NETWORK ANALYSIS OF THE MICROCIRCULATION

by

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ABSTRACT

Network hemodynamic models of the microcirculation were formulated on the basis of a phenomenological relationship between pressure and flow for each individual vessel and specific geometries for capillary vessel connectivity. These relationships were implemented with a computer program developed for this purpose using Guassian Elimination with scaled partial pivoting. The resulting system was then analyzed to determine the flow through each vessel and the pressure at each vessel branch point under control conditions. These resistances were then altered from the control values to an increase or decrease of fifty percent from the control values. These analyses demonstrate (1) the significant variability between capillary vessel flows and pressures depending on the vessel's position in the network and (2) the sensitivity of flow and pressure inindividual vessels to resistance alteration in the other vessels of the system. Furthermore, limitations in the concpet of additivity of the resistances at each level in branching systems is demonstrated. These observarions have important implications with respect to overall understanding of microcirculatory performance and control and with respect to experimental approaches in which flow and pressure parameters of numerous individual vessels are studied without identification of the vessel's relationship to the network in which it lies.

ACKNOWLEDGEMENTS

I wish to express appreciation to my advisor to my adivsor, Dr. William A. Hyman, for his continuous guidance, suggestions, and all the time and insight he put into this research. The knowledge and experience I have gained has been rewarding. I would also like to thank Jim Carollo, Mike Handwerker, and Joseph Ortiz for their help in implementing and "de-bugging" the program. I appreciate the help of Dr. Granger, the Medical Physiology Department, and TEES in obtaining materials for my presentation. I also would like to thank Dr. Mel Friedman for his support and promotion of this program.

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INTRODUCTION

The term "microcirculation" is used to designate blood flow through small vessels. It represents the only place where the body cells have direct access to the blood. A microcirculatory network includes the smallest blood vessels of the circulatory system, in particular, the arterioles, terminal arterioles (or metarterioles), capillaries, postcapillary venules, and venules.(1) It is through a network comprised of these vessels that the basic life process occurs: the exchange of nutrients into, and removal of metabolic wastes from the tissues of the body. Only across the capillary wall, and possibly post capillary venules, can this phenomenon take place.(1)

The microcirculatory bed is that portion of the vascular system which is concerned with the transfer of gases and nutrients and the removal of metabolic waste products and is properly referred to as the "exchange system."(1) The vessels designed to function in the exchange of materials to maintain the life of tissues and cells are considered separately from the vessels of the macrocirculation which are designed for maintaining the delivery of blood to the microcirculation.(1) Although there is no universally accepted nomenclature or list of specific characteristics to use as a guide in defining the vessels of the microcirculation, there are generalizations outlined by Wiedeman (1) to assist in their identification.

The microcirculation begins with arterioles. Branches from arterioles are called terminal arterioles, so named because they terminate in a capillary network. The precapillary sphincter is the portion of the terminal

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This thesis follows the format of the Microvascular Research.

arteriole that constricts or relaxes to monitor blood flow into the capillary network which lies distal to it. It is the final smooth muscle cell that separates arterial and capillary vessels, and affords the ultimate control of blood flow into the capillary circulation. A capillary vessel is a pure endothelial tube lying between distributing arterial vessels and collecting venous vessels. Most capillaries originate from terminal arterioles either singly or as a burst of vascular pathways to form interconnecting networks that ultimately end where two vessels converge to form a postcapillary venule. The convergence of capillary vessels marks the formation of the postcapillary venules which may be described as nonmuscular venous vessels whose diameter is noticably larger than that of the capillaries which lead to them. Each further convergence results in larger diameters, smooth muscle cells reappear, and finally, with the appearance of venous valves, the venules are reached.

The muscular arterial components comprised of the arterioles, metarterioles, and precapillary sphincters are the primary sites of controlled resistance to blood flow by virtue of their ability to change their caliber actively by changing the tension developed in the smooth muscle in the vessel wall.(2) The major function occurring at the level of the capillaries is the exchange of substances between the blood and surrounding tissue. The venules are the return channels which, in addition to playing a possible role in resistance control, also probably serve as volume capacitance vessels of some vascular beds, controlling the volume distribution of blood throughout the body, and may also contribute to setting the level of capillary hydrostatic pressure.(2)

Given this description, it is noted that among the functions with which the microcirculatory components are involved are: 1) blood flow control, 2) transcapillary exchange, and 3) interstitial transport.(2) The caliber of elements in the microcirculation varies in response to a wide variety of stimulations. Such adjustments constitute control of resistance to blood flow and of pressure distribution in the microcirculation. These adjustments are of paramount importance in overall control of peripheral circulation and in blood flow distribution among different organs and tissues.(2) They also influence capillary hydrostatic pressure and fluid exchange processes within the body.(2)

The regulatory features of the microcirculation are keyed to the prime prupose of the entire circulation, to sustain and nourish the body to help maintain homeostasis. Only a small portion of the capillaries in a microciruclatory bed are in series while a much larger proportion is in parallel. The parallel circuits are under control of precapillary sphincters and this regulation becomes a predominant feature during periods of increased tissue metabolic activity. Flow in the series branching predominates during resting conditions. With increased activity, increasing numbers of capillary circuits are brought into active circulation. The volume flow through the microciruclation is adjusted locally by dilation or contraction of the larger muscular arterial vessels, whereas the actual distribution within the network depends on the action of the precapillary sphincters.(3) It is a reasonable assumption that both metabolic demands of the tissue and hemodynamic forces subserving the total organism dictate whether all, some, or only one route would be open at any one time.(1)

The microvasculature exhibits a great diversity of patterns and each major tissue has a unique structural organization. In general, tissues with high metabolic activity have the most numerous side branches. This makes it possible for the basic needs of the tissue to be met by keeping the flow confined to the most direct channels and under increased activity to add as many capillary side branches as are required to meet local needs. (3) It should be recognized that there is a marked difference in the three-dimensional architecture of the micorvascular bed depending on the species, the organ, and the tissue.(4) In general terms, the spread of the microvascular bed is essentially a "monolayer" in the mesentery and the hamster cheek pouch which are organs often subjected to experimental investigation. However the monolayer is not representative of the "three-dimensional" pattern of microvascular beds found in skeletal muscle, lung tissue, or the intestinal wall.(4)

The development of blood vessel abnormalities is one of the primary factors in cardiovascular disease, a leading cause of death in Texas and the nation.(5) These abnormalities can reduce the effectiveness of the functioning of the microcirculation system. For example, narrowing of the microcirculatory vessels penetrating all tissues of the body maintains high blood pressure and long term elevation leads in turn to partial or total blocking of the larger arteries which supply all major organs. Thus heart attacks, strokes, and other clinical manifestations of chronically elevated blood pressure can be traced to early events occurring in the microcirculation.(5) There have been various approaches in the study of the micorcirculation in living tissues. At Texas A&M University, investigators in the Colleges of Medicine, Veterinary Medicine, and Engineering have been working

together in an effort to apply some advanced technologies to peripheral microvascular disorders, with special emphasis on hypertenstion, stroke and diabetes.

BACKGROUND

The distribution of flow and pressure in microvascular networks is determined by many factors, the most important of which are the topological structure of the network, dimensions of the blood vessels, and rheological properties of the blood.(6) Many investigators have acknowledged the heterogeneity in the microcirculation, e.g. (7, 8, 9, 10). Recently careful studies of microvascular morphological and hemodynamic parameters has been conducted. It has been shown that geometrical parameters of microvascular networks such as diameters and lengths of vessels of a given branching order are heterogeneous (e.g., in the skeletal muscle).(7) Studies of capillary velocity distribution also reveal wide populations of values.(8) In addition to differences in blood flow, the hematocrit in small vessels also varies from vessel to vessel.(9) Results obtained with relatively new techniques to measure velocities of red blood cells and hydrodynamic pressure in single microvessels confirms that flow and pressure distributions in the microcirculation are heterogeneous.(10)

Extensive work has been done on the mechanics of blood flow in single blood vessels, especially the capillaries, (6) and a number of attempts have been made to simulate the hemodynamics of flow in microcirculatory vessels. Schmid-Schoenbein and Devendran (11) used the data of Wiedeman (12) on the numbers of vessels, lengths and diameters for the vasuclar beds in the wings of unanesthetized bats, to calculate the intravascular pressure

and shear stress distribution in the microvasculature. The simple model in Figure 1 of a series-parallel vessel arrangement was considered with series connection of different branching order, and parallel connection of the vessels of the same branching order. A characteristic feature of this network is homegeneity of pressure and flow in vessels of the same branching order. Lee and Nellis (13) considered the vascular pattern of mesentery in the form of a two-dimensional lattice with five capillary groups and calculated the mean blood flow in different generations of vessels.

Lipowsky and Zwiefach (14) utilized data on vessel geometry to develop a more comprehensive mathematical model of the mesenteric circulation. As shown in Figure 2, a particular module of the mesentery bounded by paired arterioles and venules was chosen and hemodynamic parameters for each of the vessels were calculated. The vessels in the analytical module were interconnected in the same way as in the tissue. For each node in the network the conservation of mass relationships were written, and Poiseuille's law was used to express the volumetric flow rate through each vascular segment in terms of the pressure difference along the vessel while blood was considered a Newtonian fluid. Computed and in vivo intravascular pressure showed disparity on the arterial side of the capillaries, and fair agreement on the venous side. This was attributed to the effects of precapillary sphincter action and the non-Newtonian behavior of the blood.

Mayrovitz, et al. (15) developed a mathematical model of branching networks and applied it to the bat wing microvasculature (Figure 3). In contrast to the mesentery model of Lipowsky and Zwiefach (14), a topological description without attempting to reproduce exactly the interconnections

of particular vessels was given. Each vessel in the network was represented by a sequence of equal hydrodynamic resistance of the vascular segments with lateral resistance pertaining to daughter branches. Relationships for computation of the entire network hydrodynamic resistance were derived and the scheme was then used to study the sensitivity of the total hydrodynamic resistance to variations of vessel diameters of different branching orders. The results were presented as the ratio of resistance to a control value. The resistance was most sensitive to changes in diameter of the large vessels with control diameters of about 100μm, and showed a decrease in the degree of sensitivity as the branching order increased. The total resistance was practically insensitive to dilation of terminal arterioles, but was sensitive to constriction of these vessels. Mayrovitz et al. (15) also applied their model to calculate the mean flows and pressure in the network which were shown to be in general agreement with experimental data.

A theoretical model of the vascular network of rabbit small intestine shown in Figure 4 was constructed by Levitt, et al.(16) Poiseuille's law was again used to calcualte segemental resistances of the network. Blood pressures in arteries less than 2mm in diameter, as well as the mean capillary pressures obtained were similar to published experimental values. Prasassarakich and Walawender (17) presented a concentric annular flow model. This predicted pressure/flow behavior for a cell-free plasma layer surrounding a continuous core of cells for small tube flow as shown in Figure 5. The results calculated from the model agreed with experimental results obtained under low Reynolds number conditions. The plasma thickness was found to be independent of shear stress, tube diameter, and feed hematocrit.

Mathematical modeling has been proven to be a useful tool in studying various aspects of microcirculatory transport.(6) This research is confined to the analysis of a model of blood pressure and flow distribution in branching microvascular networks. As mentioned in the previous section, experimental approaches have dealt with either an entire network (e.g. (14)) or with individual vessel phenomena (e.g. (6)). When looking at the entire network, experimentalists have typically been concerned with measuring the net blood flow through or pressure drop across a microvascular bed. They are interested in mechanics of the entire network and not particularly with the effect of individual vessels within that network on the overall behavior of the microvascular bed. Another frequently used approach is to study single microvascular vessels independently of one another. In particular, the measurement of blood flow within a single vessel, and the pressure drop occurring across that vessel are attempted in order to generate data to assess values for a "typical" capillary or other microcirculatory vessel. These measurements are extremely difficult to make for the microvascular vessels, and once arrived at, the values for many vessels from the same or varying networks are generally averaged to determine behavior of a certain classification of vessel.

MODEL FORMULATION

The primary focus here is with the process of network interaction. This of course must include as a necessary element the mechanics and hemodynamic parameters governing single vessels, but with the insight that these vessels cannot and do not function as independent structures. Rather each vessel is influenced to some extent, by occurrences in the entire

network in which they are contained. This observation puts into perspective the data obtained from single vessel experiments that is averaged to give typical parameters of particular vessels.

The concept of network interaction was based, initially, on a qualitative investigation into the network structure and comparison to other familiar network behavior. From observing networks in general, the realization that network component behaviors are sensitive to changes in other parts of the network becomes apparent. In large vessels of the body such as the large arteries, the pressure and/or flow in one is independent of the pressure and flow in the other large arteries. This is due to the large size and the relatively few side branches off of the large arteries as compared with the complex microcirculation network geometries. In a microcirculation bed, the pressure and flow of each vessel is somewhat governed by the behavior of the remaining vessels of the network. This interdependency is the result of the varied and numerous interconnections between vessels.

Hemodynamic Model. With this qualitative analysis, an attempt to quantitatively assess network interaction has been devised. The formulation of a network model of the microcirculation requires two basic determinations. One is the hemodynamic relationships to be employed in each branch of the network and the other is the specific geometries which will be studied. A model based on the well-known hemodynamic relationships between pressure and flow has successfully been employed in a number of other studies, e.g. (18). This relationship is:

$$\Delta P = QR \qquad (1)$$

for each vessel, where ΔP is the pressure drop across the vessel, Q is the flow through that vessel, and R, the resistance to flow of the vessel. Since theoretically, both the pressure drop across, and the blood flow through a vessel can be measured, the resistance of the vessel is defined by these two parameters and equation (1). At vessel branches or nodes, the above relationship is combined with the principle of the conservation of mass or:

$$\Sigma Q = 0 \tag{2}$$

where the summation is extended across all the vessels entering or exiting a branch point.

For any individual vessel, the resistance is a function of vessel length, cross section, blood viscosity, and blood pressure. Since the cross section is itself a function of pressure, and active muscular control of the vessel, as well as numerous other events occurring in the body, the resistance is a very complex parameter to predict. For this reason, these factors have not been included in this model. Instead the resistance is assumed constant with respect to all of these variables although it's value can be changed in the analysis as desired.

Computer Program. Applying equations (1) and (2) to a microvascular network such as that shown in Figure 6 produces a system of simultaneous linear algebraic equations. This set of equations can be solved with a mathematical technique known as Gaussian Elimination. Because of the similarity of this analysis to problems in electric circuits a survey of the existing "canned" programs available through the Electrical Engineering Department here at Texas A&M was conducted, to determine if a program of this nature was readily available. The only program related to this type

of computation, called "spice," was considered too complex for this application. Instead, a program developed by Cheney and Kincaid (19) utilizing Gaussian Elimination with scaled partial pivoting was adapted to the needs of this system. This program performs forward elimination and back substitution on a set of linear equations. To increase the accuracy, a "scale" is assigned to each equation to determine the best order in which to proceed to give the most accurate results.

Implementation of this program involves establishing a set of resistance values and the overall pressure drop across the entire network. This information is fed to the program in matrix form. The values are then used to solve for the pressure at each junction and the flow through each branch. The output was also adapted to present the average pressure within each vessel. This program can be used to process any geometry desired, and is a valuable alternative to solving by hand a set of equations generated from a complex network geometry. The development of this program to implement this model represents a major segment of this research.

Geometric Model. The next consideration in an analysis of microcirculatory networks is choosing a network to work with. Rather than choose an arbitrary model envisioned by other theorists, e.g. (11), a portion of the geometry defined by Plyley et al. (20) based on actual observations of the microvasculature in the frog sartorious muscle was employed. (See Figure 7a, b.) This network of eleven nodes and eighteen branches produced a twenty nine by twenty nine matrix. These unknowns were the pressure at each of the eleven nodes, and the flow through each of the eighteen vessels. In addition to nodal pressures, the average pressure through each vessel can be computed. Initially, the resistances of each vessel were set

equal to establish a baseline condition. From here particular values of R (resistance) were manipulated through the network to examine the effect on values of pressure and flow throughout the network, specifically a fifty percent increase and a fifty percent decrease in resistance for each vessel independently, was performed.

RESULTS

Control. The control values for pressure and flow in the branches of the network studied are shown in Figures 8 and 9, respectively. The numbers pertain to the geometry labeled in Figure 7b. Some general observations about these control data can be made. It is noted that the flow through vessel 1 and 18 are equivalent - this must be true for the conservation of mass principle. Note also that flows in pairs of branches that are directly in parallel with one another, e.g. 5 and 6, 9 and 10, or 15 and 16, must be equal when their resistances are equivalent due to the identical pressures at the nodes on each end. Also obvious from the control pressure bar graph is the fact that the pressure progressively decreases from one node to the next through the network, due to the resistance to flow in each vessel. This pressure drop is not uniform from one node to the next, however because of the varying connections made at the nodes. Another point of interest is the wide distribution of flow magnitudes throughout the network which is again, a function of the relative vessel position within the network.

Sensitivity. In order to demonstrate the sensitivity of selected vessels to changes in resistance a bar graph similar to the flow bar graph for the control values is shown in Figure 10. In the left hand portion,

the effects on the flow of vessel 12 are demonstrated with respect to various other resistance changes in the network. In comparison to the control value, a fifty percent decrease in vessel 12's resistance (R_{12}) increased its flow a significant amount. Also increasing the flow of vessel 12 to a more moderate extent was the fifty percent increase in R_4. But a fifty percent increase in R_1 on the other hand, or a fifty percent decrease in R_4 both caused a reduction in flow through vessel 12. The right half of the bar graph shows the sensitivity of vessel 6. An increase in R_5 or a decrease in R_6 prodeces greater than control flow. A decrease in R_{12} or an increase in R_6 reduces flow below the control values. Vessel 6 shows a greater percentage change (and therefore higher sensitivity) when its own values of resistance are changed than that seen in vessel 12 in relation to its own resistance changes with respect to the control values.

Summary of Results. In relation to values obtained from the control case, it is seen that there is wide variability in an individual vessel's flow and average pressure depending on its actual location in the network. Also, due to the geometry of the network, the resistances of sequential vessels are not, in general, linearly additive. In regard to sensitivity of a vessel within a network, as was demonstrated in Figure 10 the flow and pressure in a given vessel is dependent on the resistance of every other vessel in the network and the specific geometry. The nature of this sensitivity may not be intuitively obvious. The flow and pressure in an individual vessel can increase or decrease with increasing resistance in other vessels depending on their relative location. This is also true for decreasing resistance in other vessels. This effect again, is not intuitively obvious until an analysis of the particular network is done.

Autoregulation. Along with these results, some general statements about autoregulation can be deduced from this data: 1) the actual location of a vessel or group of vessels in a network has a marked effect on their ability to autoregulate flow through the entire network, 2) if an individual vessel appears to autoregulate, it may be a result of: a) a reduction in its own resistance, b) a reduction in the resistance of other vessels in the network, or c) an increase in the resistance of other vessels in the network, and 3) since some vessels may be unable to achieve autoregulation under given pressure reductions, there may be recruitment in which after a vessel achieves maximum dilation, other vessels then also dilate.

CONCLUSIONS

This investigation has served to stress the importance of the role each vessel of a network has in affecting other vessels of that network. In microcirculatory beds the flow through each vessel and the pressure in each vessel is a complicated function of the actual network geometry involved. Information on the geometric relationship of a vessel to its network should be included in experimental observations of that individual vessel's hemodynamic behavior whenever possible. Without the knowledge of a vessel's location within a network, observations on that vessel will be difficult to fully interpret without simultaneous observations on other vessels in the network. Finally, averaging results of single vessel studies does not necessarily yield the behavior of an "average" vessel, i.e., there may be no vessel whose behavior is average.

Future Directions. With the implementation of the existing program, many additional areas can be explored. An extended sensitivity analysis

could include multiple simultaneous resistance changes as well as varying magnitudes of resistance change. The possibilities for combinations including these two are virtually infinite. Given that the existing program can be used for any network, it can process more complex networks with greater diversification in branching and interconnections and include multiple inlets and outlets. Whether the networks are from actual experimental observation, or are theoretically envisioned geometries would be the decision of the operator. The significance of the relative location of a vessel within a network, and its sensitivity to other vessels as well as its impact on other vessels could be compared to actual experimental observations to learn about the variables not accounted for in this model. It is important to try to integrate an analytic model with experimental observations to test the validity for its use in predictions.

Of great significance is the inclusion of one of more of the parameters affecting the resistances that were thus far held constant. Incorporation of these factors would enhance the validity in relation to actual occurrences within the microcirculation. Another possibility is simulating autoregulatory activity whereby vessels accomodate for a sudden change in pressure or flow in the network. The extent that each vessel could accomplish autoregulation as well as the actual number of vessels required to participate to achieve normal flow could then be explored.

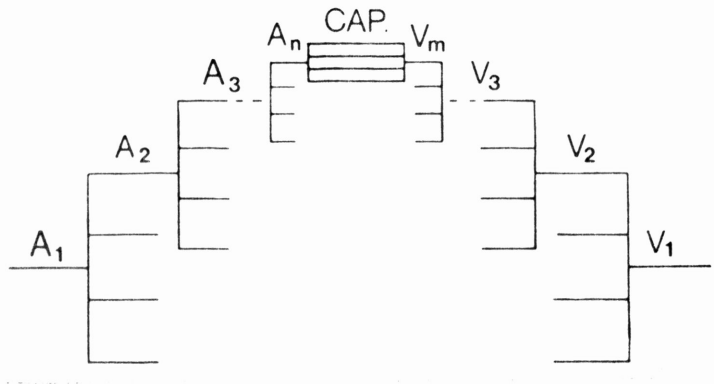


Figure 1. Schematic representation of the series-parallel network model. A = arterioles, CAP. = capillaries, V = venules.
Source: A. S. Popel, Mathematical Modeling of Convective and Diffusive Transport in the Microcirculation, in discussion of Schmid-Schoenbein, and Devendran.

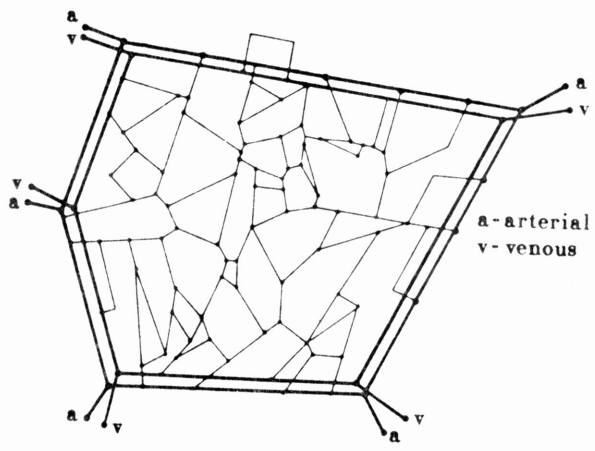


Figure 2. Schematic representation of a typical mesenteric module. Nodes labelled a and v represent boundary nodes for the hydrodynamic computation.
Source: A.S. Popel, Mathematical Modeling of Convective and Diffusive Transport in the Microcirculation, in discussion of Lipowsky and Zweifach.

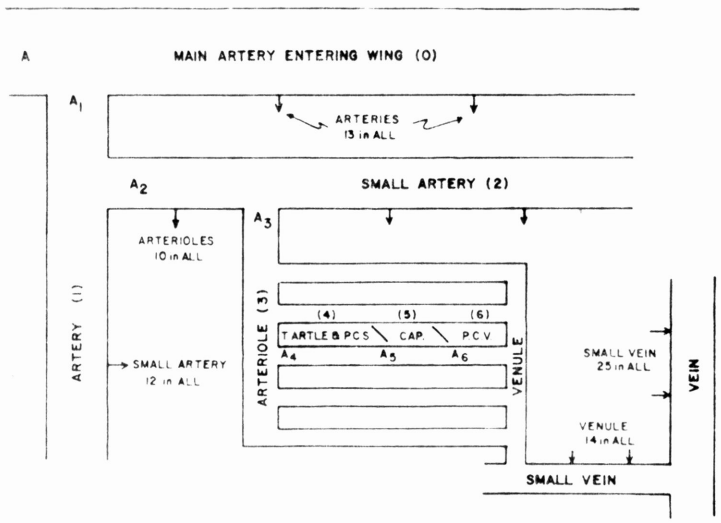


Figure 3. Topological model of the bat wing microcirculatory network. One pathway from main artery to small vein is shown in detail, and the remainder of the branches and vascular pathways are shown in straight arrows. Numbers in parentheses designate the branching order. ARTLE = terminal arteriole, P.C.S. = precapillary sphincter, CAP. = capillary, P.C.V. = postcapillary venule. Source: A.S. Popel, Mathematical Modeling of Convective and Diffusive Transport in the Microcirculation, in discussion of Mayrovitz, et al.

Figure 4. Drawing of aterial network of intramural vasculature of rabbit intestine, with terminal capillary networks indicated by symbols. Drawing was made from a composite photograph of a region injected with silicone latex and cleared in methyl salicylate. Source: Levitt, David G., et al. Model for Mucosal Circulation of Rabbit Small Intestine.

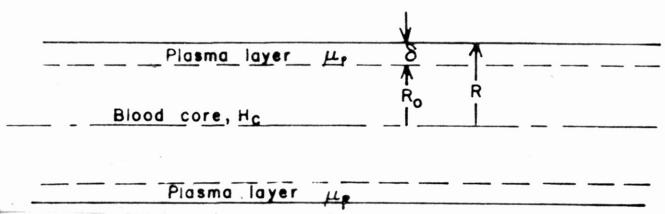
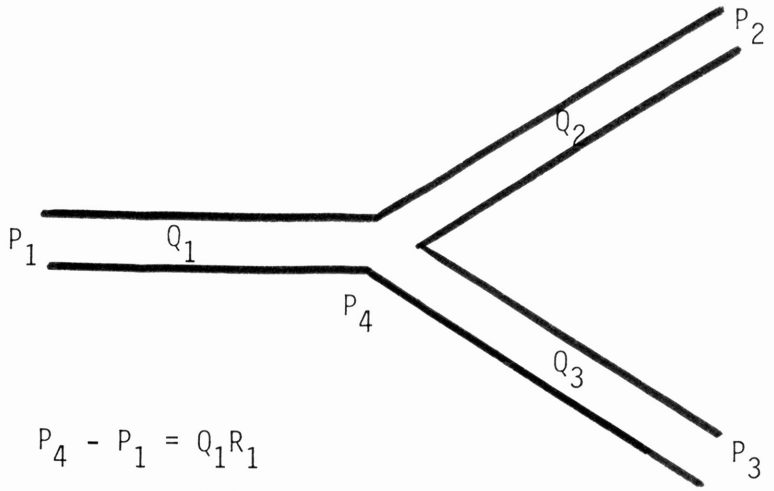


Figure 5. Concentric annular flow model.
Source: Prasassarakich Pattarapan, and Walawender, Walter P. On Application of the Concentric Annular Flow Model to the Flow of Blood in Small-Diameter Tubes.



$$P_4 - P_1 = Q_1R_1$$

$$P_2 - P_4 = Q_2R_2$$

$$P_3 - P_4 = Q_3R_3$$

$$Q_1 - Q_2 - Q_3 = 0$$

Figure 6. System of simultaneous linear algebraic equations produced from the given hemodynamic relationships.

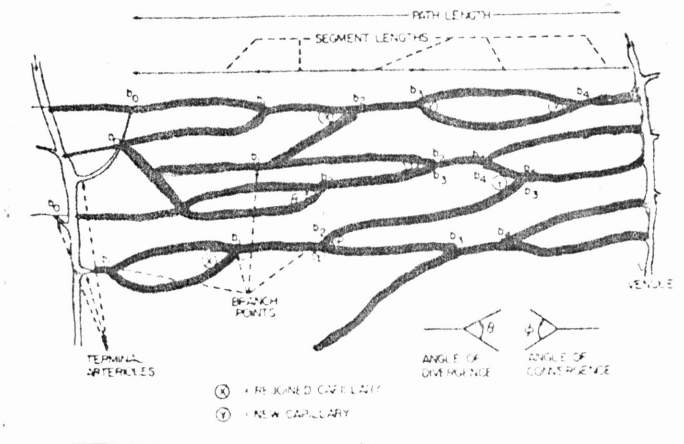


Figure 7a. Schematic representation of the vascular network showing the parameters measured and defining the terminology used in studying the capillary network.
Source: Plyle, et al. Geometry of the Capillary Network in Skeletal Muscle

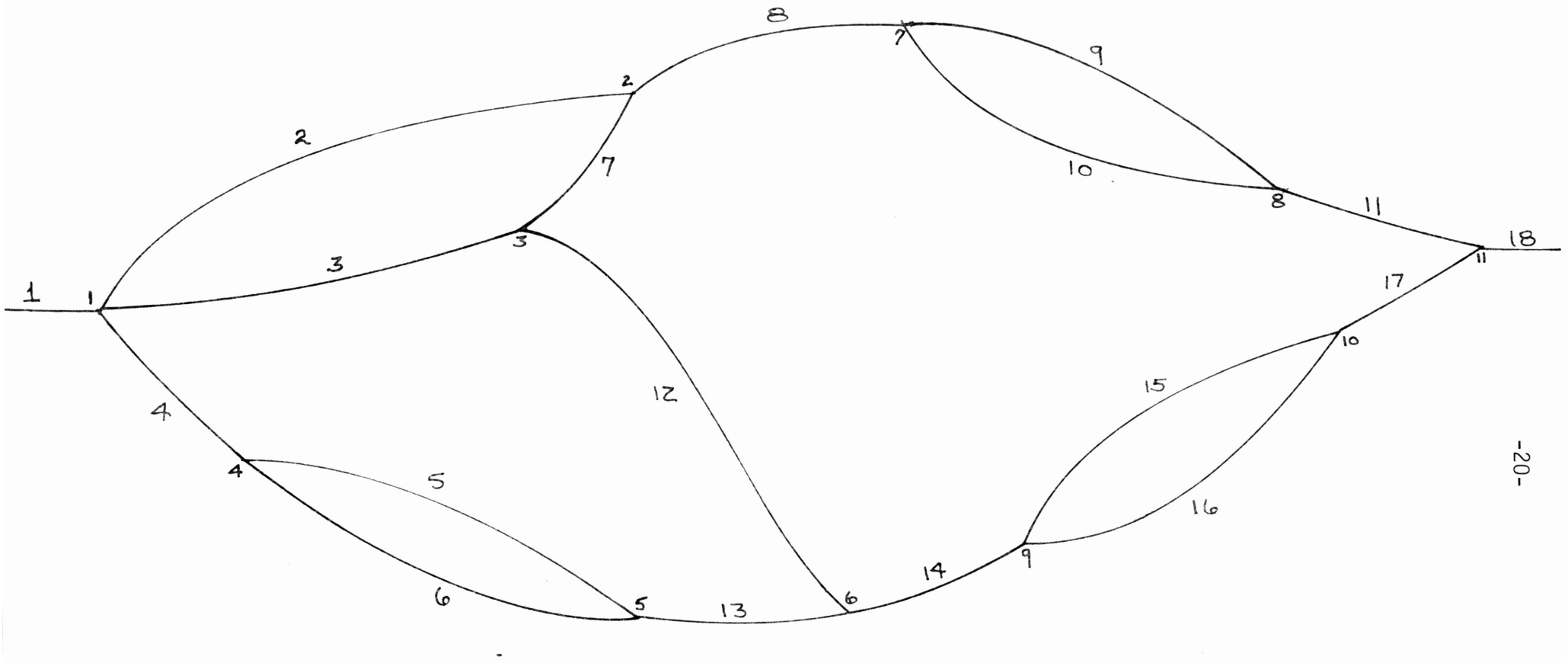


Figure 7b. Actual geometry used in this analysis. Obtained from a portion of Figure 7a from Plyley et al.

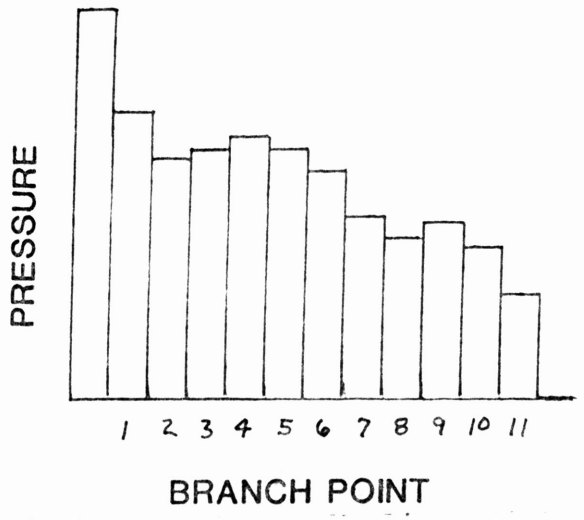


Figure 8. Actual geometry - control pressure values.

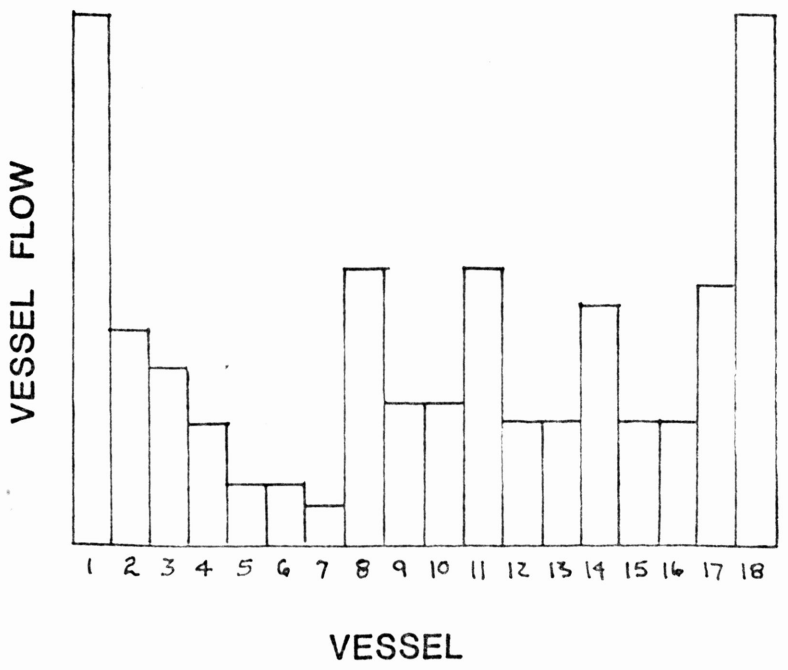


Figure 9. Actual geometry - control flow values.

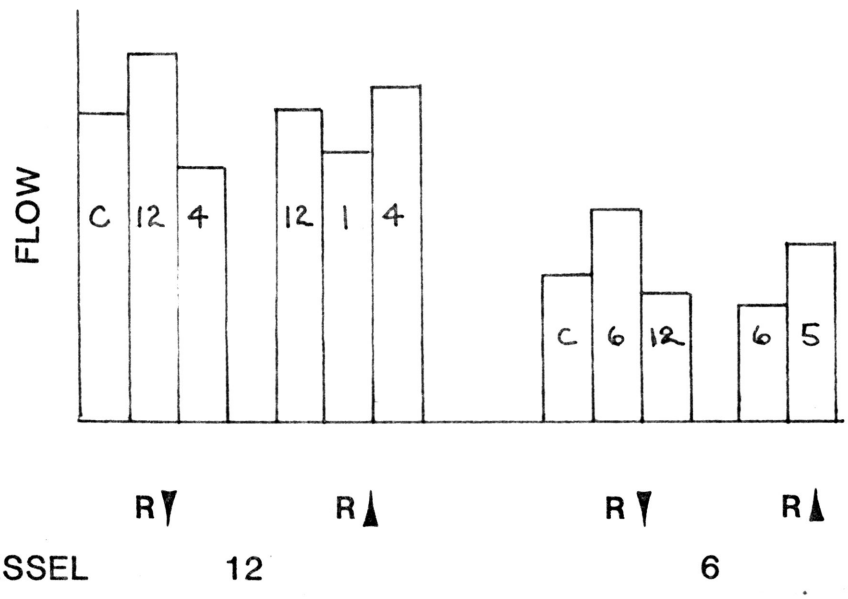


Figure 10. Actual geometry - sensitivity to resistance changes for vessels 12 and 6.

REFERENCES

1. Weideman, Mary P. 1973. Anatomy. The Microcirculation in Clinical Medicine 1-11.

2. Stromberg, D.D., M.D., Ph.D., and Wiederhielm, C.A., Ph.D. Functional Aspects of the Microcirculation. The Microcirculation in Clinical Medicine 33-45.

3. Fung, Y.C., and Zwiefach, B.W. 1971. Microcirculation: Mechanics of Blood Flow in Capillaries. Annual Review of Fluid Mechanics 3: 189-210.

4. Rhodin, Johannes, A. 1973. Ultrastructure of the Microvascular Bed. The Microcirculation in Clinical Medicine 13-31.

5. Hyman, W.A. 1981. A Network Analysis of the Microcirculation. Research proposal.

6. Gross, J.F., and Popel A. (eds.). 1980. Mathematical Modeling of Convective and Diffusive Transport in the Microcirculation. Mathematics of Microcirculation Phenomena 63-88.

7. Gray, S.D. and Renkin, E.M. 1978. Microvascular Supply in Relation to Fiber Metabolic Type in Mixed Skeletal Muscle of Rabbits. Microvascular Research 16: 406-425.

8. Burton, K.S. and Johnson, P.C. 1972. Reactive Hyperemia in Individual Capillaries of Skeletal Muscle. American Journal of Physiology 223: 517-524.

9. Schmid-Schoenbein, G.W., Skalak, R., Usami, S. and Chien, S. 1979. Cell Distribution in Capillary Networks. Microvascular Research in press.

10. Popel, A.S. 1980. A Model of Pressure and Flow Distribution in Branching Networks. Journal of Applied Mechanics 47: 247-253.

11. Schmid-Schoenbein, H. and Devendran, T 1972. Blood Rheology in the Microcirculation. Pflugers Arch. (Suppl.) 336: 84.

12. Wiedeman, M. 1963. Dimensions of Blood Vessels from Distributing Artery to Collecting Vein. Circulation Research 12: 375-378.

13. Lee, J.S., and Nellis. S. 1974. Modeling Study on the Distribution of Flow and Volume in the Microcirculation of Cat Mesentery. Annals of Biomedical Engineering 2: 206-216.

14. Lipowsky, H.H., and Zwiefach, B.W. 1974. Network Analysis of Microcirculation of Cat Mesentery. Microvascular Research 7: 73-83.

15. Mayrovitz, H.N., Wiedeman, M.P., and Noordergraaf, A. 1976. Analyt-

REFERENCES CONTINUED

ical Characterization of Microvascular Resistance Distribution. Bulletin of Mathematical Biology 38: 71-82.

16. Levitt, David G., Sircar, Bithi, Lifson, Nathan, and Lender, Jane E. 1979. Model for Mucosal Circulation of Rabbit Small Intestine. American Journal of Physiology 237: E373-E382.

17. Prasassarakich, Pattarapan, and Walawender, Walter P. 1980. On Application of the Concentric Annular Flow Model to the Flow of Blood in Small-Diameter Tubes. Microvascular Research 20: 165-181.

18. Hyman, W.A. and Brewer, M.A. 1980. The Hemodynamics of Arterial Steal. Journal of Biomechanics 13: 469-475.

19. Cheney, Ward and Kincaid, David. 1980. Numberical Mathematics and Computing 113-128.

20. Plyley, M.J., Sutherland, Gloria J., and Groom, A.C. 1976. Geometry of the Capillary Network in Skeletal Muscle. Microvascular Research 11: 161-173.