stress level \( \tau(P) \) exhibits a sigmoidal dependence on \( P \) according to experimental data (25), described as \( \tau(P) = 100 - 86\exp(-5,000 \cdot \log(\log P)) \). This equation predicts \( \tau \) values ranging from 14 dyn/cm\(^2\) for a pressure of 10 mmHg up to \(-100 \) dyn/cm\(^2\) at 90 mmHg.

For each vessel segment, the surrounding tissue supplied by this vessel is assumed to produce, in response to local \( P_o \), a metabolic signal substance that is added to the blood in proportion to vessel length \((L)\) and time. Over a single vessel segment, the flux of this substance \((J_m)\) increases by \( L \cdot \left[ 1 - \left( P_o/Q + R \right) \right] \), assuming a linear increase of production with decreasing \( P_o \) below a reference value, \( R \). The metabolic signal substance is convected downstream with an exponential time decay constant \((M_o)\) and distributes at vascular branch points in proportion to blood flow. On the basis of the resulting concentration in a given vessel segment, the metabolic stimulus is calculated as \( S_m = \log(1 + J_m/(Q + Q_R)) \), where \( Q_R \) is the reference flow.

In addition to the downstream convection with the blood flow, a signal derived from \( S_m \) is assumed to be conducted upstream. Conduction starts at any given vessel segment and proceeds to the arterial input vessel. The conducted signal flux at the upstream end of a segment, \( J_{m\text{con}} = (J_{m\text{con}} + S_m) \exp(-x/L_o) \), was calculated from its input, \( J_{m\text{con}}^0 \), plus the local metabolic stimulus, \( S_m \), and decayed exponentially over the length of the segment, \( x \), where \( L_o \) is a length constant. At each bifurcation, the conducted stimuli from the draining segments are summed and distributed evenly to the segments feeding into this branch point. From the conducted signal flux in the middle of the segment, \( J_{m\text{con}} \), and a reference flux, \( J_{m0} \), the actual conducted stimulus, \( S_{m\text{con}} \), was calculated as \( [J_{m\text{con}} + J_{m0}] \). The vascular sensitivity to metabolic stimuli in general and to the conducted stimulus are determined by the parameters \( k_m \) and \( k_{s\text{con}} \), respectively.

The resulting system of differential equations was integrated numerically to predict equilibrium diameters, using the observed diameters as the initial condition. The mean square deviation between predicted segment flow velocities and observed velocities was minimized with respect to the unknown parameters of the model \((k_p, k_m, k_i, k_{s\text{con}}, L_0, J_{m0}, \tau_{\text{ref}}, Q_R)\) using a downhill simplex method (20). This procedure led to the following mean values: \( k_p = 7.85, k_m = 0.7, k_i = 2.45, k_{s\text{con}} = 1.72, L_0 = 17.3 \) mm, \( J_{m0} = 27.9, RO_{2} = 93.2 \) mmHg, \( \tau_{\text{ref}} = 0.103 \) dyn/cm\(^2\), and \( Q_R = 0.198 \) ml/min. \( M_o \) was set to infinity.

The final distributions of hemodynamic and functional parameters were compared with their observed values and found to be in good agreement (Fig. 2). Parameter distributions resulting from a simulated adaptation process exhibited somewhat reduced heterogeneity than the measured values, as expected because no variability in vascular reaction characteristics was included in the model. The similarity between measured and predicted distributions was maintained if the adaptation was started not from the diameters measured experimentally but from either fixed (10 \( \mu \)m) or adaptive initial diameters. These results suggest that the model is able to mimic adaptive vascular responses for the tissue investigated.

Model simulation: effects of blocking information transfer mechanisms. The method used to simulate effects of blocking information transfer mechanisms is shown schematically in Fig. 3. In step 1, adaptation to convergence (relative diameter changes between runs \(< 5 \times 10^{-6}\)) with standard parameters was performed, leading to an initial adapted state. The computed strengths of conducted and convected signals as well as the local intravascular pressures and flows were recorded. To represent the effect of increased peripheral oxygen requirements, the oxygen demand of the tissue surrounding all capillaries was then increased by 0.5%. Capillaries were defined functionally as vessels connecting the divergent arterial tree with the convergent venous tree. This small increment was chosen so that the network structure is only slightly perturbed in all cases considered, and the resulting changes reflect the sensitivity of the network response to the imposed changes. During the following simulations, the pressure levels at all inflow and outflow segments were held constant and volume flow was allowed to vary. In step 2, diameter adaptation of capillaries only to the new situation was performed until a new steady state was achieved. Changes in capillary diameter, which were in the order of only 0.03% of the respective vessel diameter, and oxygen supply as well as in overall network conductance were recorded. These were used as reference levels for comparison with changes found in subsequent simulations. In step 3, all segments of the network were allowed to adapt under the influence of information transfer. This step was performed for several different cases. In one case (All), the complete model was used. In other cases, all but one component of information transfer were blocked [retained component: pressure (Press), flow coupling (Flow), downstream oxygen level (OX), convection of vasoactive metabolite(s) (Conv), and upstream conducted response (Cond)] or all components were blocked (None).

To block a specific component of information transfer, the influence of changes in the parameters determining the response (flow pressure, \( P_o \), convected or conducted signal) on adaptation of feeding or draining segments was eliminated. This was achieved by fixing these parameters at the values that were obtained after the initial adaptation (step 1) before capillary oxygen demand was increased. For calculation of hemodynamic stimuli \((S_i \text{ and } S_p)\), recorded values of flow or
pressure were used. For the conducted stimulus and the convected signal, respectively, recorded values for $S_t$ and for the influx of the metabolic signal substance ($J_m$) into vessel segments were used. In this way, the contribution of the blocked information transfer mechanism was “frozen” at the level in the initial adapted state. To block the effect of changes in the oxygen profile, a different procedure was used: the additional oxygen extraction due to increased demand was neglected in calculating $\text{SO}_2$ in segments downstream of the capillaries. For each case considered in step 3, the mean proportional changes in diameter and convective oxygen supply for each segment, i.e., (new value − control value)/control value, were calculated and expressed relative to those found for capillaries only (step 2). The changes in overall network conductance after adaptation of all vessels (step 3) were expressed as a ratio to those seen upon adaptation of capillaries only (step 2). This ratio may be interpreted as the amplification resulting from the information transfer mechanisms.

RESULTS

Results are summarized in Fig. 4. Because the overall driving pressure is held constant in the simulations, changes in network conductance (Fig. 4A) reflect changes in total flow through the network. When all mechanisms of information transfer are included, the increase in network conductance stimulated by increased oxygen uptake from capillaries is amplified.
nearly fivefold (4.9 ± 0.2, mean ± SE, n = 6 microvascular networks) relative to the increase predicted in the reference case when only capillaries respond (Fig. 4A, All). This reflects the role of information transfer mechanisms in producing coordinated increases throughout the network in response to locally increased demand (Fig. 4B, All). Although the increase in arteriolar diameter is relatively small, it can have a substantial effect on overall network conductance because a major portion of the flow resistance resides in the arterioles. The functional relevance of such changes is evident from the changes in convective oxygen supply, reflecting alterations of both flow and oxygen saturation (Fig. 4C, All), which is amplified by a factor of 9.4 relative to the reference case.

Blocking all information transfer mechanisms except the response to flow yields only a slightly smaller relative change in network conductance, 4.0 ± 0.3 (Fig. 4A, Flow). This suggests that information transfer by increases in wall shear stress, resulting from increased flow, is the major mechanism contributing to the predicted changes in overall conductance. This mechanism leads to increased diameters and rates of oxygen supply in all three classes of vessels (Fig. 4, B and C, Flow).

Fig. 3. Schematic diagram of the method used to predict functional roles of information transfer mechanisms in adaptive structural responses. Each box represents a state of the network, i.e., a set of segment diameters and flow rates. Solid arrows denote structural adaptation according to the model. Step 1: a state with arbitrary diameters is allowed to adapt according to the model, leading to an initial adapted state. This state is then perturbed by assuming a small increase in oxygen demand in all capillaries (dashed arrow). Step 2: structural adaptation of capillaries only is simulated, to provide reference levels for other cases. Step 3: structural adaptation of the entire network is simulated using the complete model (All), blocking all mechanisms of information transfer but one (Press, Flow, OX, Conv, or Cond), or blocking all mechanisms (None).

Fig. 4. Adaptive responses of microvascular networks (n = 6) to a small, sustained step increase of oxygen demand (+0.5%) restricted to capillaries. Changes (means ± SE) in diameter, oxygen supply, and overall network conductance after adaptation (step 2) are normalized to changes seen after capillary adaptation only (step 2). Results for the complete model with all information transfer mechanisms present (All) are compared with those obtained when only individual components of information transfer were active (pressure profile (Press), flow coupling (Flow), oxygen gradients (OX), convected signals (Conv), and conduction (Cond)) or with no information transfer (None). A: changes in overall network conductance. B: changes in diameters of arterioles (Art), capillaries (Cap), and venules (Ven). C: changes in oxygen supply to arterioles, capillaries, and venules.
In comparison, all other mechanisms of information transfer, when acting alone, lead to relatively small amplification of changes in overall network conductance and oxygen supply (Fig. 4, A and C) and uneven changes in vessel diameter (Fig. 4B). Among these secondary factors, pressure profile and conduction yield the strongest effects on network conductance (1.3 ± 0.06 and 1.4 ± 0.07). The effect of pressure alone (Fig. 4B, Press) causes increases in arteriolar diameters but decreases in venular diameters. Convection of vasoactive metabolites (Conv) leads to increases in the diameters of venular segments, which lie downstream of the capillaries. In contrast, upstream conducted responses (Cond) lead to increases in arteriolar diameters. These trends are expected based on the properties of these information transfer mechanisms, as discussed earlier. However, there is also a substantial decrease in venular diameter in the case of maintained upstream conduction (Cond) and a small decrease in arteriolar diameter for maintained downstream convection (Conv). These changes result from the increased intravascular oxygen level (leading to a decrease in local production of metabolic signal substances) associated with the increase in flow when capillary diameters increase. For a given level of oxygen consumption, an increase in flow implies a decrease in oxygen extraction. This effect is included in all cases considered. Even if all information transfer mechanisms are blocked (None), a small decrease in venular diameters is predicted. If changes of the oxygen profile are not blocked (OX), venular oxygen supply tends to decrease as a result of the increased consumption in the capillaries, and net diameter changes of arterioles and venules are minimal.

DISCUSSION

In vascular networks, combined effects of network hemodynamics, mass transport, and vascular responses to hemodynamic and metabolic stimuli create a complex system of interactions. In this system, several different mechanisms contribute to the adjustment of vessel diameters upstream and downstream of a segment that experiences an increase in metabolic demand. The theoretical approach used here provides a means to estimate the separate effects of these information transfer mechanisms in a way that would be difficult or impossible to achieve in experiments, because of the many complex interactions involved. The approach used to block the effects of individual mechanisms may be termed a mathematical knockout by analogy with gene-targeted knockout animal models. It has the advantage that it allows a degree of specificity and control that is not generally possible in experimental systems. With the use of small incremental changes, insight is gained into the behavior of the system near its normal physiological state. Of course, a theoretical model is only valuable to the extent that it reliably describes the biological system. The present model has been shown to provide realistic predictions of vascular diameters and network hemodynamics in rat mesentery preparations. However, the predictions of the model with respect to the roles of specific biological mechanisms, and its relevance in other in vivo systems, remain to be tested experimentally. Also, the parameters of the model have been obtained by comparing the predictions of the model with observed network structures under steady-state conditions. Therefore, the model does not yield information about the time course of structural changes.

In response to changes in oxygen demand, information transfer mediates substantial diameter changes in feeding arterial and draining venular segments. Diameter changes can affect oxygen supply by altering overall network conductance and flow distribution within the network. The data shown in Fig. 4 suggest that both mechanisms are relevant: information transfer leads to a 4.9-fold amplification of the increase in overall network conductance. However, the observed increase in capillary oxygen supply is amplified 9.4-fold, indicating an improvement of oxygen distribution.

Fig. 5. Effect of the attenuation of conduction in the upstream direction along vessels by reducing the length constant \( L_0; A \) and the downstream convection by reducing the metabolic decay time constant \( M_0; B \) on functional network parameters. Average values for six networks (± SE) are given. Mean path length is the flow-weighted mean length of all flow pathways through the network. Oxygen deficit is the relative amount of oxygen demand not met by oxygen delivery.
If all information transfer mechanisms with the exception of flow coupling are blocked, the amplification of conductance changes is reduced by only 24%, but amplification of capillary oxygen supply drops by 54%. Thus other information transfer mechanisms seem to cooperate with flow coupling in the optimization of oxygen distribution. However, their effect on oxygen supply is small or even negative when acting alone.

The central finding of this study is that, of the five information transfer mechanisms represented in the model (flow coupling, pressure, oxygen gradients, convection of metabolic signal substances, and conduction along vessel walls), flow coupling is the most powerful mechanism for the structural adaptation of vascular networks to small changes in capillary oxygen demand. In this mechanism, a locally stimulated increase in diameter and thus conductance of terminal microvessels leads to increased flow and shear stress acting on endothelial cells of upstream and downstream segments, stimulating structural increases in their diameters. In the present model, the locally stimulated diameter changes were restricted to capillaries, defined functionally as vessels that connect the diverging arterial tree with the converging venous tree. In reality, all terminal microvessels including precapillary arterioles, capillaries, and postcapillary venules may respond structurally to local changes in metabolic demand. Moreover, increases in vessel number may also be involved. Although the model does not directly simulate these cases, similar overall behavior would be expected because the same mechanisms of information transfer between peripheral and more proximal vessel segments would necessarily be involved.

The concept that wall shear stress may play an important role in structural adaptation is well established in the literature (16–18, 36, 37). However, previous studies using the present model (24, 26) indicated that information transfer by mechanisms other than flow coupling is crucial in the adaptation of networks toward stable, functionally adequate structures. The present finding that flow coupling plays a dominant role in adaptation to changes in demand may therefore be surprising.

Therefore, to further explore the role of mechanisms other than flow coupling, additional simulations were performed in which the strength of information transfer by conduction or by convection was reduced in a graded manner, by decreasing the values of the conduction length constant ($L_0$) or metabolic decay time constant ($M_0$). The parameter $k_w$ was adjusted for each value of $L_0$ and $M_0$ to maintain the total intravascular volume at its reference value. All other parameters describing the adaptive response and the bulk flow through the networks were held constant, and capillary oxygen demand was not altered. Results of these simulations are shown in Fig. 5. In each case, the rightmost data points represent the control parameter values. With reductions in either $L_0$ or $M_0$, a level is eventually reached at which the flow distribution is no longer adequate to supply oxygen throughout the network, as indicated by an increase in the oxygen deficit.

This behavior results from a redistribution of blood flow from longer flow pathways to relatively short arteriovenous shunt pathways, as indicated by the decrease in the mean path length. These effects are most pronounced in the case when the conduction length constant is reduced below about 1.5 mm. Qualitatively similar but less marked effects are seen when the metabolic decay time constant is reduced below ~1 s. These results support previous findings (24, 26) showing that information transfer by mechanisms other than flow coupling are crucial for the maintenance of functionally adequate network flow distributions.

According to these results, it is clear that the relative importance of different mechanisms of information transfer depends on the physiological function or response under consideration (24). The initial adapted state for the simulations with an incremental increase in oxygen demand reflects the combined, balanced effects of all the considered mechanisms of information transfer. In effect, the “set points” for wall shear stress in this state are appropriately adjusted to different levels depending on the location of the vessel in the network, e.g., higher in arterioles than in corresponding venules, and lower on segments forming part of long flow pathways (so that they enlarge to a greater diameter for a given level of flow and thus achieve a lower pressure gradient). If small perturbations about this state after local metabolically driven increases in capillary diameters are considered, flow coupling resulting from vascular sensitivity to wall shear stress is primarily responsible for producing the necessary readjustments of vessel diameter, so that wall shear stress in each segment is restored to its appropriate level. However, the ability of the network to reach an initial functionally adequate state is crucially dependent on information transfer by other mechanisms, represented here by upstream conduction along vessel walls and downstream convection of metabolites.

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