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Microcirculatory Network Structures and Models

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Abstract—Terminal vascular beds exhibit a high degree of heterogeneity. Pertinent parameters are nonlinearly related, and their distributions are not independent. The classical ''typical vessel'' approach using averaged values for different vessel classes may not lead to a correct understanding of physiology and pathophysiology of terminal vascular beds. Such problems can be avoided by studying microcirculatory functions at the network level using a combination of experiments and theoretical models. In this approach, distributions and relationships of pertinent parameters are measured *in vivo*, leading to the development of comprehensive databases. Such databases can be analyzed and complemented by suitable mathematical models, permitting estimation of parameters that are difficult to measure, and critical assessment of quantitative theories and hypotheses for microvascular function. This collaborative process between experimentally and theoretically oriented investigators may be facilitated in the future by the development of web-based repositories of experimental data and theoretical models.
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HETEROGENEITY, NONLINEARITY, AND INTERACTIONS

Heterogeneity represents an inherent and functionally significant property of microvascular networks. Morphological, topological, hemodynamic, and functional parameters show obvious heterogeneity[1,2,5,6,19,27,30,35,39,47] with coefficients of variation (CV=standard deviation/mean) ranging from ~0.3 up to ~2 (Table 1). Some degree of heterogeneity in the topology and morphology of microvascular networks is inevitable, given the functional requirements satisfied by terminal vascular beds. They must supply regions at varying distances from the major feeding and draining vessels, implying heterogeneity of pathway length. In addition, network structures must continually adapt during growth and upon changes of functional demands. The capacity for adaptation is inconsistent with maintenance of a strictly symmetric architecture, since local addition or removal of individual segments would result in loss of symmetry.

Structural network heterogeneity results in heterogeneity of network hemodynamics. As an example, the resistances to flow along different pathways through a network may be considered. The variation of segment length and diameter results in differences in flow resistance between alternative pathways. Heterogeneity of topological network structure implies that different pathways consist of varying numbers of vessel segments. This is an additional source for variations in pathway flow resistance which may increase or compensate the variations due to heterogeneous geometry.

This heterogeneity represents a fundamental problem when the ''typical vessel'' approach is used to analyze microvascular phenomena. In this approach, average qualities for a given class of vessels are derived from experimental studies. The properties of such typical vessels and their interaction with the surrounding tissue can then be analyzed using simplified models. The most prominent example is the Krogh tissue cylinder,[20] a model which proved to be very successful and popular among generations of physiologists and their students. The behavior of larger entities (vascular beds feeding given tissue regions) are then derived by arranging the necessary number of vessels of a given class in parallel and series coupling them with vessels of other classes, as done by Fick[9] as early as 1888 in an analysis of the pressure distribution in terminal vascular beds.

In the typical vessel approach, the problem of heterogeneity is dealt with by using averaged values of necessary parameters. However, this assumes that the relations between the pertinent parameters are linear and the distributions of these parameters are not correlated. Many significant nonlinearities are found in the relations between microvascular parameters (e.g., between vessel diameter and volume flow or between volume flow and diffusive exchange). In addition, relevant parameters are significantly correlated.[28,30,42] Therefore, results of simple typical vessel approaches have to be interpreted with caution. An alternative is the combination of experimental techniques designed to obtain comprehensive

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TABLE 1. Heterogeneity of topological, morphological, and hemodynamic parameters for 1003 capillaries in seven microvascular networks of the rat mesentery.

Parameter	AVG	CV
Generation number	11.9	0.37
Diameter (μm)	8.72	0.28
Length (μm)	424	0.65
Hematocrit (H_T)	0.23	0.60
Velocity (mm/s)	0.85	0.99
Volume flow (nl/min)	3.11	1.76
RBC flow (nl/min)	1.15	1.92
Shear rate (diam/s)	103	1.62
Pressure (mmHg)	28.3	0.33

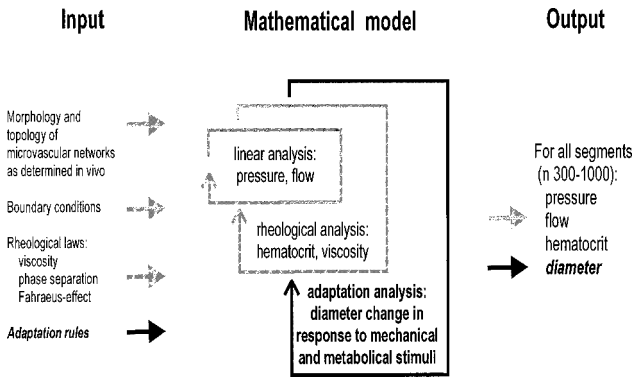

FIGURE 1. Schematic representation of the model for simulation of hemodynamics (gray) and vascular adaptation (black) in microvascular networks. Hemodynamics: the model simulation is based on the experimentally determined data on the angioarchitecture and boundary conditions (flow, hematocrit) in microvascular networks of the rat mesentery. In addition, parametric descriptions of the pertinent rheological relations (rheological laws) derived from experimental measurements in the same tissue were used. Recursive algorithms generate values for the hemodynamic parameters for all vessel segments. Adaptation: These data could be used to simulate structural changes of vessel diameter in response to vessels' hemodynamic and metabolic status according to a given set of adaptation rules.

samples of pertinent parameters for vascular networks with mathematical simulations to represent and model their complex interactions, i.e., a network/simulation approach.

NETWORK/SIMULATION APPROACH

Various models have been developed to analyze functional properties of microvascular networks.[7,8,11,16,31,33,36,45] Their validity depends on the size and precision of the experimental databases employed and on the correctness of the parametric descriptions of elementary phenomena used for the simulation. The development of simulation techniques must therefore be paralleled by the development of experimental techniques and databases.

In the present study, a simulation model (Fig. 1) described and validated earlier[33] was used to analyze the principles underlying the design and adaptation of terminal vascular beds. The model uses databases of network structures that have been established by intravital microscopy of the rat mesentery: Vascular networks with an area between 25 and 80 mm^2 were scanned. Photomontages and video recordings of the networks were then used to determine network topological structure (connection matrix) and the length, diameter, and in some networks, flow velocity of all vessel segments. The number of vessel segments per network ranged between about 300 and 900. In addition, the simulations are based on parametric descriptions of three rheological phenomena derived from *in vivo* measurements: (1) The dynamic reduction of hematocrit in blood flowing through narrow vessels (Fåhraeus effect); (2) the nonproportional distribution of red cells and plasma at arteriolar branch points (phase separation effect), (3) effective blood viscosity as a function of vessel diameter and hematocrit (Fåhraeus–Lindqvist effect).

Using an iterative process, the simulation estimates hemodynamic parameters (hematocrit, flow rate, pressure) for all vessel segments in the microvascular network. Some of these parameters, especially intravascular pressure, cannot be measured for a large number of vessels without interfering with the functional state of the network. Figure 2 shows the relationship between wall shear stress and intravascular pressure in arterioles, capillaries, and venules of mesenteric microvascular networks, along with literature data for larger arterioles/arteries and venules/veins. Literature data on shear stress for larger vessels exhibit substantial variability. However, average wall shear stress levels in larger arteries and veins agree with extrapolations of the present data, which show all three types of segments to exhibit an essentially identical variation of wall shear stress with pressure. A monotonic transition from high to low shear stress is seen as intravascular pressure falls from about 50 to 15 mmHg. From these data, a pressure-shear hypothesis with respect to vascular adaptation was derived:[29] Vascular beds grow and adapt in response to hemodynamic conditions, so as to maintain local wall shear stress at a level which depends on local intravascular pressure.

In contrast to Murray's classical minimum-cost concept,[25] the pressure-shear hypothesis provides an explanation for the physiologically vital arteriovenous asymmetry of vascular beds with low capillary pressures. According to the hypothesis, vascular diameters adjust so as to produce a decrease in wall shear stress along arteriovenous pathways, paralleling the fundamental decrease in pressure. Consequently, vessel diameters are smaller and the pressure drop is larger on the arterial compared to the venous side.[4,48] This is reflected by

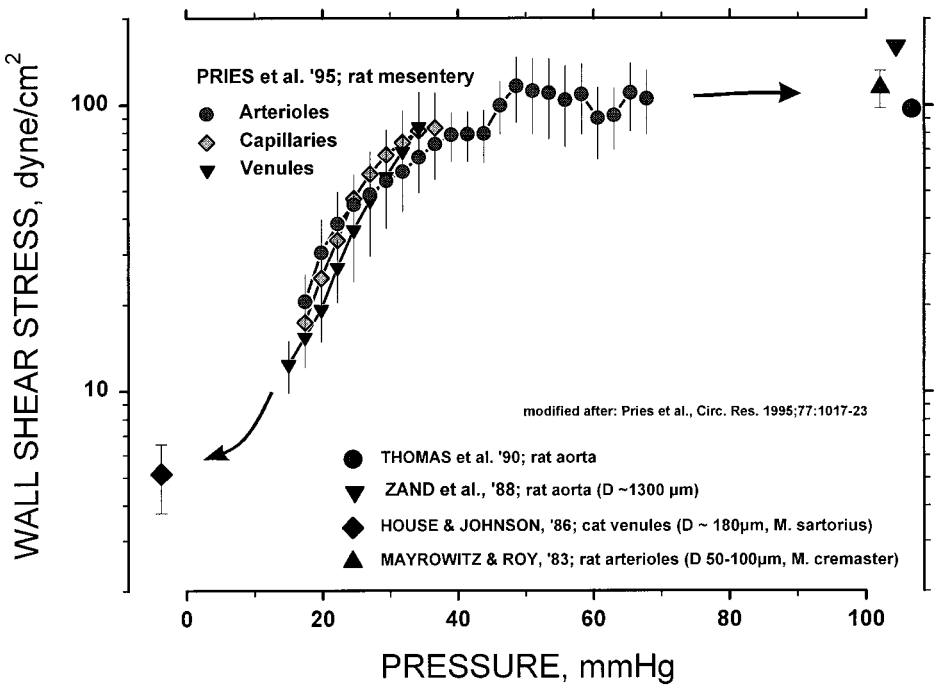

FIGURE 2. Wall shear stress in rat mesenteric arterioles, capillaries, and venules as a function of intravascular pressure. Data for vessel segments of six networks are given for arterioles (n=802), capillaries (n=745), and venules (n=1019). In addition, wall shear stress values for larger arterioles/venules and arteries/veins calculated from literature reports (Refs. 14, 23, 40, and 46) are shown.

microcirculatory pressure profiles,[18,26,34] which demonstrate that about 70% of the pressure drop are located in arterioles with diameters below 100 μm. This is true even in tissues with low or absent arterial vessel tone (as is the case for the rat mesentery), indicating that the pressure profile is dominated by structural features of the vessel networks.

VASCULAR ADAPTATION

Structural responses of vessels to the mechanical forces exerted by flowing blood, i.e., transmural pressure and shear stress at the endothelial surface[3,15,17,21,22,24,38,41,43,44] have been demonstrated in a large number of studies. Mathematical analyses[13,15] have demonstrated that adaptation of vascular segments only in response to local shear stress and pressure lead to unstable and unrealistic network properties. Therefore, the mathematical simulation of microvascular hemodynamics had to be extended to include adaptive responses to other stimuli, according to a defined set of adaptation rules (Fig. 1).[31] These adaptation rules included the known reactions to increased flow (increase of vessel diameter) and to increased pressure (decreased luminal vessel diameter). In addition, a response to the local metabolic state of the tissue surrounding a vessel (derived from blood flow) was included. This response was needed to prevent the collapse of a network to a single arteriovenous pathway (Fig. 3). The final prerequisite was a transfer of information to the upstream feeding vessels on the arteriolar side and the downstream draining vessels on the venular side to prevent the generation of proximal shunts and underperfusion of the more distal nutritive capillaries. It seems likely that conduction of electrical signals along the vessel walls[37] may play a role in this information transfer.

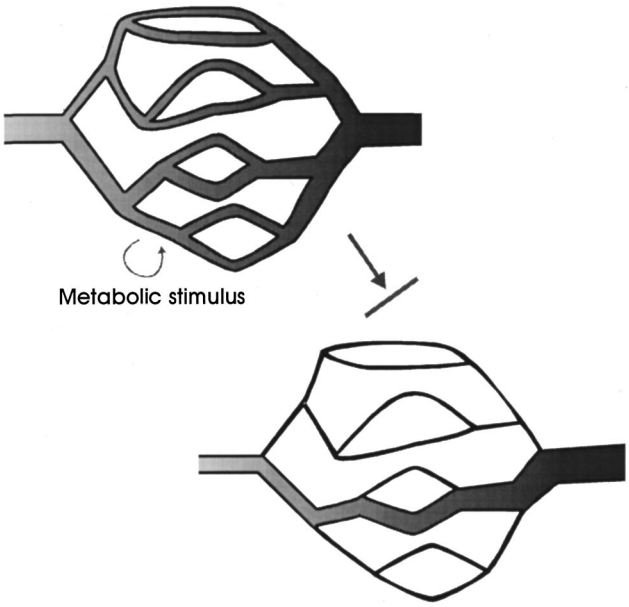

FIGURE 3. Local metabolic stimulus, reflecting a supply/demand mismatch of the tissue surrounding a vessel segment, prevents the collapse of a vascular network into a single arteriovenous pathway (modified after Ref. 31).

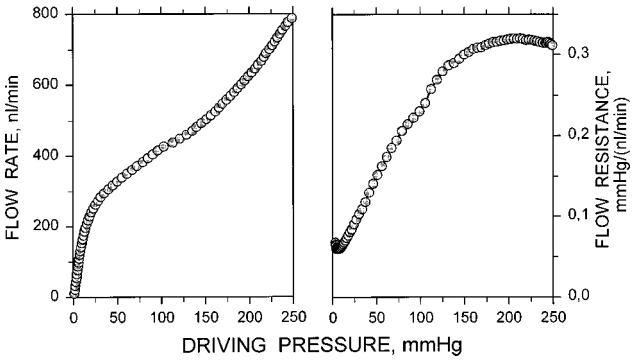

FIGURE 4. Flow rate through a microvascular network in the rat mesentery (left-hand side) and flow resistance (right-hand side) as functions of driving pressure. Results were obtained with a model simulation of blood flow and vascular adaptation according to Fig. 1. Structural autoregulation, i.e., a less than proportional increase of flow rate (due to an increase in flow resistance) with increasing driving pressure is seen for pressures ranging from about 10 to 120 mmHg.

The previously described combination of adaptive stimuli represented a minimal set needed to achieve stable and realistic network properties, in the sense that the simulated process of vascular diameter adaptation led to final distributions of vessel diameters and also of flow rates and pressures, close to the original values. Based on this validation, the model was used to predict the adaptive responses to changes of the driving pressure across the network (Fig. 4). The adaptive vascular responses in the microvascular network lead to a more than fivefold increase in flow resistance with increasing driving pressure. This is a reaction similar to the acute autoregulatory response of vascular beds such as kidney and brain, and was thus called structural autoregulation.[10,12] The model simulations[32] demonstrated that structural autoregulation is linked closely to the pressure dependence of vascular responses. As stated in the discussion of the pressure-shear hypothesis (see Fig. 2), this dependence is also crucial for the arteriovenous asymmetry of vascular beds and a low capillary pressure. Thus, the results of the model simulations suggest that structural autoregulation is a fundamental property of vascular beds that exhibit arteriovenous asymmetry.

FUTURE DEVELOPMENTS

The study of microcirculatory networks is an area where reductionist experimental approaches alone do not lead to an adequate understanding of the physiological behavior. The physical and biological interactions involved are complex and nonlinear, and must be analyzed with the help of mathematical models. Furthermore, the mathematical modeling has to be closely related to the actual situation *in vivo* and to the pertinent biological and physical mechanisms, and the model results should be validated by experiments. These seemingly simple requirements dictate changes in the approaches taken by ''experimentalists'' and ''modelers'' to their work, as well as increased cooperation between them.

In order to provide an appropriate basis for mathematical analyses, experimental data should ideally be comprehensive, consistent, and valid for the *in vivo* situation. To obtain a parametric description of a given mechanism, the relation between pertinent dependent and independent variables must be known over the range of possible values (in the model or in physiological or pathological states). While such data are routinely reported in some areas, e.g., electrophysiology of membrane channels (conductance versus potential), they are very sparse in many other areas, e.g., effects of shear stress on vascular tone in microvessels of different sizes. Many studies report averages and distributions for individual parameters (e.g., arteriolar diameter in a given preparation). However, to be useful as a basis for realistic mathematical models, data should be included on the relation between several pertinent parameters (e.g., vessel diameter, length, topological position, hemodynamic characteristics). It is perhaps ironic that the developments of molecular techniques that have permitted the accumulation of comprehensive data on the genome have also led to increased emphasis on semiquantitative approaches and thinking in the physiological sciences.

In developing model approaches, caution is required in using *ad hoc* assumptions or untested hypotheses to make up for a lack of experimental data. While this is unavoidable to some extent in any simulation, if not restricted to a minimum it may lead to unrealistic model predictions and reduce the confidence of the scientific community in the modeling approach. Theoretical models that are firmly based on comprehensive experimental databases can provide a means to predict parameters that cannot be readily measured. Perhaps more importantly, they can provide critical, quantitative tests of theories regarding microvascular network function, and can suggest new hypotheses that can be tested by refined experimental approaches.

Thus, there is a need for experimentalists and modelers to work together more closely in developing the experimental databases and the corresponding mathematical simulations required to understand the functioning of microcirculatory networks. Such collaborations may be facilitated by the future development of the Microcirculation Physiome, part of the ''Physiome'' Project, as a medium for communicating both experimental data and theoretical approaches among investigators in this area.

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REFERENCES

[1] Bassingthwaighte, J. B. Physiological heterogeneity: Fractals link determinism and randomness in structures and functions. *NIPS* 3:5–10, 1988.
[2] Bassingthwaighte, J. B., R. B. King, and S. A. Roger. Fractal nature of regional myocardial blood flow heterogeneity. *Circ. Res.* 65:578–590, 1989.
[3] Benoit, J. N., and D. N. Granger. Intestinal microvascular adaptation to chronic portal hypertension in the rat. *Gastroenterology* 94:471–476, 1988.
[4] DeLano, F. A., G. W. Schmid-Schönbein, T. C. Skalak, and B. W. Zweifach. Penetration of the systemic blood pressure into the microvasculature of rat skeletal muscle. *Microvasc. Res.* 41::92–110, 1991.
[5] Duling, B. R. Is red cell flow heterogeneity a critical variable in the regulation and limitation of oxygen transport to tissue? *Adv. Exp. Med. Biol.* 361:237–247, 1994.
[6] Duling, B. R., and D. H. Damon. An examination of the measurement of flow heterogeneity in striated muscle. *Circ. Res.* 60:1–13, 1987.
[7] Fenton, B. M., D. W. Wilson, and G. R. Cokelet. Analysis of the effects of measured white blood cell entrance times on hemodynamics in a computer model of a microvascular bed. *Pflügers Arch.* 403:396–401, 1985.
[8] Fenton, B. M., and B. W. Zweifach. Microcirculatory model relating geometrical variation to changes in pressure and flow rate. *Ann. Biomed. Eng.* 9:303–321, 1981.
[9] Fick, A. Über den druck in den blutkapillaren. *Pflügers Arch.* 42:482–488, 1888.
[10] Folkow, B. Structural autoregulation. The local adaptation of vascular beds to chronic changes in pressure. In: *Development of the Vascular System*, London: Pitman, 1983, pp. 56–79.
[11] Furman, M. B., and W. L. Olbricht. Unsteady cell distributions in capillary networks. *Biotechnol. Prog.* 1:26–32, 1985.
[12] Göthberg, G., and B. Folkow. Structural autoregulation of blood flow and GFR in the two renal vascular beds from two-kidney, one-clip renal hypertensive rats, as compared with kidneys from uni-nephrectomized and intact normotensive rats. *Acta Physiol. Scand.* 118:141–148, 1983.
[13] Hacking, W. J. G., E. VanBavel, and J. A. E. Spaan. Shear stress is not sufficient to control growth of vascular networks: A model study. *Am. J. Physiol.* 270:H364–H375, 1996.
[14] House, S. D., and P. C. Johnson. Diameter and blood flow of skeletal muscle venules during local flow regulation. *Am. J. Physiol.* 250:H828–H837, 1986.
[15] Hudetz, A. G., and M. F. Kiani. In: Oxygen Transport to Tissue XIII, edited by T. K. Goldstick, M. McCabe, and D. J. Maguire. New York: Plenum, 1992, pp. 31–39.
[16] Hudetz, A. G., J. G. Spaulding, and M. F. Kiani. Computer simulation of cerebral microhemodynamics. *Adv. Exp. Med. Biol.* 248:293–304, 1989.
[17] Hudlicka, O. Mechanical factors involved in the growth of the heart and its blood vessels. *Cell. Mol. Biol. Res.* 40:143–152, 1994.
[18] Joyner, W. L., and M. J. Davis. Pressure profile along the microvascular network and its control. *Fed. Proc.* 46:266–269, 1987.
[19] King, R. B., J. B. Bassingthwaighte, J. R. S. Hales, and L. B. Rowell. Stability of heterogeneity of myocardial blood flow in normal awake baboons. *Circ. Res.* 57:285–295, 1985.
[20] Krogh, A. The supply of oxygen to the tissues and the regulation of the capillary circulation. *J. Physiol. (London)* 52:457–474, 1919.
[21] Kuo, L., W. M. Chilian, and M. J. Davis. Interaction of pressure- and flow-induced responses in porcine coronary resistance vessels. *Am. J. Physiol.* 261:H1706–H1715, 1991.
[22] Langille, B. L., and M. P. Bendeck. Arterial responses to compromised blood flow. *Toxicol. Pathol.* 18:618–622, 1990.
[23] Mayrovitz, H. N., and J. Roy. Microvascular blood flow: evidence indicating a cubic dependence on arteriolar diameter. *Am. J. Physiol.* 245:H1031–H1038, 1983.
[24] Mills, I., J. T. Fallon, D. Wrenn, H. Sasken, W. Gray, J. Bier, D. Levine, S. Berman, M. Gilson, and H. Gewirtz. Adaptive responses of coronary circulation and myocardium to chronic reduction in perfusion pressure and flow. *Am. J. Physiol.* 266:H447–H457, 1994.
[25] Murray, C. D. The physiological principle of minimum work. I. The vascular system and the cost of blood volume. *Proc. Natl. Acad. Sci. U.S.A.* 12:207–214, 1926.
[26] Nagasaka, Y., J. Bhattacharya, S. Nanjo, M. A. Gropper, and N. C. Staub. Micropuncture measurement of lung microvascular pressure profile during hypoxia in cats. *Circ. Res.* 54:90–95, 1984.
[27] Popel, A. S. *1979 Biomechanics Symposium, Proceedings of the American Society of Mechanical Engineers*, Applied Mechanics Division, Vol. 32. New York: American Society of Mechanical Engineers, 1979, pp. 83–84.
[28] Pries, A. R., K. Ley, and P. Gaehtgens. Generalization of the Fahraeus principle for microvessel networks. *Am. J. Physiol.* 251:H1324–H1332, 1986.
[29] Pries, A. R., T. W. Secomb, and P. Gaehtgens. Design principles of vascular beds. *Circ. Res.* 77:1017–1023, 1995.
[30] Pries, A. R., T. W. Secomb, and P. Gaehtgens. Structure and hemodynamics of microvascular networks: heterogeneity and correlations. *Am. J. Physiol.* 269:H1713–H1722, 1995.
[31] Pries, A. R., T. W. Secomb, and P. Gaehtgens. Structural adaptation and stability of microvascular networks: theory and simulations. *Am. J. Physiol.* 275:H349–H360, 1998.
[32] Pries, A. R., T. W. Secomb, and P. Gaehtgens. Structural autoregulation of terminal vascular beds: vascular adaptation and development of hypertension. *Hypertension (Dallas)* 33:153–161, 1999.
[33] Pries, A. R., T. W. Secomb, P. Gaehtgens, and J. F. Gross. Blood flow in microvascular networks: Experiments and simulation. *Circ. Res.* 67:826–834, 1990.
[34] Raj, J. U., P. Chen, and L. Navazo. Micropuncture measurement of lung microvascular pressure profile in 3- to 4-week-old rabbits. *Pediatr. Res.* 20:1107–1111, 1986.
[35] Sarelius, I. H. An analysis of microcirculatory flow heterogeneity using measurements of transit time. *Microvasc. Res.* 40:88–98, 1990.
[36] Secomb, T. W., and R. Hsu. Simulation of O_2 transport in skeletal muscle: Diffusive exchange between arterioles and capillaries. *Am. J. Physiol.* 267:H1214–H1221, 1994.
[37] Segal, S. S., and B. R. Duling. Conduction of vasomotor responses in arterioles: A role for cell-to-cell coupling? *Am. J. Physiol.* 256:H838–H845, 1989.
[38] Skalak, T. C., and R. J. Price. The role of mechanical stresses in microvascular remodeling. *Microcirculation (Philadelphia)* 3:143–165, 1996.

[39] Sweeney, T. E., and I. H. Sarelius. Spatial heterogeneity in striated muscle arteriolar tone, cell flow, and capillarity. *Am. J. Physiol.* 259:H124–H136, 1990.
[40] Thomas, G. R., C. E. Walder, C. Thiemermann, and J. R. Vane. Regional vascular resistance and haemodynamics in the spontaneously hypertensive rat: the effects of bradykinin. *J. Cardiovasc. Pharmacol.* 15:211–217, 1990.
[41] Unthank, J. L., J. C. Nixon, H. M. Burkhart, S. W. Fath, and M. C. Dalsing. Early collateral and microvascular adaptations to intestinal artery occlusion in rat. *Am. J. Physiol.* 271:H914–H923, 1996.
[42] Vicaut, E. Statistical estimation of parameters in microcirculation. *Microvasc. Res.* 32:244–247, 1986.
[43] Wang, D. H., and R. L. Prewitt. Microvascular development during normal growth and reduced blood flow: Introduction of a new model. *Am. J. Physiol.* 260:H1966–H1972, 1991.
[44] Wang, D. H., and R. L. Prewitt. Alterations of mature arterioles associated with chronically reduced blood flow. *Am. J. Physiol.* 264:H40–H44, 1993.
[45] Wieringa, P. A., J. A. E. Spaan, H. G. Stassen, and J. D. Laird. Heterogeneous flow distribution in a three dimensional network simulation of the myocardial microcirculation: A hypothesis. *Microcirculation (N.Y.)* 2:195–216, 1982.
[46] Zand, T., J. J. Nunnari, A. H. Hoffman, B. J. Savilonis, B. MacWilliams, G. Majno, and I. Joris. Endothelial adaptations in aortic stenosis. Correlation with flow parameters. *Am. J. Pathol.* 133:407–418, 1988.
[47] Zheng, L., A. S. Golub, and R. N. Pittman. Determination of PO_2 and its heterogeneity in single capillaries. *Am. J. Physiol.* 271:H365–H372, 1996.
[48] Zweifach, B. W., S. Kovalcheck, F. De Lano, and P. Chen. Micropressure-flow relationships in a skeletal muscle of spontaneously hypertensive rats. *Hypertension (Dallas)* 3:601–614, 1981.