Structural Autoregulation of Terminal Vascular Beds
Vascular Adaptation and Development of Hypertension

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Abstract—It is widely accepted that the early phase of primary hypertension is characterized by elevated cardiac output, whereas in later stages the increased blood pressure is due to increased peripheral resistance. To study long-term effects of increased blood flow on peripheral resistance, structural adaptation of microvascular networks in response to changes in blood flow was simulated using a previously developed theoretical model. The diameter of each vessel segment was assumed to change in response to local levels of shear stress, transmural pressure, a metabolic stimulus dependent on blood flow rate, and a conducted stimulus. Network morphologies and topologies were derived from intravital microscopy of the rat mesentery. Adaptive responses to the 4 stimuli were quantitatively balanced to yield stable and realistic distributions of vascular diameters and blood flow rates when the total flow rate was set to observed levels. To simulate effects of increased cardiac output, network flow resistance after structural adaptation was determined for a range of flow rates. Resistance increased with increasing flow, and increases in pressure were up to 3-fold greater than proportional to the increases in flow. According to the model, flow-dependent changes of network resistance result mainly from the vascular response to transmural pressure, which also causes arteriovenous asymmetry of diameters and pressure drops. Therefore, in vascular beds that exhibit arteriovenous asymmetry, increased flow may trigger increased flow resistance by a mechanism involving the tendency of vascular segments to reduce their luminal diameters in response to increased transmural pressure. (Hypertension. 1999;33:153-161.)

Key Words: stress, shear  pressure  hemodynamics  modeling, mathematical

Although the pathophysiological mechanisms of primary hypertension are not fully understood, there is general agreement that in established hypertension, cardiac output is approximately normal and the increase in blood pressure is caused by a proportional increase in peripheral resistance. 1-3 This resistance increase evidently results from structural changes of the vasculature because it is seen under conditions of resting tone and at maximal vasodilatation. 1-4 In contrast, an increase in cardiac output is seen only in young and borderline hypertensive patients 2 and also transiently in some line hypertensive patients 2 and also transiently in some circumstances. 2-4 The initial changes of cardiovascular function in primary hypertension may result from a decreased capacity of the kidneys to excrete fluid at a normal and the increase in blood pressure is approximately normal and the increase in blood pressure is caused by a proportional increase in peripheral resistance. 1-3 This resistance increase evidently results from structural changes of the vasculature because it is seen under conditions of resting tone and at maximal vasodilatation. 1-4 In contrast, an increase in cardiac output is seen only in young and borderline hypertensive patients 2 and also transiently in some circumstances. 2-4 The initial changes of cardiovascular function in primary hypertension may result from a decreased capacity of the kidneys to excrete fluid at a given arterial pressure level. 7,8 Indications that the altered vascular structure typical for established hypertension represents a secondary adjustment 9 support the theory of "structural resetting" of systemic resistance 6 by adaptation of vascular diameters to increased levels of blood flow and driving pressure. 10-12

This concept implicitly assumes continuous structural adaptation of vessel diameters to local hemodynamic conditions. It is known that vessels react chronically to the mechanical forces exerted by the flowing blood, i.e., wall shear stress and transmural pressure, 13-21 and continuous adaptation to local shear stress at the endothelial surface has been suggested to control vascular structure and to optimize vascular design. 22,23 However, vascular growth in response to shear stress alone would result in unstable adaptation under most circumstances. 24,25 If 2 parallel flow pathways experience the same driving pressure, the pathway with lower flow resistance receives a higher flow fraction and experiences a higher level of wall shear stress. If, as suggested by experimental data, an increase of shear stress triggers an increase of vessel diameter (and vice versa), the flow resistance in this pathway would decrease further while that of the high-resistance pathway would increase. This process would continue until 1 pathway is completely eliminated and lead eventually to the collapse of a vascular network to a single large arteriovenous channel. If a response to transmural pressure on vascular structure is considered in addition (pressure-shear hypothesis 26), such unstable adaptive behavior is not eliminated. Therefore, additional local mechanisms, e.g., metabolic factors, 27 must be involved.

In a recent theoretical analysis, a minimum set of stimuli required to produce stable microvessel networks with realistic morphology and hemodynamic properties 28 was defined by

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comparing results of simulations with experimental data from complete microvascular networks in the rat mesentery. It was demonstrated that adaptation of vascular diameters can yield stable and realistic network structures only if it entails responses to a combination of at least 4 stimuli: shear stress at the endothelial surface; transmural pressure; local metabolic conditions, related to local red cell flow; and a conducted stimulus coupling terminal branches to their feeding or draining vessels. The responses to shear stress and transmural pressure create and maintain the arteriovenous asymmetry of microvascular networks with respect to pressure drop, wall shear stress, and vessel diameter. The metabolic stimulus prevents the collapse of vascular networks to single arteriovenous pathways, and the conducted stimulus suppresses the generation of large shunts connecting proximal arterial and venous vessel segments.

The long-term reaction of a vascular network to changes of systemic hemodynamic conditions will largely depend on these adaptive responses. For example, if blood flow rate is increased, the equilibrium state achieved by structural adaptation is perturbed and vessel diameters must change until a new equilibrium is reached. The extent of these changes, and the resulting alteration of flow resistance, depends on the relative magnitudes of the vessels’ adaptive responses. In the present study, our previously developed model for local vascular adaptation\(^{26}\) was used to predict the effect of changes in flow rate on flow resistance, and the results are considered in the context of changes occurring in arterial hypertension.

Methods

Microvessel Network Structure

The animal preparation and the setup used for the measurement of network geometry and structure by intravital microscopy have been described in detail elsewhere.\(^{26,27}\) Male Wistar rats (n=3; body weight, 300 to 450 g) were anesthetized (atropine 0.1 mg/kg IM, pentobarbital sodium 20 mg/kg IM followed by ketamine 100 mg/kg IM). During the experiments, the level of anesthesia and fluid balance were maintained by intravenous infusion of physiological saline (24 mL/kg per hour) containing 0.3 mg/mL pentobarbital sodium. After cannulation of the trachea, jugular vein, and carotid artery and after abdominal midline incision, the animals were transferred to the stage mounted on an intravital microscope equipped with a 25×/NA.0.6 salt-water immersion objective (Leitz). Heart rate and arterial blood pressure (range, 105 to 140 mm Hg) were continuously monitored via the catheter in the carotid artery. The small bowel was exteriorized and superimposed continuously with a temperature-controlled (36.5°C) bicarbonate-buffered saline containing papaverine (10 \(^{-4}\) mol/L) as a precaution to prevent the development of tone and variation of vessel diameters during the experiments.

In each experiment, a vascular network in the fat-free portion of the mesenteric membrane with an area between 25 and 80 mm\(^2\), supplied by a feeding arteriole (inner diameter, \(\sim 30 \mu m\)) and drained by a venule (diameter, \(\sim 45 \mu m\)), was selected. These networks were scanned and recorded on videotape and on black-and-white film. A complete scan took \(\sim 30\) minutes and consisted of \(\sim 300\) individual fields of view (300×400 \(\mu m\)). In 2 networks, an additional scan was performed using strobe-light asynchronous illumination to allow off-line determination of flow velocity in each vessel segment with a digitized image-analysis system.\(^{28}\) The photographs exposed during the scanning procedure were used to assemble photomontages of the complete microvascular networks, from which network topological structure (connection matrix) and the length of all vessel segments between branch points were determined. The diameter of vessel segments was determined from the video recordings obtained with the strobe-light flash illumination, where available (n=2 networks), and from the photonegatives for the remaining networks (n=4). The numbers of vessel segments in the 3 networks analyzed here were 383, 546, and 913.

Mathematical Simulation of Blood Flow

Details of the mathematical flow simulation and its validation have been described previously.\(^{29,30}\) Volume flow rates and hematocrit values in each segment and pressures at each branch point within a network were calculated using an iterative algorithm. The phase separation effect (nonproportional partition of red cell and plasma flows at diverging bifurcations) was taken into account, based on observations of arteriolar bifurcations of the rat mesentery.\(^{31}\) The assumed dependence of effective blood viscosity in microvessels on vessel diameter and hematocrit was based on data obtained previously for the same tissue.\(^{29}\) Boundary conditions for the calculations include hematocrit values and volume flow rates in all vessel segments feeding the network and volume flow rates of those segments leaving the network, with the exception of the main venular draining segments. In the network with 546 segments, only 1 large draining vessel was present. This segment was assigned a pressure of 13.8 mm Hg according to previous measurements of micropressures in similar-sized venules in the same tissue.\(^{29}\) For the 2 other networks, 2 (383-segment network) or 7 (913-segment network) additional larger draining segments were assigned pressures slightly above (14 and 15 mm Hg) that of the main draining segment. Measured flow velocities in the boundary segments were used to calculate overall volume flow rates in 2 of the 3 networks. For the third network, volume flow rates were assigned to match experimental values for corresponding vessel diameters.

Mathematical Simulation of Structural Adaptation

A model of structural adaptation was developed on the basis of the experimentally determined network structure.\(^{26}\) According to this model, each segment in the network adapts by changing its diameter at a rate that is proportional to a net growth stimulus for this segment, \(S_{\text{net}}\):

\[
\Delta D = S_{\text{net}} \cdot D \cdot \Delta t
\]

\(S_{\text{net}}\) is calculated as the sum of 4 terms representing stimuli needed to generate stable network structures with realistic morphological and hemodynamic properties (wall shear stress, transmural pressure, local metabolic stimulus, conducted metabolic stimulus), and a term representing a basic shrinking tendency:

\[
S_{\text{net}} = \log \tau_c - \log \tau_c \cdot \log(Q_{\text{ref}}/Q_{\text{Hg}} + 1) + k_S/(S_c + S_0) - k_c
\]

The rationale for each term is explained as follows. The tendency of vessels to increase in diameter in response to increased wall shear stress is represented by the term “\(\log \tau_c\).” The logarithmic dependence ensures the sensitivity of \(S_{\text{net}}\) to changes in \(\tau_c\) over a wide range of \(\tau_c\) values. The tendency of vessels to decrease in diameter in response to increased transmural pressure is represented by the term “\(-\log \tau_c\),” where \(\tau_c\) increases sigmoidally with \(P\) according to experimental data relating \(\tau_c\) and \(P\) in rat mesentery networks:\(^{26}\)

\[
\tau_c(P) = 100 - 86 \cdot \left[\exp\left(-5000 \cdot \log(\log P)\right)\right]^{1/4}
\]

The response of a vessel segment to local metabolic conditions is assumed to depend on the red blood cell flux through the segment and is represented in Equation 2 by the term “\(+k_S/(S_c + S_0)\)” where \(Q_{\text{Hg}}\) is the volume flow rate of red blood cells, \(Q_{\text{ref}}\) is a reference flow (40 nL/min), and \(k_S\) determines the sensitivity of the vessel to blood flow.

The conducted metabolic stimulus is represented by the term “\(+k_c\) \(S_c/(S_c + S_0)\).” Here, \(S_c\) is the summed conducted signal entering a given segment. It is assumed to be generated in each segment and propagated upstream in the arteriolar tree (downstream in the venular tree) and to decay exponentially with distance traveled (length constant, 1500 \(\mu m\)). Calculation of \(S_c\) proceeds from the most distal branch points of the arteriolar tree proximally to the main feeding vessel.
bifurcation, $S_i$, is calculated as the sum of the metabolic stimuli of the downstream vessel segments and the conducted stimuli from the next downstream bifurcations. The same procedure is used in the inverse direction for the venular tree. For a given arteriolar or venular vessel, the resulting conducted stimulus is calculated from $S_i$ using a saturating response, with a reference value of $S_i = 20$. The parameter $k_c$ represents the relative strength of the conducted stimulus.

Finally, a constant term “$-k_s$” is included to represent the shrinking tendency, i.e., the tendency of vessels to shrink in the absence of growth-stimulating stimuli. The values of the constants included in the mathematical expressions were obtained by minimizing the mean square deviation in flow velocities between experimentally measured values for the networks considered and the values predicted by the mathematical flow simulation. The resulting values used for the metabolic parameter $k_m$ were 0.63, 0.83, and 0.97 for the 3 networks with 383, 546, and 913 segments, respectively. For the 4th network, the respective values were 3.19, 2.74, and 2.85, and for the shrinking tendency, $k_s$, 1.57, 1.79, and 1.57.

Satisfactory agreement between predicted and observed network structures and velocity distributions was possible only when all 4 stimuli were included. Each stimulus determines distinct characteristics of the adapted network. Vessel shear stress at the endothelial surface ($\tau_e$) controls the diameter distribution over the successive generations of microvessels. Vascular adaptation in response to pressure ($P$) generates the difference in average vessel diameters between the arterial and the venous side of the vascular bed. According to the pressure-shear hypothesis, vascular reactivity to $\tau_e$ and $P$ is needed to create the functionally important arteriovenous asymmetry with respect to pressure drop, shear rates, diameters, and intravascular volume. Stability of the adaptive response can only be achieved if the metabolic stimulus, reflecting the metabolic state of tissue adjacent to a vessel segment, is included. This prevents the collapse of the network to a single large arteriovenous pathway. In the present model, the metabolic stimulus was assumed to depend directly on red cell flow rate in a given vessel segment. In reality, the metabolic stimulus experienced by a given segment must depend not only on the flow in the segment but also on the extent and metabolic demand of the region it serves. However, inclusion of such effects would require further information about the spatial distribution of vessels and of metabolic demand, which is not available for this tissue. The conducted stimulus is needed to maintain the diameter of vessels feeding or draining larger numbers of terminal vessels. Without a growth signal transmitted from dependent segments to their supply vessels, these vessels would shrink and blood would flow mainly through short arteriovenous shunts, bypassing the nutritive capillaries.

**Mathematical Simulation of Network Reaction to Changes in Bulk Flow Rate**

For a given network flow resistance, any change in volume flow rate will be associated with a proportional change in driving pressure. However, vascular responses to the changed hemodynamic conditions, elicited by an initial change of the flow rate, may change the flow resistance, and in turn $\Delta P$, constituting a feedback loop (Figure 1). The sensitivity of relative resistance changes ($dR/R$) to relative changes in pressure is represented by the gain (G) of the feedback loop:

$$G = \frac{dR}{R} \cdot \frac{\Delta P}{\Delta P}$$

The proportional change of the output relative to that of the input, or in the situation discussed above the quotient of the (final) change of pressure after structural vascular adaptation to the (initial) change of flow rate, is the amplification (A) of the feedback loop, which depends on $G$:

$$A = \frac{\Delta P/\Delta P}{dQ/Q} = 1 - G$$

where $Q = \Delta P/R$ is the bulk flow rate through the boundary segments feeding a network. In the case of positive feedback, when an increase of pressure leads to an increase in flow resistance, $G > 0$, and $A > 1$.

To investigate the influence of changes of bulk flow rate on network flow resistance, the flow rates in boundary segments were varied. The volume flow rate under control conditions calculated from experimental measurements (networks with 383 and 546 segments) or estimated from typical flow velocities for mesenteric arterioles of a given diameter (network with 913 segments) was multiplied with a factor ranging from 0.03 to $\sim 3$. $\Delta P$ was calculated as the average pressure difference across the network ("driving pressure"), i.e., the difference between the flow-weighted means of the pressure in the feeding and draining boundary vessels of the network. For the network with 546 segments, additional simulations were performed in which the combination of adaptive stimuli or the numerical values of parameters used in the simulated vascular adaptation were altered.

**Results**

Figure 2 shows results of simulations of network adaptation for a range of volume flow rates, using the adaptation model as described above. For all 3 networks, $\Delta P$ increased with $Q$ in a sigmoidal fashion. In an intermediate range of flow rates, the increase of $\Delta P$ was markedly greater than proportional, reflected by a steep increase of flow resistance (R). For the 3 networks, the percentage increase in flow resistance over the entire flow rate range varied between about 440% and 660%.

The substantial increase of flow resistance with volume flow rate in an intermediate range implies that vascular adaptation leads to a strong positive feedback with respect to pressure changes. Initial changes of volume flow rate lead to greater than proportional changes of driving pressure with an amplification (A) $> 1$. Figure 3 shows that the amplification is maximal in an intermediate range of driving pressures, close to the values normally observed for microvascular networks in the same tissue. In this range, initial variations of pressure caused by flow changes are amplified because of vascular adaptation by a factor of $\approx 2.8$, corresponding to a gain of $\approx 0.64$.

In the text that follows, results of simulations are described in which the parameters of the adaptation model were modified to investigate the importance of different characteristics of the adaptive response for the observed positive feedback mechanism. Figure 4 shows that changes of the sensitivity to the metabolic stimulus result in only very minor changes of the pressure/flow relation. There is a weak correlation between metabolic sensitivity and maximal feedback amplification. However, the network adaptation becomes increasingly unstable at higher pressures or flow rates if the metabolic sensitivity is reduced. This confirms theoretical considerations showing that below a certain level of metabolic sensitivity the stability of the adaptive response is lost. With the form of the metabolic stimulus used here, this instability occurs first at high flow rate levels, because the metabolic stimulus (M) is assumed to decline when the flow
rate in a given segment approaches a preset reference value ($Q_{ref}$). As shown in Figure 5, the feedback amplification is not affected by changes of $Q_{ref}$, but a proportional shift of the pressure-flow relationships to higher flow rate levels occurs with increasing $Q_{ref}$.

The responses of vascular networks to variations of bulk flow rate were sensitive to the relationship between expected shear stress and transmural pressure in vessel segments (the $\tau/P$ relationship). When the pressure scale of this relationship was stretched or compressed (Figure 6), the resultant flow rate and resistance levels for given driving pressures and the feedback amplification were substantially altered. Even more marked effects resulted from alterations in the amplitude of the $\tau/P$ relationship (Figure 7). A flatter $\tau/P$ relationship resulted in reductions of the resistance increase with driving pressure and of amplification of pressure changes. In the case of constant $\tau$, ie, no pressure sensitivity of the vessels, flow resistance decreased with increasing driving pressure. As a consequence, initial changes of flow rate led to smaller changes of pressure after vascular adaptation ($A < 1$, corresponding to a negative gain), indicating a negative feedback with respect to pressure.

**Discussion**

Vessel segments in the microcirculation can adapt continually to their local environment by structural changes of diameter. This adaptation should lead to stable network structures under a variety of hemodynamic conditions and levels of tissue demand. Vessels should not grow or shrink excessively and an adequate number of parallel flow pathways has to be maintained to adequately supply the tissue. Adaptive responses of individual vessels affect the flow resistance and thus the pressure/flow relation of vascular beds. The relation between responses of individual vessels and those of complete networks is complex. Any vessel reacting to its local environment influences the flow distribution in the whole network, including the vessel itself. Therefore, in extrapolations from the behavior of isolated vessels to that of vascular networks, interactions among vessel segments must be taken into account. Theoretical simulations can describe the overall network behavior that results from interactions of many individual vessels exhibiting local responses (as inferred from experimental studies and/or theoretical considerations). This approach is used here to study the fundamental consequences of adaptive responses of vessels for the relation between flow rate, driving pressure, and flow resistance of vascular beds.

For a given vascular bed, changes of systemic arterial pressure, caused for example by modifications of cardiac function or flow resistance in other vascular beds, will initially lead to parallel, proportional changes of flow and pressure: The fundamental vascular reactions to hemodynamic stimuli, which have been described in many studies, predict opposite vascular reactions to these shear stress (or flow) and pressure signals. It is generally accepted that an increase in shear stress leads to an increase in diameter of the vessel lumen, acutely by reduction of vessel tone and chronically by vessel growth. Conversely, increased pressure results in a diameter decrease, acutely by an increase of myogenic tone and chronically by remodeling or concentric growth. A number of studies have investigated the relation between these reactions under defined experimental conditions. However, the complex nonlinear interactions...
in complete vascular networks discussed above render the interpretation of such measurements difficult and prevent their generalization to complete vascular beds.

Moreover, vascular response to shear stress alone cannot generate stable and realistic network structures. Stability can be achieved by balancing the shear stress signals ($\tau_s$) with a metabolic signal ($M$) that decreases with increasing blood flow in a given vessel. These 2 stimuli represent a minimal set of signals for stable local adaptation. A conducted signal ($C$) prevents the generation of short, large-diameter arteriovenous shunts, which would otherwise carry a large fraction of the total flow. The inclusion of a pressure sensitivity ($P$) of the vascular response establishes the arteriovenous asymmetry of vascular networks. Shear stress, pressure drop, and flow velocity are greater on the arterial side of the systemic circulation, whereas vessel diameters and intravascular volume are greater on the venous side. This asymmetry is functionally important because it determines physiological characteristics, including the low average capillary pressure level.

According to the model, an increase in arteriolar pressure causes an adaptive reduction in vessel luminal diameters until a new equilibrium state is reached. If pressure is held constant, the resulting increase in flow resistance attenuates the change in flow rate. This long-term behavior can be characterized according to Folkow as "structural autoregulation." It resembles acute functional autoregulation in that flow variations are damped, and the capillary bed is protected from large pressure changes (Figure 8). For a reduction (increase) of the bulk flow rate by 20%, arteriolar driving pressure decreases (increases) from 88 mm Hg to 49 (137) mm Hg, whereas mean capillary pressure, which is 24 mm Hg under control conditions, is decreased (increased) to only 20.8 (31.8) mm Hg. It is of note that the value for the gain of "structural autoregulation" determined in the present study ($\alpha = 0.64$) is close to the experimental values reported for the gain of acute "whole body autoregulation," which ranges from 0.4 to 0.6. Because of structural autoregulation, the long-term level of volume flow rate into a vascular bed is primarily under local control and can be modified by changes of the local metabolic demand. In the present model such
modifications are represented by changes of the reference flow value (Figure 5).

Local control of flow rate and conserved capillary pressure levels resulting from structural autoregulation are potentially beneficial for the function of the tissue involved. However, as changes of flow rate are attenuated, changes of driving pressure are amplified (Figure 3). Structural adaptation of individual vessels in response to local stimuli results in a positive feedback of vascular beds with respect to pressure (Figure 1). Thus, an initial small and functional pressure increase elicited, for example, by an increase of cardiac output can lead to a larger structural increase in pressure and flow resistance. In the development of hypertension, the initial cause may thus be elusive and lead to only small rises of pressure, whereas the progression of the disease with strong, sustained pressure escalation is related to adaptive responses according to the positive feedback mechanism and vascular hypertrophy.44

Folkow’s theory of structural autoregulation43 is based on the assumption that vessels adapt to keep average circumferential stress (wall tension per unit of wall thickness) to a constant level throughout vascular networks and for different systemic hemodynamic conditions. According to Laplace’s law, \( \sigma = P \cdot r/w \), where \( \sigma \) is average circumferential stress, \( P \) is transmural pressure, \( r \) is vessel radius, and \( w \) is wall thickness, this implies that an increase of pressure elicits a proportional increase of normalized wall thickness, \( w/r \). If this change of wall structure involves a decrease of the luminal diameter of the vessel, vascular flow resistance will be increased. Folkow also hypothesized that the thickening of the vessel wall would amplify the hemodynamic effect of vascular smooth muscle tone, as for a given shortening of the smooth muscle layer the degree of luminal narrowing would increase with increasing \( w/r \).

The effects of pressure on wall structure and the effects of wall structure on flow resistance and sensitivity to smooth muscle tone described above are generally accepted. How-

Figure 6. Results of simulations in which the relation between expected shear stress (\( \tau_e \)) and the transmural pressure (\( P \)) was shifted to the right (or to the left, respectively) by multiplying pressures with a factor of 1.2 (○), or 0.8 (●). The \( \tau_e/P \) relationships used are shown in the inset. The continuous lines indicate the standard \( \tau_e/P \) relationship and corresponding results. Data were obtained from the network with 546 segments.

Figure 7. Comparison of simulations with reduced (○) and without (●) dependence of the expected shear stress in a given vessel segment (\( \tau_e \)) from the local transmural pressure (\( P \)) with those obtained using the experimental \( \tau_e/P \) relationship (continuous line). The \( \tau_e/P \) relationships used are shown in the inset. Data were obtained from the network with 546 segments.
ever, the question of what physical quantity represents the main signal for the vascular responses is unresolved. Experimental data from morphometric studies show a strong increase of \( w/r \) with decreasing vessel diameter for arterioles and venules (Figure 9). The relatively thick walls of small microvessels may serve structural and functional needs other than the hemodynamic control of a vascular bed. As a result, average circumferential stress in the smallest microvessels is only about 1/10 of that in the larger feeding vessels, making it an unlikely candidate to be the main signal for the vascular adaptation that leads to increased flow resistance in hypertension. In contrast, vascular reactivity to changes of pressure renders the adaptation to hemodynamic conditions independent of specific differences in wall thickness. Furthermore, pressure is the only hemodynamic parameter that exhibits a predictable monotonic decline along arteriovenous pathways and can thus serve to control systematic structural differences between arterial and venous parts of the circulation. It is not known what sensing mechanisms could generate the proposed vascular reactions to pressure. However, such mechanisms are physically conceivable. If, for example, the circumferential tension is primarily carried by a specific circumferential structure in the vessel wall, whose thickness is proportional to vessel diameter, the circumferential stress in this structure could serve as a signal proportional to pressure.

The response of a network to a change in pressure or flow depends on the response characteristics of the vessels, which in this discussion are assumed to be identical for all vessels. Simulations with modified vascular response characteristics show that the presence and extent of structural autoregulation depends on the pressure sensitivity, defined in the model by the relationship between expected wall shear stress, \( \tau_c \), and pressure, \( P \). In contrast, changes in other parameters of the response do not lead to major changes in the reactive pattern, as long as pressure stability is maintained (see Figure 4). The initial increase of driving pressure used to test the adaptive characteristics of vascular beds leads to a proportional increase of flow and wall shear stress (\( \tau_c \)). The separate vascular responses to increases of pressure (diameter reduction) and wall shear stress (diameter increase) result in opposite changes of flow resistance. Therefore, when both parameters are increased, the final change of flow resistance is difficult to predict. In the standard model considered, a \( \tau_c/P \) relationship based on experimental findings is used, which predicts a strong sigmoidal increase of \( \tau_c \) with changes in \( P \). Here, the increase of \( \tau_c \) dictated by the initial increase of...
pressure is greater than the parallel increase of $\tau_v$ for most vessels. The resultant vascular reaction is thus dominated by the effect of increased pressure and vessel diameter decreases. This in turn leads to an increase of flow resistance and hence driving pressure (Figure 6). If in contrast the pressure sensitivity is abolished ($\tau_v$ constant), the increase of $\tau_v$ determines vascular responses to increased driving pressure, and a decrease of flow resistance results (Figure 7).

Current knowledge concerning structural responses of vessels during adaptation is far from complete. Experiments at the scale of individual cells and vascular segments have not yet provided sufficient data on the quantitative relationships between hemodynamic conditions, tissue metabolic state, and structural vascular reactions to allow us to predict the behavior of terminal vascular beds in a “bottom up” inductive approach. Therefore, the present model was based on a “top down” deductive approach, in which observed properties of microvascular networks were used to deduce a minimal set of stimuli and their quantitative effects.28 Available experimental data on the underlying mechanisms were used to guide the process. This approach has led to new hypotheses and predictions on the interaction of adaptive vascular reactions and on the effects of changing hemodynamic conditions on network adaptation. However, further experimental work is required to test the model and its predictions. The approach used here may help to stimulate the necessary experiments and can provide a framework for interpreting their results.

Vascular beds of the systemic circulation are characterized by hemodynamic arteriovenous asymmetry, as evidenced by capillary pressure levels that are much lower than the arithmetic mean of arterial feeding and venous draining pressures. The pressure sensitivity of vascular adaptation is largely responsible for generating this asymmetry.26,28 The present study shows that such pressure sensitivity can also lead to increased flow resistance when driving pressure is increased, ie, to structural autoregulation. This phenomenon may have an important role in amplifying and stabilizing the sustained increase of arterial blood pressure seen in essential hypertension.

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