Remodeling of Blood Vessels
Responses of Diameter and Wall Thickness to Hemodynamic and Metabolic Stimuli
Axel R. Pries, Bettina Reglin, Timothy W. Secomb

Abstract—Vascular functions, including tissue perfusion and peripheral resistance, reflect continuous structural adaptation (remodeling) of blood vessels in response to several stimuli. Here, a theoretical model is presented that relates the structural and functional properties of microvascular networks to the adaptive responses of individual segments to hemodynamic and metabolic stimuli. All vessels are assumed to respond, according to a common set of adaptation rules, to changes in wall shear stress, circumferential wall stress, and tissue metabolic status (indicated by partial pressure of oxygen). An increase in vessel diameter with increasing wall shear stress and an increase in wall mass with increased circumferential stress are needed to ensure stable vascular adaptation. The model allows quantitative predictions of the effects of changes in systemic hemodynamic conditions or local adaptation characteristics on vessel structure and on peripheral resistance. Predicted effects of driving pressure on the ratio of wall thickness to vessel diameter are consistent with experimental observations. In addition, peripheral resistance increases by \( \approx 65\% \) for an increase in driving pressure from 50 to 150 mm Hg. Peripheral resistance is predicted to be markedly increased in response to a decrease in vascular sensitivity to wall shear stress, and to be decreased in response to increased tissue metabolic demand. This theoretical approach provides a framework for integrating available information on structural remodeling in the vascular system and predicting responses to changing conditions or altered vascular reactivity, as may occur in hypertension. (Hypertension. 2005;46:725-731.)

Key Words: hemodynamics ■ hypertension ■ remodeling

Blood vessels are capable of continuous adaptive structural change (remodeling) in response to varying conditions and functional demands.\(^1—to^5\) It is reasonable to assume that each vessel segment reacts, through regulation of gene expression and cellular functions, to the local conditions and stimuli that it experiences, according to a common set of genetically determined responses or “rules.”\(^6\) Continuous dynamic reactions according to such rules can in principle lead to development of structures that are functionally adequate and capable of adaptation to changing conditions.\(^7\,8\)

The concept that vessels in peripheral vascular beds adapt dynamically according to a generic set of response rules has important implications for vascular function in normal and diseased conditions. Vascular adaptive reactions can attenuate initial changes in conditions. For instance, reactions to decreased tissue oxygen levels can lead to increased perfusion in a state of increased metabolic demand. However, initial changes can also be augmented. For example, increases in blood pressure caused by increased cardiac output may lead to increased peripheral resistance, amplifying the initial pressure increase.\(^9\)\(^,10\) Also, changes in vascular response characteristics to hemodynamic and/or metabolic stimuli may result in changes in functional properties of vascular beds. Acquired or genetically predetermined modifications in cellular signaling pathways or neuro-humoral control mechanisms could lead, for example, to increased peripheral resistance and thereby contribute to the development of hypertension.\(^11\)\(^,12\)

The goal of the present study is to describe quantitatively how basic mechanisms of vascular adaptation affect functional characteristics of terminal vascular beds. Such understanding is not readily achieved using reductionist experimental approaches alone, because many interacting elements are involved. An alternative strategy is to develop theoretical models using a top-down systems approach: underlying “rules” are deduced by considering observed network properties and the constraints imposed by the requirements that the resulting system is functionally adequate, stable, and robust. Here, this approach is used to develop a model in which vessels remodel structurally in response to local stimuli derived from shear stress, circumferential wall stress, and oxygen partial pressure. The “rules” applied are based as far as possible on known and accepted aspects of vascular responses to hemodynamic and metabolic stimuli, additional

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Charité in Berlin, were prepared for intravital microscopy in accordance with the German Animal Protection Act, monitoring heart rate, arterial pressure anesthetic level, and fluid balance. Blood flow in microvascular networks of the rat mesentery was observed by intravital microscopy. Papaverine (10⁻² M) was continuously applied to suppress active vessel tone. Diameter, length, hematocrit, and flow velocity were measured in all segments between branch points using a digital image analysis system. Results are presented for a microvascular network containing 913 vessel segments. Additionally, a small hypothetical network with 23 asymmetrically connected segments was used for rapid scans of parameter values. Experimental data on wall thickness were derived from a compilation of published experimental observations.¹⁰

**Materials and Methods**

**Theoretical Model Approach**

The model is based on the hypothesis that the internal diameter (D) and wall thickness (w) of each segment in a network are subject to continuous structural adaptation in response to stimuli that the segment experiences. Responses to wall shear stress (τ) generated by flowing blood, circumferential stress (σ) generated by intravascular pressure, and metabolic status, as represented by partial pressure of oxygen (pO₂), are considered. Mechanisms are included for transmission of information about the metabolic state of the tissue, upstream by conductive responses in vessel walls and downstream by convection of a metabolic signal substance.⁸,¹³ To simulate structural adaptation, distributions of hemodynamic and metabolic conditions, such as hypertension or altered oxygen consumption as well as functional consequences of changes in the intrinsic vascular adaptation characteristics.

**Experimental Data**

After obtaining approval by the University and State authorities for animal welfare, male Wistar rats from the animal facilities of the University of Charité in Berlin, were prepared for intravital microscopy in accordance with the German Animal Protection Act, monitoring heart rate, arterial pressure anesthetic level, and fluid balance. Blood flow in microvascular networks of the rat mesentery was observed by intravital microscopy. Papaverine (10⁻² M) was continuously applied to suppress active vessel tone. Diameter, length, hematocrit, and flow velocity were measured in all segments between branch points using a digital image analysis system. Results are presented for a microvascular network containing 913 vessel segments. Additionally, a small hypothetical network with 23 asymmetrically connected segments was used for rapid scans of parameter values. Experimental data on wall thickness were derived from a compilation of published experimental observations.¹⁰

**Simulation of Network Blood Flow and Oxygen Transport**

The flow resistance of each vessel segment was estimated using Poiseuille’s law, taking into account the experimentally determined variation of apparent viscosity of blood with vessel diameter and hematocrit.¹⁴ Unequal partition of hematocrit in diverging bifurcations was represented using empirical relationships. The flows in each segment were computed by an iterative procedure, with blood flow being conserved at each branch point. Values of τ and σ in each segment were calculated from the flow and pressure values. Oxygen transport and consumption in the network were simulated as previously described, giving an estimate of intravascular pO₂ in each segment.

**Development of a Model for Structural Adaptation**

Results of many experimental studies¹⁵–¹⁷ on structural vascular responses to changes in blood flow or pressure can be represented schematically as shown in Figure 2A. Flow and pressure are physically related to wall shear stress (τ) and circumferential stress (σ), which can be sensed at the luminal surface or in the vessel wall and elicit vascular responses. Increased τ leads to increase in structural diameter, whereas increased σ stimulates increase in wall thickness or wall mass. These responses to τ and σ each imply a negative feedback loop; for a given driving pressure, τ is inversely proportional to the third power of diameter (τ=32Q/(πD³)), where Q is blood flow rate and η is viscosity, and σ is inversely proportional to wall thickness (σ=PD/(2w)), where P is transmural pressure difference.

Operating in isolation, these processes would lead to structural control of τ and σ to fixed values in each segment.¹¹ In reality, vascular reactions may be coupled in several respects, as indicated by additional links in Figure 2B and 2C: (i) the circumferential stress σ increases with increasing diameter, in accordance with the Law of Laplace; (ii) changes in diameter may be coupled to changes of wall thickness and vice versa;¹⁰ (iii) biological responses to τ and σ may depend on wall thickness which affects the diffusion into smooth muscle of substances produced by endothelial cells. Also, wall structure, including the distribution of passive load-bearing elements in the wall, and hence the distribution of stress, may vary with wall thickness; (iv) responses to the metabolic stimulus may involve both diameter and wall mass; and (v) changes in τ may elicit changes in wall mass, and changes in σ may lead to diameter changes. Vascular responses (ii) and (v) are supported by available experimental evidence, whereas (iii) and (iv) are biologically reasonable but not directly supported by available data.

In the model, structural changes in each segment are represented as a combination of two modes of vascular reactions: change of mid-wall diameter (Dₘ) at constant wall cross-section area (Aₜ), proportional to wall mass, and change of Aₜ at constant Dₘ. Wall thickness and internal diameter are then given by w=Aₜ/(2πDₘ) and D=Dₑₘ+w/2, so that increasing diameter decreases wall thickness and increasing wall mass decreases internal diameter. The scheme shown in Figure 2B was implemented mathematically by assuming that the changes in Dₑₘ and Aₜ at each time step are given by:

1. \[ \Delta Dₑₘ = Sₑₘ \times Dₑₘ \times \Delta t \]
2. \[ \Delta Aₜ = Rₑₘ \times Sₑₘ \times Aₜ \times \Delta t \]
where the stimuli $S_m$ and $S_m$ derived from $\tau$ and $\sigma$, each including effects of the metabolic state represented by $S_m$ and $S_m$, as described, are defined by:

\begin{align}
S_m &= k_{sm} \log(\tau/\tau_{ref}) [1 + k_{sw} \log(w/w_{ref} + \epsilon)]^{-1} + k_{md}(S_m + k_s S_m) - k_{sd} \\
S_m &= k_{sm} \log(\tau/\tau_{ref}) [1 + k_{sw} \log(w/w_{ref} + \epsilon)]^{-1} + k_{md}(S_m + k_s S_m) - k_{sd}
\end{align}

The first terms in these equations represent the basic stimuli dependent on $\tau$ and $\sigma$ respectively. Here, $\tau_{ref}$, $\tau_{ref}$, and $w_{ref}$ are reference levels of $\tau$, $\sigma$, and $w$, and $\epsilon$ is a small constant added to avoid singular behavior. Dependence on wall thickness was found to be necessary to obtain predictions consistent with experimental data. The factors $[1 + k_{sw} \log(w/w_{ref} + \epsilon)]^{-1}$ and $[1 + k_{sw} \log(w/w_{ref} + \epsilon)]^{-1}$ establish an attenuating effect of wall thickness on $S_m$ and $S_m$, where $k_{sw}$ and $k_{sw}$ represent the respective sensitivities. Logarithmic functions were chosen to give consistent sensitivity to $\tau$, $\sigma$, and $w$ over wide ranges of these variables.

Because metabolic stimuli may cause structural responses, signals derived from the metabolic status are included in equations 3 and 4. Sensing of the metabolic status was assumed to occur through a metabolic signal substance that enters flowing blood at a rate dependent on the pO2 in each segment, whenever the intravascular pO2 falls below a reference level RO2. The metabolic stimulus ($S_m$) is assumed to vary logarithmically with the intravascular concentration of the metabolite. In addition, a conducted signal (Jc) is assumed to originate in each segment in proportion to the local value of the metabolic stimulus, to be conducted in the upstream direction with summation or equal partition at each bifurcation, and to decay exponentially with distance. The corresponding stimulus ($S_m$) is assumed to depend on the value of Jc evaluated at the mid-point of each segment, with a saturable response. The model described in Figure 2B uses the simplifying assumption that the change in $D_m$ depends only on the $\tau$-derived stimulus $S_m$ and that the change in $A_m$ depends only on the $\sigma$-derived stimulus. This assumption probably does not apply in reality, and a more general model was therefore considered in which both stimuli could elicit changes in both $D_m$ and $A_m$ (Figure 2C). In this case, equations 1 and 2 are replaced with:

\begin{align}
\Delta D_m &= (R_{s_m} S_m + R_{c_m} S_m) D_m \times \Delta t \\
\Delta A_m &= R_{c_m} S_m + R_{s_m} S_m \times A_m \times \Delta t
\end{align}

where the relative contributions of the stimuli are controlled by the constants $R_{s_m}$, $R_{c_m}$, $R_{s_m}$, $R_{c_m}$, and $R_{s_m}$. Although these constants influence the time course and stability of diameter and wall thickness changes, they do not affect eventual steady-state values. This possibly counterintuitive conclusion follows from the fact that any steady-state solution ($\Delta D_m$, $\Delta A_m=0$) must satisfy the conditions that the stimuli $S_m$ and $S_m$ are zero, independent of the values of $R_{s_m}$, $R_{c_m}$, $R_{s_m}$, $R_{c_m}$, and $R_{s_m}$. Therefore, all combinations of vascular reactions to $\tau$ and $\sigma$ that lead to a stable steady-state yield the same distributions of diameter and wall thickness.

To simulate structural adaptation, values of $D_m$ and $A_m$ were updated according to equations (1) to (4), and values of $\tau$, $\sigma$, $S_m$, and $S_m$ were recalculated as described. These 2 steps were iterated until the averages of $\Delta D_m$ and $\Delta A_m$ were $< 10^{-4}$ and $10^{-6}$, indicating satisfactory convergence. The constants $k_{sw}$, etc. represent the unknown strengths of the various biological reactions and define the rates at which diameter and wall mass change in response to each stimulus. Information on their relative values could be obtained by comparing the predicted eventual steady states of the network ($S_m$=$S_m$=0 in every segment) with observed network properties. All constants were varied relative to those for the hemodynamic responses, which were set as $k_{sw}$=$k_{sw}$=1. The constants $k_{sw}$ and $k_{sw}$ control baseline levels of vascular growth or regression. The parameter $R_{c_m}$ in equation (2) determines the relative rates of wall mass and diameter changes but the final equilibrium state was independent of...
this parameter. Values for unknown parameters were established by minimizing overall deviations between predicted segment diameters and flow velocities and corresponding measured values. 

Results

For a microvessel network in the rat mesentery, Figure 3A shows the relationship between pressure and wall shear stress derived from simulation of network hemodynamics using measured vessel diameters. A strong decrease of wall shear stress with decreasing pressure is found. To obtain the corresponding results shown in Figure 3B and in Figure 4 (lower panel), structural adaptation of diameter and wall thickness was simulated according to the scheme shown in Figure 2B. The distribution of data (Figure 3B) obtained with the optimized parameters \( \text{RO}_{2}/\text{H}_{9270} = 94.4 \text{ mm Hg}, \ \tau_{w} = 0.5598 \text{ dyn/cm}^2, \ \sigma_{w} = 32050 \text{ dyn/cm}^2, \ \text{w}_{\text{ref}} = 0.804 \text{ m}, \ K = 1.66, \ \text{w}_{\text{ref}} = 0.374, \ \text{w}_{\text{ref}} = 3.077, \ K_{c} = 0.0177, \ K_{c} = 0.114, \ k_{w} = 0.609 \) agrees well with that obtained using measured diameters (Figure 3A). In the case of the model shown in Figure 2C, the stability of simulated vascular adaptation depended on the values of the parameters \( R_{d}, R_{g}, \) and \( R_{w}. \) In general, stable adaptation required that \( R_{d} > 0 \) and \( R_{g} > 0, \) ie, increasing wall shear stress stimulates diameter increase and increasing circumferential stress stimulates increase in wall mass.

Figure 3C shows compiled results of published experimental observations on the relationship between circumferential wall shear stress and vessel diameter in arterioles and venules. A linear relationship between \( \log(\text{wall stress}) \) and \( \log(\text{diameter}) \) is seen with both arterioles and venules showing the same dependence. Corresponding predictions from the simulated adaptation of diameter and wall thickness are given in Figure 3D and in Figure 4. For the range of diameters present in the network, the predicted values of circumferential wall stress and their variation with vessel diameter are similar to those observed. The lower variability in the simulation results may correspond to additional hemo-
dynamic and biological parameters that influence vascular adaptation but are not represented in the model (eg, pulse pressure) and correspond to experimental measurement errors (eg, vessel diameter).

In further simulations, the model was used to predict the effects of increasing systemic pressure on arteriolar structure. The nearly linear increase of the wall thickness to vessel radius ratio \( w/r \) (Figure 5) with increasing systemic pressure.
Figure 5A corresponds to reports for normotensive and hypertensive animal models. The variation of w/r with diameter extends findings in somewhat larger microvessels to a lower diameter range (Figure 5B). At all vessel diameters, the wall thickness for higher levels of blood pressure is above that for normotensive situations.

Figure 6 shows the predicted variation of flow resistance with flow rate and with driving pressure for the 23-segment network. Vascular remodeling in response to increased perfusion, evoked for instance by increased cardiac output and central arterial pressure, leads to an increase in peripheral resistance. For example, peripheral resistance increases by \( \approx 65\% \) for an increase in driving pressure from 50 to 150 mm Hg. This effect, which limits augmentations of tissue perfusion at the expense of even stronger increases of blood pressure, was named structural autoregulation. According to the model, an increase in peripheral resistance can be counteracted by an increase in metabolic demand (+50%). Conversely, even a relatively small decrease (~5%) in vascular responsiveness to shear stress results in substantially increased flow resistance.

**Discussion**

The concept that all segments in a microvascular network continuously undergo dynamic structural angioadaptation is well-supported by experimental observations. The results of the present model show for the first time that long-term regulation of both vessel diameter and wall thickness in terminal vascular beds can be explained quantitatively by assuming vascular reactions to hemodynamic and metabolic stimuli with uniform response characteristics. In this model, the equations and parameters representing structural changes in diameter and wall thickness resulting from a given set of stimuli are identical for every segment in the network. The different structural properties of individual microvessels as well as the overall functional characteristics of the microvascular network (eg, flow resistance) are emergent attributes of the entire system that are not prescribed directly by the assumed vascular responses. The model used here to predict vascular adaptation involving 11 optimized reference values and parameters may seem overly complicated. However, every term and parameter was included only because omitting it caused biologically unrealistic results or significantly worse...
agreement between best-fit model predictions and corresponding experimental data. Thus, the complexity of the model seems to reflect the inherent complexity of the biological system it represents. This modeling approach may stimulate new experiments to test the validity of the assumptions made and analyze the underlying biological mechanisms.

The present data were derived for a vascular bed in which any potential spontaneous tone was abolished by the application of Papaverine to avoid changes in vascular resistance during the experiments. Thus, the results directly apply for relaxed vessels and absolute values for luminal diameter wall thickness will vary with vessel tone. It is, however, likely that the relationships obtained here (eg, between diameter and circumferential stress) are similar to those applying when spontaneous vessel tone is present. This is supported by reports demonstrating a close correlation of resting and relaxed flow resistance for various conditions,27 suggesting a similar correlation for vessel diameters.

Separate considerations of the effects of wall shear stress and pressure or circumferential wall stress on vascular remodeling have led to the “uniform shear” and “uniform circumferential stress” hypotheses1,18,28 based on negative feedback regulation (Figure 2A). These hypotheses are helpful for understanding vascular reactions if only one parameter (eg, shear stress) is changed. In vascular beds, however, shear stress and circumferential stress show systematic variations and correlations with other parameters.10,21,25,29 This implies more complex interactions on physical and biological levels (Figure 2B) that are of physiological and pathophysiological significance.

Two striking observed correlations, the variation of wall shear stress with pressure21 and of circumferential stress with diameter10 (Figure 3A and 3C) involve parameters that are not linked through the separated feedback loops of shear stress and wall stress (Figure 2A). Even so, these correlations emerge from the present model without corresponding a priori assumptions, and the predictions agree well with experimentally derived data. Thus, the model accounts for the structural control of diameter and wall thickness, based on a limited set of underlying “rules.”

A mechanism for the observed relationship between pressure and wall shear stress is suggested by the present model. Along flow pathways through a microvascular network, pressure necessarily decreases. Intravalvular levels of PO2 also tend to decline, leading to the generation of increasing metabolic stimuli.30–32 The net stimulus for diameter growth, which must be zero at equilibrium, is the sum of contributions from the metabolic stimulus and from the wall shear stress (Figure 2B). Increasing metabolic stimulus along flow pathways therefore implies decreasing wall shear stress, resulting in the positive correlation of wall shear stress with intravascular pressure (Figure 3). This correlation is of major functional significance because it controls the high flow resistance in arterioles relative to capillaries and venules.21

Experimental and model data exhibit a linear increase of circumferential wall stress (σ) with diameter (D) in a double logarithmic graph (Figure 3). The maintenance of σ at a given level according to the “uniform circumferential stress” hypothesis would imply a linear increase in wall thickness with diameter, ie, a constant w/D ratio (σ = ½ P[w/D]). To obtain realistic results of the model, however, it was necessary to assume that responses to wall shear stress and pressure depend on wall thickness. The level of σ needed to generate a given σ-derived stimulus thus increases with increasing wall thickness, implying that the ratio w/D decreases with increasing vessel size (Figure 5). The biological reasons that might underlie such a reduction in sensitivity to σ with increasing wall thickness are not known. One possibility is that the relative amount of passive load-bearing elements in vessel walls33,34 (eg, internal elastic lamellae) increases with increasing vessel size, thereby reducing the force experienced by each smooth muscle cell at a given level of σ.

The present model emphasizes that shear stress and circumferential stress are not separately controlled variables (Figure 2A), because responses to each one can affect the other (Figure 2B). It shows the role of metabolic responses in establishing the gradient in shear stress along pathways through the circulatory system, and the effect of wall thickness on vascular response to stresses. The ability of the system to control vessel diameter and wall thickness does not depend on the precise nature of the vascular responses to shear stress and circumferential stress. A more general model was considered in which the stimuli derived from τ and σ could elicit changes in both diameter and wall thickness (Figure 2C, equations 5 and 6). Within a range of reaction modes, satisfying the condition that increasing wall shear stress leads to diameter increase and increasing circumferential stress leads to increase in wall mass, stable network structures were predicted. In this sense, the control mechanisms represented by the model exhibit an unexpected degree of robustness.

Perspectives

Integrative modeling approaches based on experimental investigations are well-suited for analyzing possible cause/effect relations in complex biological settings.7,10,35 The results obtained here, including the effect of wall thickness on responses to wall stress, the involvement of conducted signals in remodeling, and the reactions of networks to external conditions or changes of remodeling reactions provide a basis for experimental investigations to relate the responses assumed in the model to biological events on cellular or molecular levels.15,19,36–38 With regard to hypertension, the present model has several implications. Firstly, it supports the previously proposed concept that structural autoregulation contributes to the maintenance of elevated pressure.6,9 Second, it provides a quantitative explanation for the increased wall thickness seen in hypertension in terms of vascular responses to increased circumferential stress. Third, it supports the concept that increased metabolic demand, simulated for instance by exercise, can reduce peripheral resistance. Finally, it shows how changes in vascular adaptation characteristics related, for example, to changes in endothelial autacoid production or expression of ion channels or connexins2 may play a role in generating high blood pressure via elevated peripheral resistance.
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