Control of blood vessel structure: insights from theoretical models

A. R. Pries1,2 and T. W. Secomb3

1Department of Physiology, Charité, Universitätsmédizin Berlin, Campus Benjamin Franklin, Berlin; 2Deutsches Herzcentrum Berlin, Berlin, Germany; and 3Department of Physiology, University of Arizona, Tucson, Arizona

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Pries, A. R., and T. W. Secomb. Control of blood vessel structure: insights from theoretical models. Am J Physiol Heart Circ Physiol 288: H1010–H1015, 2005; doi:10.1152/ajpheart.00752.2004.—Blood vessels are capable of continuous structural adaptation in response to changing local conditions and functional requirements. Theoretical modeling approaches have stimulated the development of new concepts in this area and have allowed investigation of the complex relations between adaptive responses to multiple stimuli and resulting functional properties of vascular networks. Early analyses based on a minimum-work principle predicted uniform wall shear stress in all segments of vascular networks and led to the concept that vessel diameter is controlled by a feedback system based on responses to wall shear stress. Vascular reactions to changes in transmural pressure suggested feedback control of circumferential wall stress. However, theoretical simulations of network adaptation showed that these two mechanisms cannot, by themselves, lead to stable and realistic network structures. Models combining reactions to fluid shear stress, circumferential stress, and metabolic status of tissue, with propagation of stimuli upstream and downstream along vascular segments, are needed to explain stable and functionally adequate adaptation of vascular structure. Such models provide a basis for predicting the response of vascular segments exposed to altered conditions, as, for example, in vascular grafts.

microvascular networks; microcirculation; vessel grafts; wall stress; shear stress

A MATHEMATICAL APPROACH to analyze the diameter distribution in vascular networks (or any network of perfused tubes) from the standpoint of minimization of energy consumption (cost) for maintaining vessels and blood volume and for pumping the blood was introduced about 80 years ago by Murray (22). The combined cost was shown to be minimal if the wall shear stress is uniform in all vessels (“Murray’s law”). Later, Rodbard (36) and Kamiya and co-workers (15, 16) suggested that the observed tendency of vessels to enlarge upon an increase in blood flow could establish and maintain a diameter distribution according to Murray’s law. According to this concept, all vessels possess a uniform set point for wall shear stress (or drag). If the blood flow (Q) changes, wall shear stress (τ) will change in proportion as follows: \( \tau = \frac{32\eta Q}{\pi D^3} \), where \( \eta \) is viscosity and \( D \) is luminal vessel diameter (Fig. 1A). The increase (decrease) in wall shear stress stimulates a response of vessel wall cells, leading to an increase (decrease) of vessel diameter, resulting in a decrease (increase) of shear stress until the respective set point is reached again. Such responses to changes in shear stress are supported by experimental observations (4, 16–18, 40). A significant number of studies have indeed shown that the arterial and, to a somewhat lesser degree, venous vessel tree and a number of other biological fluid transport systems are consistent with the requirements of Murray’s law.

The uniform shear stress concept, based on negative-feedback control, has two major shortcomings, both of which are stated in Rodbard’s comprehensive discussion (36). First, in any vascular arrangement with more than one vessel, including parallel flow pathways, a simple feedback control of shear stress would lead to instability. From the existing parallel pathways, the one with the highest shear stress would grow at the expense of all other pathways (10, 12). These pathways would collapse, leaving a single arteriovenous connection. Second, arteries are usually narrower than corresponding veins. Thus they have a substantially higher shear stress, with a difference of about one order of magnitude (11, 39, 41, 42). The arteriovenous difference in diameter and shear stress is of great functional importance in terms of high arterial flow resistance and low capillary pressures (29, 32).

Besides shear stress, vessel walls are also subjected to circumferential stress generated by blood pressure. Much experimental evidence, including the thickening of vessel walls observed in hypertension, indicates that increased transmural pressure difference leads to an increase in wall thickness and sometimes also in wall mass (19–21). This biological reaction may affect the transmural pressure acting on the vessel only via changes in pressure distribution within the vascular network. However, an increase in wall thickness directly results in a decrease in circumferential stress (σ) as follows: \( \sigma = \frac{PD}{w} \), where \( P \) is transmural pressure and \( w \) is wall thickness. This relation suggested that circumferential stress is controlled at a preset level by a biological feedback mechanism (8, 9) (Fig. 1A).

Similar to the concept of uniform shear stress, the concept of uniform circumferential stress can account for vascular reactions to experimental challenges, in which specific hemodynamic parameters (flow and pressure) were changed and shear stress and circumferential stress were restored to close to their initial values by vascular adaptation. Vascular responses to circumferential stress were also shown to be central for the maturation of capillary microvessels into arterioles (24, 38).

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However, experimental data clearly show that circumferential stress is far from uniform in vascular beds (29, 30, 36). On the contrary, circumferential stress exhibits a strong, positive relation to vessel diameter for arterial and venous vessels (Fig. 2B).

The major function of the vascular system is to meet the metabolic needs of the tissues. Metabolic stimuli are therefore likely to play a role in structural adaptation, in addition to hemodynamic stimuli (1–3). Theoretical arguments (see Appendix A in Ref. 31) show that structural responses to metabolic stimuli are capable of stabilizing parallel flow pathways in networks, avoiding the above-mentioned instability resulting from responses to wall shear stress. Thus separate reactions to shear stress or wall stress as indicated in Fig. 1A are not sufficient for stable adaptation resulting in realistic, functionally adequate vascular networks. The actual situation must be more complex, with vessel diameter and wall thickness varying in response to changes in hemodynamic and metabolic conditions, as indicated schematically in Fig. 1B. The composition and balance of the biological reactions to several stimuli, implied by this scheme, are crucial for the stability and the structural and functional properties of the resulting system. It is difficult to investigate such system properties in direct biological experiments, which are designed to isolate effects to well-defined challenges to avoid ambiguity of the results obtained. Also, the complexity of the system exceeds the level amenable to intuitive interpretation. Theoretical approaches have proved useful in addressing this problem.

THEORETICAL APPROACHES

Mathematical simulations based on theoretical models represent a powerful tool for the analysis of complex biological interactions and their functional implications. To produce meaningful results, such approaches should satisfy several conditions. The individual components of the model should be based on experimental observations, the assumed reaction patterns should be as simple as possible, and results should be validated by comparison with experimental observations. Depending on the degree to which these conditions are met, model simulations can provide several types of information. They can define prerequisites of adaptive systems with respect to the number and characteristics of the individual biological responses involved to achieve stable and realistic results. This may include the prediction of biological reactions that have not been observed experimentally (23, 28). They can also reveal unforeseen consequences of adaptive behavior under normal and pathophysiological conditions and guide further experimental studies. The power of modeling approaches comes from the access to and control of all pertinent parameters, reactions, and interactions in the model. Thus, even in a complex system, the emerging characteristics can, in principle, be traced back rigorously to the assumed biological reaction patterns and physical relations. The strength of individual reactions can be reduced, increased, or eliminated (28, 31, 32). In such mathematical “knock-outs” or “knock-ins,” there are no uncontrolled interactions or compensations, which, to different degrees, are unavoidable in corresponding biological experiments.

We have used a combined experimental and theoretical approach to investigate mechanisms and consequences of continuous structural vascular adaptation (26, 31, 33). The theoretical models include vascular reactions to wall shear stress and circumferential wall stress and also responses to the local metabolic state of the tissue, including information transfer along vessels by conduction (upstream) and convection (downstream) of related signals. In addition, they include interactions between stimuli derived from the hemodynamic and metabolic variables and the elicited structural responses of vessel diameter and wall thickness or wall mass.

Simulations were performed for network structures derived from intravital microscopy of suitable vascular beds, particularly the mesentery. The network data consist of the topological pattern (connection matrix) and the lengths and diameters of the vascular segments (up to 913 for the networks analyzed) in the networks and the flow or pressure in the segments entering or leaving the investigated area (boundary conditions). Vessel flow velocities and hematocrits, which were used to assess the hemodynamics of the network in the observed state, were also measured. A second type of experimental evidence was used in the form of parametric descriptions of rheological properties of blood flowing through microvessels and microvascular bifurcations as measured in vivo. In particular, the apparent blood viscosity as a function of vessel diameter and hematocrit (34) and the distribution of red blood cells and plasma at microvascular bifurcations (33) were considered.

The modeling procedure involves three nested levels of iterative computational procedures. At the innermost level, the
volume flow rate in each vessel segment and the pressure at each branch point were calculated by iteratively solving a system of linear equations for prescribed values of the diameter, length, and apparent viscosity of blood in each segment. At the next level (“rheological analysis”), hematocrit and viscosity in each segment were calculated using the parametric rheological laws. Segment flows were then recalculated. These procedures were repeated until parameters achieved stable values. The resulting distributions of pressure and wall stress, blood flow, and shear stress, as well as $P_{O_2}$, were then used to estimate a net signal for change of diameter and wall mass in each segment. After vascular diameter and wall mass were updated, calculations of the two inner loops were repeated. This procedure was repeated iteratively until vascular structure and the other hemodynamic and functional parameters approached equilibrium values. Unknown parameters in the rules used to update diameter and wall mass were estimated and optimized by minimizing the overall deviation of predicted from measured values of hematocrit and flow velocity in all vessel segments.

The estimation of changes in diameter and wall mass in each segment relies on assumptions regarding adaptive vascular reactions to local stimuli. In the initial version of the model (31), only changes in luminal diameter were simulated. The hemodynamic stimuli were expressed in terms of the local wall shear stress and the intravascular pressure. Structural increases in diameter were assumed to be stimulated by increases in local wall shear stress or decreases in intravascular pressure. The local metabolic stimulus was expressed as a function of vessel flow rate on the basis of the assumption that a metabolic signal is generated when blood flow drops and surrounding tissue is poorly supplied with $O_2$ or other metabolites. The inclusion of such a metabolic signal was found to lead to the generation of stable network structures, including multiple parallel flow pathways, as expected on the basis of the theoretical arguments (see above). However, the resulting network structures, based only on these three stimuli, were unrealistic, in that short arteriovenous pathways (shunts) received high flows, whereas long pathways were underperfused relative to observed hemodynamic parameters. To avoid such behavior, it was necessary

Fig. 2. Functionally relevant relations between hemodynamic and morphological parameters in vascular networks as obtained by hemodynamic modeling of blood flow through microvascular networks in rat mesentery on the basis of measured vessel diameters [A (adapted from Ref. 29)] or compiled from published experimental observations for a variety of experimental systems [B (adapted from Ref. 27)]. A: shear stress decreases by a factor of $10$ as pressure declines from arterial to venous levels. Arterial and venous shear stress levels for humans are $1$ order of magnitude lower than those for small rodents, indicating different set points or sensitivities for vascular responses to shear stress. B: linear relation between logarithm of circumferential wall stress and logarithm of vessel diameter; $r^2$ for linear regression to all data points is 0.85. Separate regressions to arterial and venous data do not differ significantly.

Fig. 3. Comparison of diameter values obtained after simulated adaptation ($D_{sim}$) with those measured during intravital microscopy ($D_{meas}$). Data are shown for a mesenteric network with 913 vessel segments. Parameters of linear regression line to all data points are as follows: $D_{sim} = 1.02D_{meas} + 0.50$. Art, artery; Cap, capillary; Ven, vein.
to assume, in addition, the existence of mechanisms for the transmission of stimuli from distal to proximal vessels along flow pathways. Information transfer in the upstream direction was postulated to occur by conducted responses along vessel walls. The role of conducted responses in acute regulation of blood flow had been considered for many years (6, 37), but their role in long-term structural adaptation was first suggested on the basis of this theoretical modeling study.

A number of other theoretical studies have yielded insights into various aspects of structural adaptation in vascular networks. Price and Skalak (25) considered the role of hemodynamic forces in the remodeling of capillaries to arcade arterioles. Their results supported the hypothesis that this process is stimulated by elevated circumferential wall stress. Quick et al. (35) showed how structural adaptation of small conductance vessels can restore perfusion in the case of arterial hypotension. Pries et al. (26) modified the model such that the metabolic signal was estimated from local PO2 levels based on an analysis of O2 transport within the network. This study explicitly showed the importance of the metabolic signal in ensuring adequate tissue oxygenation. Decreasing the strength of this signal resulted in increased O2 deficit but decreased viscous energy dissipation in the network (for a fixed total blood volume). This result emphasizes that adequate functional behavior necessitates departures from the “optimal” behavior as predicted by Murray’s law. The role of structural adaptation in the development of increased peripheral resistance in hypertension was considered by Pries et al. (27). In the models cited above, changes in diameter were simulated, but changes in wall thickness were not explicitly considered. Recently, Jacobsen et al. (13) developed a theory for simultaneous changes in wall thickness and luminal diameter. In their model, the stimulus for changes in wall thickness was based on an assumed empirical dependence of the ratio of wall thickness to luminal diameter on intravascular pressure.

A possible deficiency of the models discussed above is that structural responses are assumed to depend on intravascular pressure, whereas the dominant stress in the wall resulting from intravascular pressure (and, hence, the likely stimulus for changes in wall thickness or mass) is the circumferential stress. Using a scheme in which diameter and wall thickness vary in response to changes in shear stress, circumferential stress, and PO2, we recently extended our previous models to include changes in wall thickness. All the interactions and effects implied by Fig. 1B are explicitly represented in the equations of the model, which was used to simulate adaptation in mesenteric networks. As shown in Fig. 3, there is a strong, linear relation between the original, measured vessel diameters and those obtained after simulated adaptation according to this model. This result is obtained whether the adaptation was started with the original vessel diameters or a uniform value for all segments. The residual discrepancies between measured

![Fig. 4. Structural adaptation of venous vessel segments grafted to an arterial position (top, A–C) and interpretation based on theoretical models (bottom). Left: shear stress at the venous position is low because of a strong metabolic signal based on local PO2 and downstream convection of signal substances produced in the capillary bed. After the vessel is grafted to the arterial position, shear stress initially increases only slightly as a result of passive distension of the vessel (with the assumption that volume flow is increased relative to the original location). However, adaptation to the reduced metabolic signal leads to a strong decrease in luminal diameter, establishing a high, arterial shear stress level. Right: after grafting, circumferential wall stress is high because of high transmural pressure and vascular distension. Structural adaptation to local signals leads to an increase in wall thickness and a normalization of circumferential wall stress.](image-url)
and predicted vessel diameters may result from measurement errors, conditions not considered in the model (e.g., spatial arrangement of vessels or local variation of tissue metabolic demand), biological heterogeneity in adaptive responses between vessel segments, or systematic deficiencies in the assumed adaptation rules.

DISCUSSION

The vascular system consists of an extremely large number of segments. The structural properties of each segment, including diameter and wall thickness, have to be adjusted according to the position of the segment in the network and the functional needs of the surrounding tissue. Furthermore, each segment must possess a high degree of plasticity, allowing continuous vascular adaptation to changing local conditions. Evidently, the structure of each segment cannot be individually prescribed by genetic information but must emerge from the governing physical relations and biological reactions. These reactions, involving cellular sensing mechanisms, signal transduction, regulation of protein function and gene expression, and other processes, must lead to overall behavior that is stable and responsive to changing tissue needs. The theoretical models described here provide a framework for understanding how this can be achieved.

Consistent with the above-mentioned concepts, a basic assumption of the theoretical models described here is that a generic set of adaptive responses or rules governs the behavior of all vessels in the networks considered. Although this set of responses was derived using data from the mesentery, it seems to represent a minimal selection to avoid degeneration (e.g., arteriovenous shunting or loss of parallel flow pathways) of microvascular networks in general. It is, however, very likely that the relative strength of vascular reactions to individual stimuli varies between organ beds, and additional factors must be taken into account.

According to the assumptions that were made, the different structures of arterioles, capillaries, and venules are the result of the different hemodynamic and metabolic conditions to which they are exposed. This assumption may also apply to the adaptation of larger vessels. Figure 4 schematically shows the responses of a vein grafted to an arterial position, as in cardiac bypass surgery. In the original position (Fig. 4A), shear rate is on a low, venous level. Circumferential wall stress corresponds to vessel diameter, because transmural pressure difference and wall thickness are low. After transposition (Fig. 4B), the transmural pressure is increased by a factor of ~10, leading to a passive distension of the vessel. Both effects combine to produce a very substantial increase in circumferential wall stress, which elicits vascular remodeling and an increase in wall mass (5, 7, 14). Consequently, vessel wall thickness is increased and luminal diameter is reduced (Fig. 4C). These changes bring the vessel back on the curves describing the relation of wall shear stress to pressure and the relation of wall stress to diameter. The final wall stress level is close to the initial one according to the limited change in vessel diameter. On the other hand, shear stress is increased to arterial levels consistent with the increased pressure. Thus the observed reactions cannot be explained simply by using the concepts of uniform shear stress or uniform wall stress. Further development of theoretical models along the lines described in this review can be expected to yield additional insights into this and other aspects of structural control of blood vessels that are of great biological and clinical significance.

REFERENCES


