Structural adaptation and stability of microvascular networks: theory and simulations

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Pries, A. R., T. W. Secomb, and P. Gaehlens. Structural adaptation and stability of microvascular networks: theory and simulations. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H349–H360, 1998.—A theoretical model was developed to simulate long-term changes of vessel diameters during structural adaptation of microvascular networks in response to tissue needs. The diameter of each vascular segment was assumed to change with time in response to four local stimuli: endothelial wall shear stress ($\tau_w$), intravascular pressure ($P$), a flow-dependent metabolic stimulus ($M$), and a stimulus conducted from distal to proximal segments along vascular walls ($C$). Increases in $\tau_w$, $M$, or $C$ or decreases in $P$ were assumed to stimulate diameter increases. Hemodynamic quantities were estimated using a mathematical model of network flow. Simulations were continued until equilibrium states were reached in which the stimuli were in balance. Predictions were compared with data from intravital microscopy of the rat mesentery, including topological position, diameter, length, and flow velocity for each segment of complete networks. Stable equilibrium states, with realistic distributions of velocities and diameters, were achieved only when all four stimuli were included. According to the model, responses to $\tau_w$ and $P$ ensure that diameters are smaller in peripheral than in proximal segments and are larger in venules than in corresponding arterioles, whereas $M$ prevents collapse of networks to single pathways and $C$ suppresses generation of large proximal shunts.

Shear stress; pressure; conducted response; mathematical modeling

VASCULAR BEDS are capable of continuous adjustment in response to the functional needs of the tissues that they supply. The inverse fourth-power dependence of flow resistance on luminal diameter implies that blood flow in vascular networks is very sensitive to vessel diameters. Acute regulation of flow is achieved largely by constriction or relaxation of smooth muscle in vessel walls. However, accommodation to chronic changes in tissue needs involves long-term structural adaptation of vessel diameters, in which each vessel segment responds to the local mechanical and biochemical stimuli that it experiences (27).

Many studies have shown that vessels respond structurally to the mechanical forces exerted by flowing blood, i.e., transmural pressure and shear stress at the endothelial surface (2, 11, 12, 14–16, 34, 35, 37, 38). In response to sustained increases of shear stress, vessels generally exhibit a structural increase of luminal diameter, and at constant volume flow, this reduces shear stress. Therefore, it was proposed that shear stress is regulated by structural adaptation of vessel diameters (13, 41). However, model studies (8, 11) showed that adaptation of individual segments in response to local shear stress alone cannot produce realistic hemodynamic conditions in vascular networks.

In addition to wall shear stress, circumferential wall stress produced by transmural pressure is the main hemodynamic force acting on vessel walls. Chronic increase of transmural pressure results in changes of vascular morphology (10, 17) and network structure of terminal vascular beds (7, 9, 20). Simulations of the hemodynamics of microvascular networks suggest that circumferential wall stress influences arteriolar proliferation and rarefaction (21, 22).

Studies of terminal vascular beds of the rat mesentery have yielded information on the interaction between effects of transmural pressure and wall shear stress (23). A characteristic relationship was observed between intravascular pressure and wall shear stress, independent of vessel type (arteriole, capillary, or venule). On the basis of these data, a “pressure-shear” hypothesis was proposed stating that vascular adaptation in response to hemodynamic conditions tends to maintain wall shear stress at a set point that is a function of local transmural pressure.

Structural adaptation of vascular beds involves responses not only to mechanical stimuli but also to the metabolic state of the tissue (33). Furthermore, the signals causing vascular adaptation may be transmitted from one segment to another in a manner analogous to the conduction of acute vasoactive responses (30). Responses to hemodynamic and metabolic stimuli may be difficult to distinguish experimentally, because reactions of one segment affect flow and pressure in other segments and thus contribute to adaptive responses throughout the network.

In the present study, a theoretical model was developed to simulate the changes that occur with time in vessel diameters during adaptation of microvascular networks. Each segment in the networks considered was assumed to adjust its diameter in response to the local stimuli described earlier. The following main criteria were used in developing the model. It should predict stable network structures, i.e., segment diameters should approach finite equilibrium values if the simulation is continued over a sufficient time, in the absence of externally imposed time-dependent effects. Furthermore, the equilibrium network structures should be consistent with experimentally observed networks in terms of total flow resistance, distribution of pressure along arteriovenous flow pathways, and distribution of flow among pathways.

The model was developed in two stages. First, analyses of simplified hypothetical networks (networks 1, 2,
and 3) were used to establish a minimal set of adaptive responses that must be included in the model for it to predict stable, realistic network structures. The model was then applied to microvascular networks (networks I, II, and III) of the rat mesentery to test whether the assumed adaptive responses can lead to equilibrium distributions of morphological and hemodynamic parameters in quantitative agreement with experimental observations.

**METHODS**

**Experimental Observations of Microvessel Network Structure**

The animal preparation and the setup used for intravital microscopy have been described in detail elsewhere (23, 25, 26). Male Wistar rats \((n = 3, 300–450\) g body wt) were prepared for intravital microscopy of the mesenteric microcirculation following premedication (atropine 0.1 mg/kg im and pentobarbital sodium 20 mg/kg im); anesthesia (ketamine 100 mg/kg im); cannulation of trachea, jugular vein, and carotid artery; and abdominal midline incision. The animals were then transferred to a special stage mounted on an intravital microscope. The small bowel was exteriorized, and fat-free portions of the mesentery were selected for investigation with a \(\times 25/0.6\) saltwater immersion objective (Leitz). During the experiments, the level of anesthesia and fluid balance were maintained by intravenous infusion of physiological saline \((24\) ml·kg\(^{-1}\)·h\(^{-1}\)) containing 0.3 mM pentobarbital sodium. In this preparation of the exposed mesentery, vessels generally exhibit no spontaneous smooth muscle tone. However, as a precaution to prevent the development of tone and thus temporal variation of vessel diameters and flow resistance during the measurement period, papaverine \((10^{-4}\) M) was continuously superfused. Heart rate and arterial blood pressure \((ranging from 105 to 140\) mmHg) were continuously monitored via the catheter in the carotid artery.

The networks selected for this study were supplied by feeding arterioles with inner diameters of \(~30\) µm and drained by venules of \(~45\) µm. The volume flow rate through the networks varied between \(~200\) and \(1,000\) nl/min. A selected area of the mesenteric membrane \((ranging from 35 to \(80\) mm\(^2\)) was scanned with an \(SW 25/0.6\) saltwater immersion objective \((Letz)\) and recorded on both videotape and black-and-white film. The complete scan took \(~30\) min and consisted of \(~300\) individual fields of view \((300 \times 400\) µm). There were no indications of changes in vessel diameters or blood flow velocities during the recording period.

In networks I and II, the flow velocity in each vessel segment was determined with a digitized-image analysis system \((26)\) from an additional second scan using a strobed asynchronous illumination. From the original video recordings, the light-intensity pattern of a line along the centerline of the image of a microvessel was repeatedly determined at two closely spaced time instances. The intensity patterns corresponding to moving blood cells were shifted in position between the two successive recordings. A measure of the centerline flow velocity was calculated as the length of this spatial shift divided by the time delay between the two recordings \((spatial correlation principle)\) \((6)\). Centerline velocities determined by spatial correlation were averaged over \(~4\) s, corresponding to 100 individual measurements, and then converted into mean blood velocity according to a procedure described previously \((26)\).

The photographs exposed during the scanning procedure were used to assemble photomontages of the complete microvascular networks that were then used to determine network topological structure \((connection matrix)\) and the lengths of all vessel segments between branch points. The diameters of all vessel segments were determined from the video recordings obtained with the strobed flash illumination in networks I and II and from the photonegatives for network III. The number of vessel segments per networks I, II, and III was 546, 383, and 913, respectively.

**Simulation of Network Blood Flow**

Mathematical simulations of blood flow in microvascular networks with prescribed structures were used to estimate mean wall shear stress, pressure, and volume flow rate in each vessel segment. Details of the simulation have been described earlier \((26)\). For any given network, the volume flow rate in each segment and the pressure at each branch point were calculated using an iterative algorithm. The following information and assumptions were required for these calculations. 1) Network structure data was necessary, including topology \((connection matrix of vessel segments)\) and geometry \((diameters and lengths of each segment)\). 2) Boundary conditions were required, including the volume flow rates and hematocrits in all vessel segments feeding the network, and the volume flow rates for those segments leaving the network, with the exception of the main venular draining segment. This segment was assigned a pressure of \(13.8\) mmHg according to previous measurements in similar-sized venules in the same tissue \((26)\). For two of the rat mesentery networks \((networks I and II)\), volume flow rates in the boundary segments were derived from the measured flow velocities. For the third experimental network \((network III)\) and the simple hypothetical networks \((networks 1, 2, \text{and } 3)\), volume flow rates were assigned to match measured values for corresponding vessel diameters. 3) Equations were necessary to describe rheological phenomena in the microcirculation: the phase-separation effect \((nonproportional partition of red cell and plasma flows)\) at diverging bifurcations, and the effective viscosity of blood flowing through microvessels. The parametric description of phase separation was based on experimental data obtained previously in arteriolar bifurcations of the rat mesentery \((25)\) and describes the distribution of blood and red cell flow at individual bifurcations. The flow resistance in microvessels as a function of vessel diameter and hematocrit was derived previously for the same tissue \((26)\).

At each step in the iteration, current values of segment hematocrits were used to estimate the flow resistance of each segment, from which updated nodal pressures and segment flows were computed. The rheological equations were then used to calculate updated values of segment hematocrits and flow resistance. This process was repeated until convergence was achieved, usually within 20–30 iterations. The simulation yielded predicted values of pressure, volume flow rate, flow resistance, and hematocrit in all segments, with the exception of the pressure in the main draining venule and the flows in all other boundary segments, which were prescribed.

**Simulation of Adaptive Diameter Changes**

For each segment in the network, the change of its diameter \((\Delta D)\) for a time step \(\Delta t\) was assumed to be proportional to the sum of terms representing different adaptive stimuli \((Stot)\) and to the vessel diameter \((D)\) as

\[
\Delta D = S_{tot} \cdot D \cdot \Delta t
\]

As outlined in results, contributions of the adaptive stimuli to \(S_{tot}\) were expressed in terms of hemodynamic variables calculated in the simulation of network blood flow. They were based on consideration of three simple hypotheti-
cal 22-segment network structures. Network 1 has symmetric topology as evidenced by the equal “generation number” for all capillaries. The generation number of a vessel segment is defined as the number of branch points on the arterial (for arterioles and capillaries) and venous (for venules and capillaries) pathways from the respective main feeding vessel to the given segment. In addition, network 1 exhibits regular morphology (all segments with the same generation number have identical length and diameter). Network 2 has symmetric topology and irregular morphology, and network 3 has asymmetric topology and irregular morphology (Fig. 1).

Adaptation of microvascular networks was simulated as follows. An initial set of segment diameters was chosen for each of the hypothetical networks. The flow and hematocrit in each segment were computed using the network flow simulation and were used to estimate Stot (see RESULTS). The diameters were updated according to Eq. 1. This process was repeated until the set of segment diameters reached either an equilibrium steady state or unrealistic values.

Optimization of Parameter Values

The model used to simulate adaptive diameter changes involves several unknown parameters. Comparisons between experimentally observed network states and model predictions were used to estimate the values of these parameters. Measured values of segment diameters, together with flow, resistance, and hematocrit values resulting from the network flow simulation, represented the initial (observed) state. To simulate adaptation for a given set of parameter values, vessel diameters were changed according to the combined adaptation stimulus, S
\text{tot}
. The final distributions of hemodynamic parameters, when all vessel segments reached equilibrium (S
\text{tot} = 0), depended on the assumed parameter values.

The experimentally observed network states themselves reflect the result of the adaptation occurring in the tissue. A model that best represents this in vivo adaptation process should therefore minimize the differences between the initial (observed) state and the final (predicted) state. In principal, differences in either flow velocities or segment diameters can be used to assess these differences. For networks I and II, in which velocities were measured, differences in velocities were used because they more sensitively reflect changes in flow resistance distribution within the networks. For these networks, the unknown parameters in the adaptation model were adjusted to minimize the velocity error (EV), i.e., the root mean square deviation of the predicted segment flow veloc-

Fig. 1. Results of simulated adaptation for small (22 segments) networks. A–D represent results after successive incorporation of stimuli for adaptation in different network structures: network 1 (A and B); network 2 (C); and network 3 (D). Schematic drawings (top) indicate resulting diameter distributions, with arteriolar inflow indicated by arrows. Graphs provide predicted distributions of wall shear stress (middle) and diameter (bottom) for arteriolar segments (Art), capillaries (Cap), and venular segments (Ven).
ties \( (V_p) \) from the measured velocities \( (V_m) \)

\[
E_V = \sqrt{\sum_{i=1}^{n} \frac{(V_{pi} - V_{mi})^2}{(V_{pi} + V_{mi})^2}}
\]

Sensitivity analyses were performed to determine the dependence of \( E_V \) on model parameters. For network III, velocities were not measured, so the root mean square diameter deviation \( (E_D) \) between predicted diameters \( (D_p) \) and measured diameters \( (D_m) \) was minimized where

\[
E_D = \sqrt{\sum_{i=1}^{n} \frac{(D_{pi} - D_{mi})^2}{D_{mi}}}
\]

**RESULTS**

Theory for Effects of Adaptation on Network Properties

Wall shear stress. Several previous studies have assumed that vessels adapt so as to maintain a preset level of wall shear stress. This assumption was used as a starting point by setting

\[
S_{tot} = \log \tau_w - \log \tau_0
\]

where \( \tau_w \) is the wall shear stress in the segment. Logarithmic dependence was introduced to achieve constant sensitivity of \( S_{tot} \) to a given proportional change in \( \tau_w \) over a wide range of \( \tau_w \) values. The constant \( \tau_0 \) defines the set point of the adaptation process and was set at \( \tau_0 = 100 \ \text{dyn/cm}^2 \) as found in larger arteriolar vessels of the rat. Values above this level lead to increasing vessel diameters. When this adaptation model was applied to the symmetric network 1, the results shown in Fig. 1A were obtained. In Fig. 1A, vessel diameters and \( \tau_w \) are plotted as a function of intravascular pressure, the only parameter that varies unidirectionally with distance from the arteriolar inflow into the network. Segment diameters in the resulting equilibrium structure decreased with increasing generation, as expected. In contrast to the experimental findings, however, corresponding vessels on the arterial and venous sides of the network had equal diameters. This unrealistic behavior was a result of assuming identical responses to wall shear stress on both the arterial and venous sides of the network.

Transmural pressure. Observations of blood flow in vascular networks show that wall shear stress is higher on the arterial side than on the venous side. Pries et al. (23) proposed that structural adaptation tends to maintain a preset relationship between wall shear stress and local transmural pressure. This was introduced in the present calculations by setting

\[
S_{tot} = \log \tau_w - \log \tau_0\text{e}(P)
\]

where \( P \) is transmural pressure and \( \tau_0\text{e}(P) \) is the corresponding expected level of wall shear stress, which follows a sigmoidally increasing function of pressure, according to experimental data obtained in the rat mesentery. When applied to the symmetric network 1, this adaptation model generated a structure with strong arteriovenous asymmetry of shear stress, pressure, and diameter, as observed in vivo (Fig. 1B). In each segment, wall shear stress corresponded to pressure according to the assumed pressure-shear relationship.

Metabolic stimulus. Network 1 is a special case in which parallel segments with the same generation numbers have identical lengths and diameters. In vivo, parallel pathways exhibit unequal lengths and diameters, as in network 2. Such a network is unstable when wall shear stress alone acts as the stimulus for adaptation, as shown by Hacking et al. (8). This may be seen by considering two segments connected in parallel, which initially experience the same pressure drop. Whichever segment has the larger wall shear stress tends to dilate, receiving more flow and still higher wall shear stress, whereas the parallel segment tends to shrink. This process continues until only a single pathway through the network remains (Fig. 2). The same instability is found if both shear stress and pressure are used as adaptive stimuli (APPENDIX A). Therefore, the model including only hemodynamic stimuli cannot adequately represent network adaptation.

In reality, structural adaptation of vessel networks must also respond to the metabolic needs of the tissue that they supply. If, at a given metabolic demand of the tissue, flow in a segment drops so that the surrounding tissue is poorly supplied with oxygen or other metabolic materials, then the segment must be stimulated to increase its diameter to enhance perfusion. Therefore, an additional contribution to \( S_{tot} \) was included in the model, dependent on the volume flux of red blood cells passing through the segment (represented by \( QH_0 \), where \( Q \) is the blood volume flow and \( H_0 \) is the discharge hematocrit) and increasing with decreasing flux. The resulting total stimulus was represented in the model by

\[
S_{tot} = \log \tau_w - \log \tau_0\text{e}(P) + k_\text{m} \log \left(\frac{Q_{ref}}{QH_0} + 1\right) - k_s
\]

The functional form given in Eq. 3 was chosen so that the metabolic stimulus is always positive and increases with decreasing red cell flux. The value of the constant \( k_\text{m} \) reflects both the sensitivity of the tissue metabolic state to blood flow and the adaptive response of vessel diameter to changes in metabolic state. Changes in the functional state of the tissue would be expected to influence the value of \( k_\text{m} \) but a constant value was assumed here. For flux levels below the reference flow \( (Q_{ref}) \), which was assumed to be larger than actual fluxes in most segments, the relation between the red cell flux and the resulting metabolic component of the stimulus is logarithmic. In this range, \( k_\text{m} \) gives the increase of the metabolic stimulus \( (M) \) for a decrease of the red cell flux by one order of magnitude. Inclusion of a positive metabolic stimulus tends to drive all diameters to large values. A further constant, \( k_s \) ("shrinking tendency"), was therefore introduced in Eq. 3, which is subtracted from the hydrodynamic and metabolic terms. The shrinking tendency can be interpreted as reflecting the basal need of vessels for factors stimulating growth to maintain or increase their cell mass and diameter.
In the present context, these factors are positive hydrodynamic, metabolic, or conducted stimuli (see Conducted stimulus). Atrophy or degradation in the absence of positive tropic stimuli is generally seen in organs, e.g., denervated muscle, and in cell cultures if no growth/survival factors are added to the culture medium.

Inclusion of the metabolic stimulus in the model tends to stabilize network structure. When flow in a segment drops to a low level, the effect of declining \( \tau_w \) is compensated by the increasing metabolic stimulus. The analysis in Appendix A shows that a single segment connected to a fixed pressure source has a stable diameter if the metabolic stimulus is sufficiently strong. Such a segment is denoted as “pressure stable.” In terms of Eq. 3, pressure stability requires that \( k_m > 1/4 \). For a pair of segments in parallel, supplied by a constant-pressure source in series with a fixed resistance, the configuration is stable if the segments are pressure stable, but not otherwise. For a more complex network, pressure stability of individual segments is sufficient to ensure stability of the entire network under the conditions stated in Appendix A. The behavior according to this model of a network with irregular morphology is illustrated in Fig. 1C, with \( k_m = 0.7 \). A stable equilibrium state is reached, with flow in all segments. Because of the different metabolic stimulus acting on each segment, the levels of wall shear stress for individual segments are scattered around the single functional relationship of shear stress with pressure according to Eq. 2.

Conducted stimulus. Inclusion of a sufficiently strong local metabolic stimulus ensures the stability of segment diameters, but the resulting diameters do not necessarily agree with observations in the mesentery. Observed networks contain low-generation capillaries that provide short pathways between the major feeding arterioles and draining venules. These low-generation capillaries have larger pressure gradients but smaller diameters and flows than their parent vessels. In contrast, the model including only shear stress, pressure, and local metabolic stimuli leads to structures in which segments with larger pressure gradients have higher flows, as proven in Appendix B. In this model, low-generation capillaries increase in diameter and flow at the expense of the more distal segments, as illustrated in Fig. 3. A realistic model of structural adaptation must predict that segments that feed a large, dependent network have larger diameters and flows than nearby segments that experience similar pressures and metabolic environments but that supply relatively short and nonramified “shunt” pathways through the network. To satisfy this requirement, it is necessary to introduce a further stimulus that reflects the topological position of a segment in the network, i.e., the number of dependent segments fed or drained.

Regulatory signals can be propagated along microvessels (30, 32). In the arteriolar network, such signals can be propagated upstream so that a parent vessel receives a signal that is the result of signals originating in its dependent branches (28). Conducted signals reaching a given segment provide an additional stimulus to which the segment may respond by long-term adaptation, the “conducted stimulus” (C). The effect of including such a stimulus in the model is shown in Fig. 1D. In accordance with experimental data, arteriolar and venular diameters are larger than those of the capillary vessels fed, and capillary diameters increase with generation number (24). In the corresponding model, it was assumed that metabolic stimuli generated in individual segments are propagated upstream in the arterioles.
riolar vessel tree and downstream in the venular vessel tree.

The calculation of the assumed conducted stimulus started at the most distal branch points of the arteriolar tree and proceeded proximally until the main feeding vessel was reached. The conducted stimulus at each junction \( S_c \) was assumed to be the sum of the metabolic stimuli \((\text{Table 1}) \) of the two downstream vessel segments \((\text{segments} a \text{ and } b)\) together with conducted stimuli from the two downstream bifurcations. The conducted signals were assumed to decay exponentially with distance traveled as \( \exp (-x/L) \), where \( x \) is the length of the vessel segment between bifurcations and \( L \) is a length constant. Therefore, at each bifurcation

\[
S_c = M_a + M_b + S_{ca} \cdot \exp (-x_a/L) + S_{cb} \cdot \exp (-x_b/L)
\]

where subscripts \( a \) and \( b \) denote the two daughter vessels. At the most distal branch points, whose downstream bifurcations lie within the venous tree, \( S_c = M_a + M_b \). The same procedure was used proceeding downstream from the most distal branch points in the venular tree. Possible nonlinearity of the summation was accounted for by a saturable response, with a reference value \( S_0 \), giving

\[
S_{\text{tot}} = \log \tau_w - \log \tau_e(P) + k_m \log \left( \frac{Q_{\text{ref}}}{Q_H D} + 1 \right) + k_c \left[ S_c/(S_c + S_0) \right] - k_s
\]

where \( k_s \) is a conducted stimulus constant.

Clearly, this involves a number of assumptions that cannot be fully justified on the basis of available physiological data. However, the exact form of the response is not crucial. A number of modifications of the model, all of which included the conduction of a signal generated in peripheral vessel segments along vessel walls to feeding or draining vessels, were found to produce realistic distributions of vessel diameters and hemodynamic parameters. For example, this was true for a model assuming generation of a conducted signal only in capillary segments (and not in arteriolar or venular segments) and also for a model assuming generation of a conducted signal of equal strength in all vessel segments independent of their blood flow. In contrast, diffusion of metabolites across the tissue, from capillary vessels to the feeding and draining segments, cannot replace the conductive mechanism. Such a process would affect both the main feeding vessels and low-generation capillaries in a given area and could not prevent the development of low-generation capillaries into large arteriovenous shunts.

The inclusion of responses to these four types of stimuli \( (\tau_w, P, M, \text{ and } C; \text{ Table 1}) \) is thus a minimal requirement for a realistic description of diameter adaptation. To test the adequacy of the resulting model, its predictions were compared with observed network structures in the rat mesentery.

Simulation of Observed Network Structures

Estimation of parameters in adaptation model. Preliminary simulations using data obtained from the

<table>
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<th>Table 1. Summary of steps in development of mathematical model for structural adaptation</th>
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<tr>
<td><strong>Stimulus</strong></td>
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<td>Wall shear stress</td>
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<td>Pressure</td>
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<tr>
<td>Metabolic stimulus</td>
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<tr>
<td>Conducted stimulus</td>
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<td>Shrinking tendency</td>
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Summation of all adaptive stimuli \( (S_{\text{tot}}) \) is presented in mathematical form in Eq. 4 (see RESULTS) for detailed explanation. \( \tau_w \) is a conducted stimulus constant; \( Q_{\text{ref}}, \text{ reference blood flow; } Q, \text{ blood flow; } H_D, \text{ discharge hematocrit; } k_m, \text{ metabolic stimulus constant; } k_c, \text{ conducted stimulus constant; } S_c, \text{ sum of conducted stimuli; } S_0, \text{ reference sum; } k_s, \text{ shrinking constant.} \)
experimental networks were carried out in which the adaptation model was used with various combinations of only some of the full set of stimuli. These tests confirmed that all four stimuli were needed to prevent strong deviations of the model results from observed data in terms of segment diameters or flow velocities. For the complete model, the parameters \( k_m, k_c, \) and \( k_s \) were chosen to minimize \( E_V \) in networks I and II and \( E_D \) in network III. Their final values are given in Table 2. A further optimization was performed with respect to the function \( \tau_e(P) \) describing the effect of pressure on the set point for \( \tau_w \). The experimentally observed variation of \( \tau_w \) with \( P \) (23) reflects the combined effects of all adaptation stimuli and does not necessarily represent the equilibrium relationship \( \tau_e(P) \) that would be found in the absence of metabolic stimuli. Therefore, the functional form of \( \tau_e(P) \) was chosen empirically to reflect the observed dependence (23), but the parameters were adjusted to minimize \( E_V \), yielding

\[
\tau_e(P) = 100 - 86 \cdot \exp \left[ -5,000 \cdot \log \left( \log P \right) \right]^{5.4}
\]

Resulting \( \tau_e \) values start at 14 dyn/cm\(^2\) for pressures of 10 mmHg, increase sigmoidally with increasing pressure, and reach 100 dyn/cm\(^2\) at 90 mmHg. In the intermediate range of \( P \), the curve shows a slight rightward shift compared with the observed dependence (23).

Distributions of hemodynamic variables. Detailed results are presented for one of the three experimental networks, network I containing 546 segments. Experimental values of segment wall shear stress and diameter and values obtained after the adaptation model was applied are shown in Fig. 4 as functions of intravascular pressure. Results for the other two networks were very similar. Despite significant changes for individual segments, the distributions of morphological and hemodynamic parameters were largely conserved. \( E_V \) ranged between 0.31 and 0.36 (Table 2), indicating that typical diameter changes during adaptation were below 30%. Although diameter changes of up to \( \pm 30\% \) can strongly influence the flow resistance of individual vessel segments, these changes were distributed within the networks in such a way as to produce only minimal changes in the overall distributions of pressure and wall shear stress (Fig. 4).

For networks I and II, in which velocity was measured, the initial relative \( E_V \) were 0.63 and 0.79. These errors reflect both measurement uncertainties, particularly those of diameters, and limitations of the hemodynamic model. During the simulated adaptation, vessel diameters were free to adjust independent of their initial values. The final errors were similar (0.65 and 0.75) to the initial values, i.e., the segment velocities predicted from the diameters obtained after adaptation were no less accurate than the velocities predicted from measured diameters. These results show that the adaptation model can predict stable, realistic distributions of diameters and hemodynamic parameters.

Distributions of stimuli. Figure 5 shows the initial and final strengths of the adaptive stimuli for network I. Results for networks II and III were nearly identical. On average, the two hydrodynamic stimuli balance each other over the whole pressure range. The strength of both the pressure \( P \) and shear stress \( \tau_w \) stimuli increased with increasing pressure, reflecting the assumed effects of shear stress and pressure on vascular growth. A similar balance is seen in the metabolic \( M \) and conducted \( C \) stimuli. According to its mathematical formulation, the metabolic stimulus was larger in vessels with lower blood flow, whereas the conducted stimulus showed the opposite behavior. The coupling of the conducted stimulus to flow is indirect: vessels with high flow generally feed larger-vessel trees containing more capillaries, which generate the conducted stimuli. The distributions of the individual stimuli are very similar in the initial and final states. The combined stimulus \( S_{tot} \) is distributed around zero in the initial state, with a value of 0.08 \( \pm \) 0.44 (mean \( \pm \) SD) for network I, shown in Fig. 5. In the final state, \( S_{tot} \) is zero in every segment, as required by convergence of the model.

Sensitivity analysis. To test the sensitivity of the results to the most important parameters \( (k_s, k_m, \) and \( k_c) \), these parameters were varied around the values obtained by minimizing \( E_V \). Results for networks I and II (Fig. 6) showed that \( E_V \) is highly dependent on the shrinking constant, \( k_s \), with a narrow, well-defined minimum. When \( k_s \) was varied over the range shown, the pressure drop across the network increased strongly from 9 and 7 mmHg to 323 and 217 mmHg for the two networks, respectively. However, at the optimal values of \( k_s \) yielding minimal \( E_V \), pressure drops in the realistic range were predicted: 69 mmHg for the larger network, and 37 mmHg for the smaller. In further sensitivity tests, \( k_m \) was optimized with respect to minimal \( E_V \) for each value of \( k_m \) and \( k_c \) tested. The level of both the metabolic and conducted stimuli depends on \( k_m \) because it was assumed in the model that the conducted response originates from the metabolic stimuli of individual segments. Therefore, \( k_m \) determines the balance between these two stimuli and the hydrodynamic stimuli. The balance between metabolic and conducted stimuli is set by \( k_c \). Figure 6 shows results of varying \( k_m \) and \( k_c \). The resulting minima of \( E_V \) were much broader than those for \( k_s \). Reasonable agreement between model predictions and observations was obtained over a range of about \( \pm 20-30\% \) in these parameters.

Table 2. Summary of parameters for three experimental networks

<table>
<thead>
<tr>
<th>Network</th>
<th>No. of segments</th>
<th>( k_m )</th>
<th>( k_c )</th>
<th>( k_s )</th>
<th>( E_V )</th>
<th>( E_D )</th>
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<tr>
<td>I</td>
<td>546</td>
<td>0.83</td>
<td>2.74</td>
<td>1.79</td>
<td>0.63</td>
<td>0.65</td>
</tr>
<tr>
<td>II</td>
<td>383</td>
<td>0.63</td>
<td>3.19</td>
<td>1.57</td>
<td>0.79</td>
<td>0.75</td>
</tr>
<tr>
<td>III</td>
<td>913</td>
<td>0.97</td>
<td>2.85</td>
<td>1.57</td>
<td>0.79</td>
<td>0.75</td>
</tr>
</tbody>
</table>

For all networks, values for conduction length constant \( L \), \( Q_0 \), and \( Q_{ref} \) yielding minimal velocity \( (E_V) \) and diameter errors \( (E_D) \) were 1,500 \( \mu \)m and 20 and 40 nl/min, respectively.
DISCUSSION

Growth and adaptation of vascular beds are complex processes, involving many interacting stimuli and responses. A number of potential mechanisms have been identified in experiments at the vascular and cellular level (1, 3, 4, 15). Such experiments could provide a basis for an integrated, quantitative description of adaptation in complete networks, but this has not been achieved. A different approach was used here: a theoretical model for network adaptation was combined with measurements of network properties representing a single instant in time to deduce information about the principles governing the system dynamics. Previous studies (8, 21–23) have shown the value of theoretical models for gaining insight into the processes of network growth and adaptation. The approach used here additionally takes advantage of extensive data sets on in vivo network structure and flow derived from previous studies. It also provides a framework for interpreting results of experiments at the cellular and single-vessel levels and suggests future directions for experimentation. The mesenteric preparation is especially suited for the purpose of analyzing the long-term structural adaptation of vessel diameters. The vessels constituting the analyzed networks exhibit no spontaneous tone, so the experimental results are not confounded by interactions between short-term regulation of vessel diameter via changes in tone and structural diameter adaptation.

The approach used here has some inherent limitations. Because the observations are made at a single instant, no information is provided about the time scale of the process. Also, to obtain useful results, some a priori assumptions are needed. The key assumptions of the present study are that each segment responds autonomously to the local stimuli that it receives, including those transmitted along the vessel wall, and that the response characteristics as defined by the equations (Table 1) are identical for all vessel segments. These assumptions are reasonable, because it is difficult to imagine a mechanism that could provide centralized control over the diameters of very many segments and yet retain their responsiveness to local conditions and need. In addition, the assumptions are supported by the adaptive responses seen in vessels grafted to positions with different hemodynamic conditions (5, 18, 19). Further assumptions had to be made about the specific forms of the responses to these stimuli so that they could be expressed in terms of a reasonable number of unknown parameters. Here, information from other experimental studies has been incorporated where possible. Also, the arguments used to develop the model for adaptation, including the analyses in APPENDIXES A and B, are largely independent of the specific functional forms used. Therefore, although the present model for adaptation is not the only one possible, other models capable of predicting the observed structures will probably be at least as complex and are likely to incorporate, in some form, the types of response included in the present model.

The present analysis leads to the following conclusion: continuous diameter adaptation, which leads to stable networks with structures and hemodynamic properties consistent with observations, can be explained by responses of each segment to a set of four stimuli. These are the shear stress $t_w$ at the endothelial surface, the transmural pressure $P$ (corresponding to circumferential wall stress), a metabolic stimulus $M$ dependent on blood flow in the segment, and a conducted stimulus $C$ dependent on the number and also,
possibly, the metabolic state of the exchange vessels supplied by the segment. Adaptation in response to pressure and shear stress is necessary to obtain the existing and functionally significant arteriovenous asymmetry with respect to pressure, diameter, and flow velocity (23). A local metabolic stimulus is needed to prevent the collapse of networks to single arteriovenous pathways, and a conducted metabolic stimulus suppresses the generation of large, short arteriovenous shunts.

Because the exact definitions of these stimuli and the corresponding vascular responses cannot be deduced from available experimental measurements, their implementation in the adaptive model was arbitrary to some extent. A number of different assumptions and formulations of the model were tested and found to yield similar results, provided the parameter values were optimally chosen. This was true for the expressions used to describe the effects of shear and pressure and particularly for those of the metabolic and conducted stimuli. The assumption that the local metabolic stimulus depends only on the red cell flux in a segment is clearly a gross simplification. In reality, this stimulus should reflect the balance between oxygen supply and demand in the region surrounding each segment and should depend on the size of the region supplied by the segment, the oxygen saturation of the blood flowing in the segment, and the flows in neighboring segments. Metabolites other than oxygen may also play a role. Inclusion of these effects would complicate the model and involve further arbitrary assumptions because the mechanisms by which metabolic needs influence adaptation are not established. Therefore, only the crucial dependence on red cell flux is included here.

The relevance of wall shear stress, intravascular pressure, and local metabolic conditions to vascular adaptation was already evident from numerous previous studies using a variety of experimental approaches, as described in the introduction (2, 7, 9–12, 14, 16, 17, 20, 33–35, 37, 38). The necessity for a fourth, distinct stimulus is an important conclusion of the present work. Again, the precise form of this stimulus is not known, and different assumptions could lead to similar predicted behavior. For example, if the conducted stimulus was assumed to depend only on the number of capillaries that a given segment feeds or drains ("magnitude") but not on metabolic stimuli or local blood flow,
then similar results were obtained. On the other hand, the conducted stimulus cannot be interpreted as a purely diffusive process from capillaries to feeding and draining segments. Such a process would lead to a continuous spatial distribution of the stimulus, with similar signals in different types of vessels in a given tissue area. In particular, this would apply to neighboring arterioles feeding large capillary networks and short arteriovenous connections. Thus a diffusive mechanism would not be able to prevent the growth of the vessels constituting such arteriovenous connections and would not inhibit generation of short, large-diameter shortcuts.

In the present model, the conducted stimulus is assumed to originate in individual segments and to be conducted from daughter to parent vessels in the vascular tree, assuming summation at junctions and exponential decay with distance traveled, with a length constant of 1500 µm. This assumption is consistent with many studies showing that vessel walls conduct information created locally, most likely by a mechanism involving changes of the membrane potential and transmission via gap junctions (28, 31, 39, 40). Although these studies were concerned with acute changes of vascular tone, the long-term adaptive responses analyzed in the present work require structural changes of the vessel wall. Investigation of the local reactions of cells and vessels to mechanical stimuli, however, suggests that short- and long-term reactions are closely linked (4). An essential feature of the model is that stimuli are transmitted unidirectionally upstream (for arteriolar segments) and downstream (for venular segments). Without this assumption, the conducted stimulus would enter small segments branching from larger feeding vessels, causing formation of short, large-diameter arteriovenous shunts. Although this aspect of the model is at present not supported by direct experimental evidence in the microcirculation, it may be linked to unidirectional coupling and rectification observed at gap junctions (29, 36).

As shown in this study, vessel diameter adaptation in response to a set of four stimuli can lead to realistic network structures. Many further questions remain, however. The present model was used to simulate the approach of a network to an equilibrium state, assuming constant functional demands. In principle, a similar approach could be used to model the dynamic adaptation of a network subject to varying demands. Adaptation may involve responses to stimuli other than the four considered here. Although some experimental information is available on adaptive responses at the single-vessel level, it is not clear how such information can be incorporated into the present model. The existence of a conducted stimulus for adaptation, predicted from the model, remains to be verified experimentally. Finally, the addition or loss of segments from a network is a crucial aspect of the adaptation process for which satisfactory theoretical models remain to be developed.

**APPENDIX A**

Stabilization of Segment Diameters by a Flow-Dependent Metabolic Stimulus

Adaptation of vascular diameters in response to wall shear stress alone leads to instability (8). Here, the goal is to establish conditions under which the inclusion of a flow-dependent metabolic stimulus stabilizes diameter. Responses to pressure and conducted stimuli are neglected here, and constant H2 and apparent viscosity (η) are assumed. Suppose that segment i adjusts its diameter (Di) with time (t) in response to its wall shear stress (τi) and flow (Qi). If continuous variation with time is assumed, Eq. 1 can be expressed as

\[
\frac{dD_i}{dt} = D_i[f(\tau_i) + g(Q_i)]
\]

where \(f(\tau_i) = \log \tau_i - \log \tau_0\) and \(g(Q_i) = k_m \log (\dot{Q}_i/\dot{Q}_0 H_D + 1) - k_v\). Here, it is assumed only that \(f(\tau_i)\) is an increasing function and \(g(Q_i)\) is a decreasing function. From Poiseuille’s law

\[
\dot{Q}_i = \pi D_i^4 \Delta P_i/(128L_i \eta_i) \quad \text{and} \quad \tau_i = D_i \Delta P_i/(4L_i)
\]

where \(L_i\) is the segment length and \(P_i\) is the pressure drop.
across segment i. Insight into the conditions for stability can be obtained by considering a configuration in which one active segment or two in parallel are fed by a constant-pressure source (ΔP0) in series with a fixed resistance (R0). The ratios of the fixed resistance to the active segment resistances are \( p_i = R_0 \cdot \Delta P_i / (128 \cdot \eta) \).

First, consider one active segment in series with a fixed resistance \((i = 1)\) so that \( ΔP_1 = P_0 / (1 + p_1) \). At equilibrium, \( f(\tau_1) + g(\dot{Q}_1) = 0 \). For stability, the derivative of this quantity with respect to \( D_1 \) must be negative at equilibrium so that \( D_1 \) returns to equilibrium after a perturbation. From Eq. 2A, we find

\[
\frac{\partial}{\partial D_1} (f(\tau_1) + g(\dot{Q}_1)) = (1 - 3p_1) \tau_1 f(\tau_1) + 4Q_1 g(\dot{Q}_1) < 0
\]

where \( f'(\tau_1) > 0 \) and \( g'(\dot{Q}_1) < 0 \). Control by shear stress alone corresponds to \( g = 0 \), and if there is no fixed resistance \((p_1 = 0)\), the diameter is unstable, shrinking to zero or growing unboundedly (8). However, the system can be stabilized by a sufficiently large fixed resistance (if \( p_1 > \sqrt{2} \)), or by a flow-dependent response. If there is no fixed resistance, so that the pressure drop across the segment is fixed, then its diameter is stable (i.e., it is pressure stable) if and only if \( g'(\dot{Q}_1) \) is sufficiently negative that \( \tau_1 f'(\tau_1) + 4Q_1 g'(\dot{Q}_1) < 0 \). In the simulations, this condition is satisfied if \( k_m > \sqrt{2} \), assuming \( Q_0 < Q_{\text{crit}} \).

Next, consider two parallel active segments in series with a fixed resistance \((i = 1, 2)\) so that \( P_1 = P_2 = P_0 / (1 + p_1 + p_2) \). From the theory of ordinary differential equations, a pair of equilibrium diameters \((D_1, D_2)\) is stable if and only if the eigenvalues of the matrix \( A \) are negative or have negative real part. This leads, after some manipulations, to conditions for stability

\[
(3p_1\alpha_1 - \beta_1)(3p_2\alpha_2 - \beta_2) > (3p_1\alpha_1)(3p_2\alpha_2)
\]

and

\[
3p_1\alpha_1 + 3p_2\alpha_2 - (1 + p_1) \beta_1 - (1 + p_2) \beta_2 > 0
\]

where

\[
\alpha_i = \tau_i f'(\tau_i) > 0 \quad \text{and} \quad \beta_i = \tau_i f'(\tau_i) + 4Q_i g'(\dot{Q}_i)
\]

and \( \beta_i < 0 \) is the condition for pressure stability. Examination of the regions of the \( \beta_1-\beta_2 \) plane defined by these inequalities shows that the system is stable if \( \beta_1 < 0 \) and \( \beta_2 < 0 \) but is unstable if \( \beta_1 > 0 \) and \( \beta_2 > 0 \). (If only one of \( \beta_1 \) and \( \beta_2 \) is positive, stability is possible if the positive one is sufficiently small.) In the absence of a flow-dependent response, \( \beta_1 = \alpha_1 > 0 \), and any equilibrium is unstable, independent of the fixed series resistance, as shown by Hacking et al. (8). However, if both segments are pressure stable, then stability is guaranteed.

The analysis of larger networks is more complex. However, such networks are likely to contain pairs of parallel segments, and such segments must be pressure stable to ensure the stability of the whole network. In fact, it can be shown that if all segments in the network are pressure stable, then the network as a whole is stable, subject to the additional condition that \( \tau f'(\tau) + Qg'(Q) > 0 \) in all segments. In the simulations, this condition is satisfied if \( k_m < 1 \). The main steps in the proof are as follows. The general form of the matrix \( A \) is shown to have the same eigenvalues as a real symmetric matrix. Therefore, the eigenvalues are real, and the system is stable if they are all negative. Suppose, on the contrary, that there is a positive eigenvalue. The corresponding eigenvector represents a disturbance to the system in which all segments whose diameters increase experience an increased pressure gradient, and vice versa. However, such a disturbance can be ruled out using a minimum-dissipation argument, completing the proof.

The introduction of a pressure-dependent stimulus for adaptation complicates the above analysis and could produce different behavior in some cases. However, the dominant mode of instability in networks with shear response occurs when two segments are connected in parallel, with one shrinking while the other grows. In this case, both segments are subject to the same pressures, so a pressure stimulus cannot provide a differential stimulus to stabilize the pair. This suggests that inclusion of a flow-dependent metabolic stimulus as described here leads to stability even in the presence of a pressure-dependent response.

**APPENDIX B**

Stability of Networks With Low-Generation Shunts

Consider a network of segments, whose adaptation is governed by Eq. A1. In each segment, \( Q = \pi D^4G / 128 \eta \) and \( \tau = DG/4 \), where \( G \) is the pressure gradient. Therefore, \( \tau = (QG/2^4)^{1/2} \). The condition for equilibrium, \( F(Q,G) = f(\tau, Q,G) + g(\dot{Q}) = 0 \), implicitly defines a functional relationship between \( Q \) and \( G \). From well-known properties of partial derivatives

\[
\frac{dQ}{dG} = -\frac{fG}{f\dot{Q}} = -\frac{\dot{Q}}{G} - \frac{3f'(\tau)}{G^{3/4}Q(\dot{Q})}
\]

The condition that the segments are pressure stable implies that \( f'(\tau) + 4Qg'(Q) < 0 \), and so \( dQ/dG > 0 \). Thus, in a network of segments with equilibrium diameters, segments with higher pressure gradients must have higher flows. This contradicts the observed occurrence of low-generation shunts with relatively high pressure gradients and small diameters that carry much lower flows than their parent vessels. The existence of such shunts implies the need for an additional stimulus, dependent on the number of segments fed or drained by a given vessel, to permit structures of the type observed.

The expert technical help of B. Giesicke and M. Ehrlich as well as the assistance of A. Scheuermann in preparing the manuscript is gratefully acknowledged.

This study was supported by Deutsche Forschungsgemeinschaft Pr 271/1-1, 1-2, 5-1, and 5-2 and by National Heart, Lung, and Blood Institute Grant HL-34555.

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Received 1 December 1997; accepted in final form 6 April 1998.

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