

THE MICROCIRCULATION: THEORY AND EXPERIMENT

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PART 4 - CHAPTER 6 AND APPENDIX

CHAPTER SIX... SIGNIFICANCE OF MICROCIRCULATORY INTERACTIONS DEDUCED
FROM EXPERIMENTAL STUDIES AND MODEL PREDICTIONS

I. Introduction

The Microvascular Model results described in the previous chapter included a number of predictions regarding the hemodynamic effects of venomotion. Comparison of these results with experimental data showed that the Model overall pressure transmission properties, dynamic pressures, and control aspects were consistent with the experimental findings. However, these results do not give insight into the venomotion process itself, nor do they illustrate those factors which influence or control venomotion. One of these factors, for example, would appear to be the vascular topology. In the Microvascular Model, venomotion is included as a venous vessel with rhythmically varying diameters. Thus, the complex topology of the post capillary vasculature is in effect "lumped", and the venomotion representation is a functional characterization. Further, as characterized in the Model, the venomotion frequency may vary, but is still essentially a periodic phenomenon. In order to extend our understanding of the effects of venomotion and its physiological implications, it is necessary to utilize the Microvascular Model results together with additional experimental data to clarify the mechanisms responsible for the detailed time course of the diameter variation and the factors which influence both the time course of individual venomotion cycles and the basic rhythm. The principal objective of the work to be reported in this chapter was to obtain and analyze

information for this purpose.

To meet this objective, the approach adopted was to first gain familiarity with the detailed topological characteristics of the post capillary vasculature of the experimental preparation. This includes the vessels' general spatial distribution, location, and type of valves present, and other special features which might have a bearing on the dynamic patterns observed. In Section II-A, we have attempted to describe these lengthy microscopic observations in a way which will provide an insight into these aspects of the vascular field being studied. In addition, to serve as a brief introduction to the more detailed investigation of the dynamics of venomotion, the general characteristics of the observed dynamics are described in Section II-B.

The experimental observations documented in Section II contain the initial data for the development of the post capillary region of the Microvascular Model, in addition to providing the foundation for the extended analysis to be described. They are presented in this chapter so that these initial and the further experimental studies may be presented without loss of continuity.

Once sufficient familiarity with these aspects was obtained, the focus of attention turned to examining the detailed dynamic properties of the venomotion process.

To accomplish this, an electro-optical system was designed and built to be used in conjunction with a Closed Circuit Television System (CCTV) to measure the time course of the diameter variations

and the flow patterns in the microvessels. This system is described in Section III.

Using this system, the normal patterns of venomotion were first measured and recorded. These measurements formed the basis of the dynamic aspects included in the Microvascular Model. Results of these measurements are presented in Section IV-A, and, with the aid of the Microvascular Model results of Chapter Five, a discussion and analysis (Section IV-B) is presented to explain the pattern of venomotion that is observed in terms of a complex interaction between vascular topology, vessel characteristics (passive and active), hemodynamics (proximal, within and distal to a particular observation site), and valve presence (type, location, and mode of action).

That part of the analysis of the dynamics which requires knowledge of the intravascular microvessel pressures may be viewed as an hypothesis, because these pressures were not measured. Though a few workers have been able to develop and utilize adequate (but expensive) dynamic micropressure measuring systems (Fox and Wiederhielm, 1973; Intaglietta, 1973), the necessary resources were not available to this author. However, by utilizing perturbations selected to alter intravascular pressure, measurement of diameter and flow responses, and armed with the Microvascular Model predictions of the hemodynamic consequences of these perturbations, it was possible to substantially reduce the hypothetical component and to further probe the microvascular properties.

In Sections V and VI, the results obtained using thermal and

arterial pressure perturbations are presented. In Section V, the effect of thermal perturbations on post capillary dynamics is examined with the objective of determining the changes in venomotion frequency. In Section VI-A, the manifestation of the arterial pressure perturbation on the arterial region of the microvasculature is documented and analyzed, and in Section VI-B, the effect of the perturbation on post capillary dynamics is presented and analyzed. Finally, in Section VI-C, the transit times of hemodynamic perturbations through different regions of the microvasculature are recorded and analyzed in order to clarify the significance of both the vascular topology and post capillary dynamics.

II. Post Capillary Vascular Topology and General Character of Vessel Dynamics

A. Topology

The anatomical and functional distribution of vessels and their associated structures, such as valves, may play an important role in determining the overall microvascular hemodynamics. In order to better understand the relationship of this topology to hemodynamics, the basic features of the post capillary vasculature are examined in this section.

In figure 6.1 is shown a reconstruction of a portion of the post capillary vasculature of the bat wing obtained by microscopy. This figure, though constructed from observations on a single preparation, illustrates the basic patterns observed in all preparations. For reference purposes, vessel types will be referred to by order number as indicated in the figure. Note that in figure 6.1, no attempt is made to represent the differing vessel diameters. The general topological pattern is one in which vessels starting at the capillary (designated as zero order vessels) successively converge with other vessels. The vessels formed after the confluence of two similar vessels are generally larger than those feeding them. Thus for example, as the second order vessels continue along, other vessels feed into them as side branches. Some of these side branches enter perpendicular to the collecting vessel and others at an acute angle to the direction of flow.

At some point, two or more second order vessels will

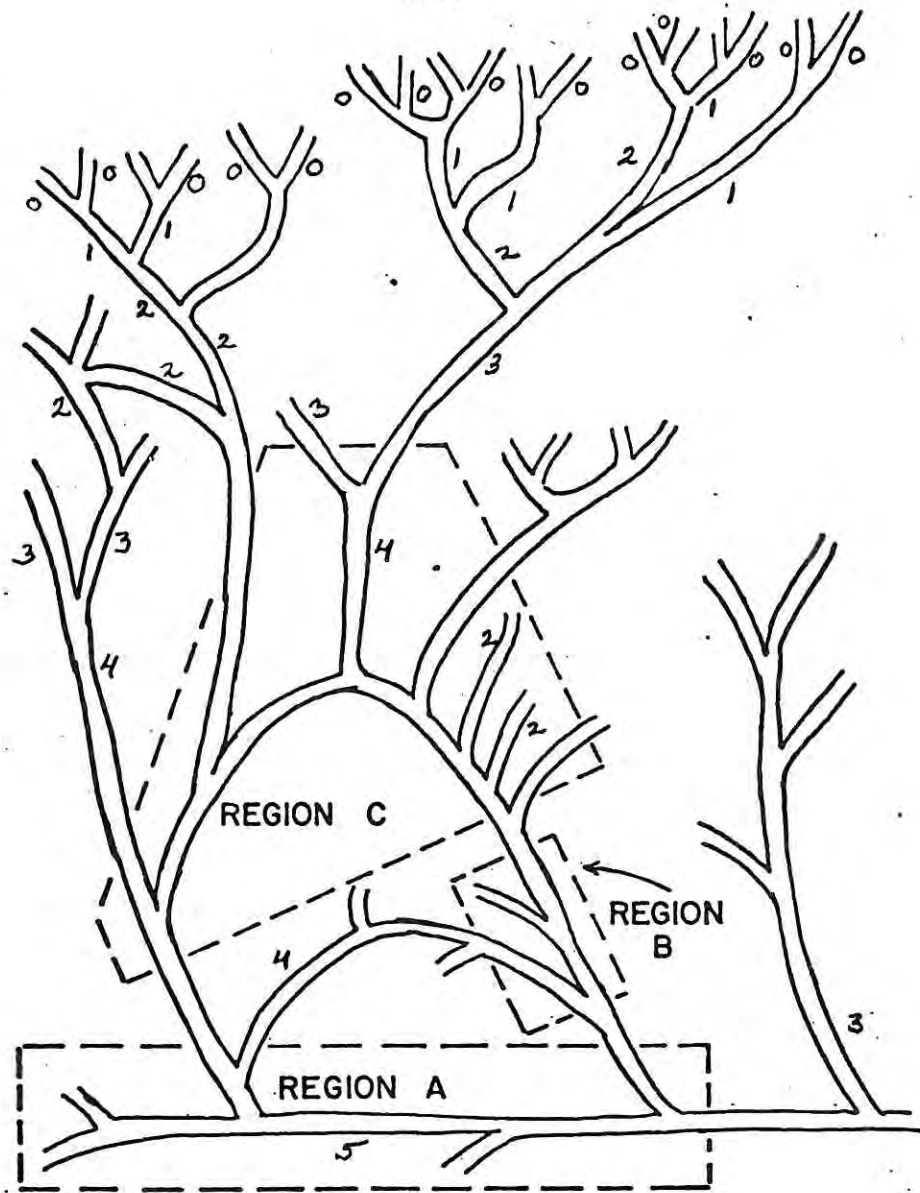


Figure 6.1. Illustration of prominent aspects of post capillary topology. Numbers adjacent to vessels represent vessel branching sequence according to the following scheme. 0 = capillary, 1 = post capillary venule, 2,3 = muscular venules, 4,5 = small veins. Regions marked A, B and C are expanded in subsequent figures.

converge together to form the origin of what may be called a third order vessel. As the third order vessels continue along, other vessels feed into them as side branches. Again some of these side branches are close to being perpendicular to the collecting vessel, while others enter at an acute angle. It has been my observation that for vessels feeding the fourth and fifth order vessels (although I have few hard statistical data to back it up), the larger the angle, the smaller is the feeding vessel diameter. Further, the smaller vessels often represent more or less direct pathways from the capillary bed, i.e., there are fewer intervening vessels before they join the collecting vessels.

The process of vessel convergence continues through a hierarchy of vessels of increasing size until all such pathways enter the major vein leaving the wing.

Though the general pattern of branching in the post capillary vasculature is convergent (as opposed to divergent on the arterial side), there are examples of divergence as well. These topological patterns are most prevalent at the third order vessel level and higher. The divergence occurs, for example, when two third order vessels which have been coursing their way through different regions (collecting the capillary outflow of these regions via first and second order feeding vessels) meet.

Figure 6.1 illustrates the interrelationships of the various vessels, including the branching pattern and the characteristic looping and inter-anastomosing. However, it does not depict

the characteristics of the branching points or the position and characteristics of valves. In order to look more closely at this aspect and examine in more detail the characteristics of specific regions, the portions of figure 6.1 marked A, B, and C shall be "magnified". Region A is shown magnified in figure 6.2.

There are three characteristics which figure 6.2 is intended to illustrate. First is the presence of valves in both the collecting and feeding vessels. The second point is concerned with the location of the valves, and the third is the point that the characteristics of the valves in the feeding vessels are, depending on their location, different from those of the next order collecting vessels.

The presence of the valves is ascertained by observation. Their outline as they open and close leaves no doubt as to their presence. The most often observed location of the valves in a collecting vessel is at or slightly upstream from the entry site of a feeding vessel whose diameter is not much smaller than the collecting vessel. Thus, for example in the segment marked S_3 , there are in fact a number of small side branches (these are not shown in this figure), but the valve lies slightly upstream to a larger feeding vessel (S_5). The vessel marked S_5 , though a feeding vessel to S_4 , is a collecting vessel for the segment designated S_7 , and appropriately, there is a valve as shown slightly upstream from the entry site of S_7 .

At the site in which a feeding vessel joins a collecting vessel, there may or may not be a valve. When a valve is observed, it is often of a different configuration than of those observed in the

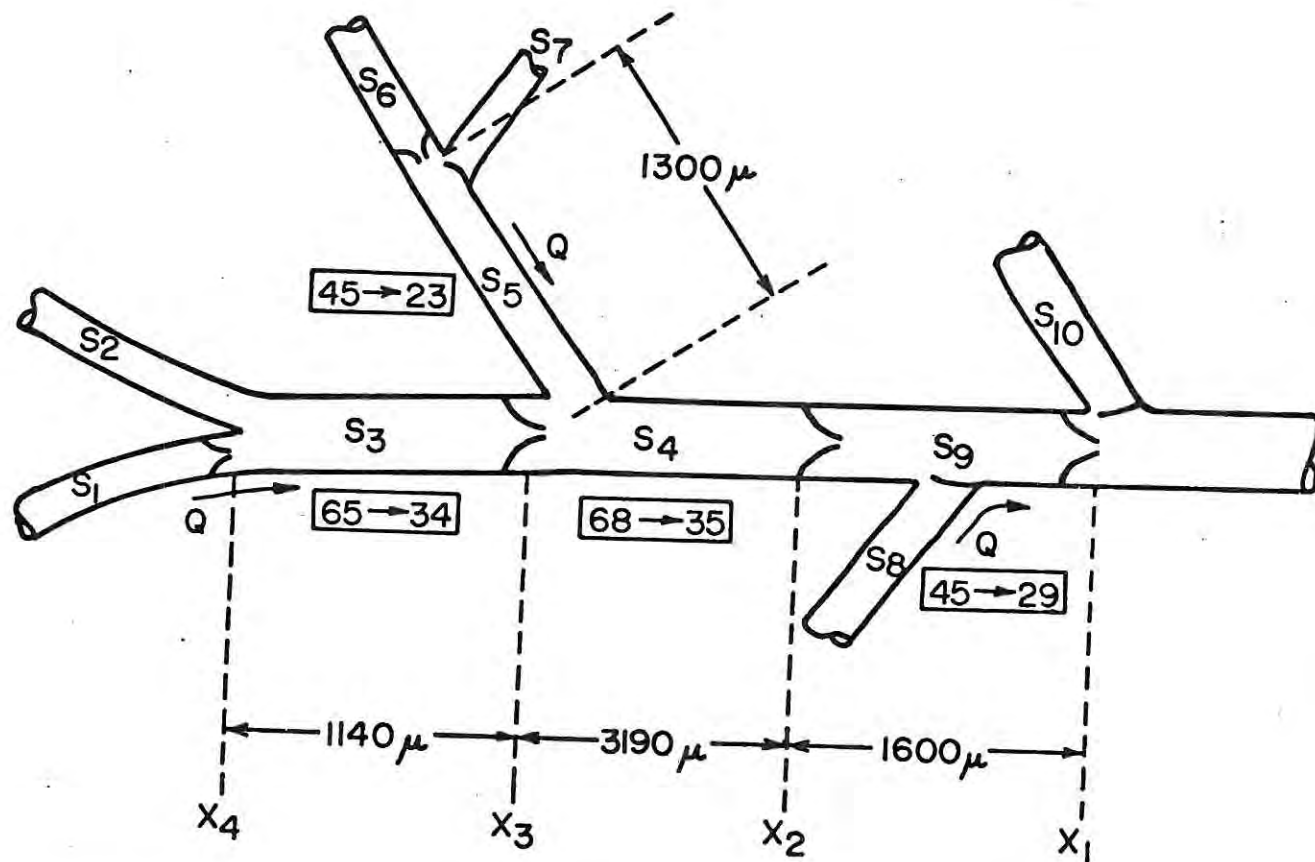


Figure 6.2. Topology of small vein and feeding branches. Expanded representation of Region A of figure 6.1. S denotes vessel segments and x valve positions. Boxed in numbers adjacent to vessel segments are maximum (dilated) and minimum (contracted) inside diameters in microns. Q denotes the normal flow direction.

higher order collecting vessels. The principal difference which appears in outline is the existence of a single cusp rather than two or more projecting from one side of the vessel wall into the lumen.

Vessels segments S_7 , S_8 , and S_{10} were observed to have this valve configuration, which is really quite a typical one. In those feeding vessels in which no valve is observed, the feeding diameter is usually smaller in relation to the collecting vessel than those feeding vessels having one.

In figure 6.3 are illustrated the details of a typical region in the vicinity of the junction of two vessel segments. The bicuspid valve in the collecting vessel is seen to be located quite close to the entrance of the feeding vessel (about 35μ). The entrance of the feeding vessel is guarded by a unicuspid valve-like projection. The dimensional details concerning the precise location and size of valves will not be included in the subsequent illustrations. Rather, line drawings will be used to indicate the topology of the regions dynamically studied.

It is interesting to note that many of the topological characteristics of the human post capillary vasculature are present in the wing vasculature. This includes the existence of several types of valves, the similarity of their general appearance to those in the wing, and their typical distribution throughout the post capillary vasculature. According to the accounts of Burch (1950), for example, the feeding vessels of the internal jugular, facial, lingual, superior thyroid and temporal veins have valves at their entry points. Further, according to Burch, the external jugular has a valve near its union

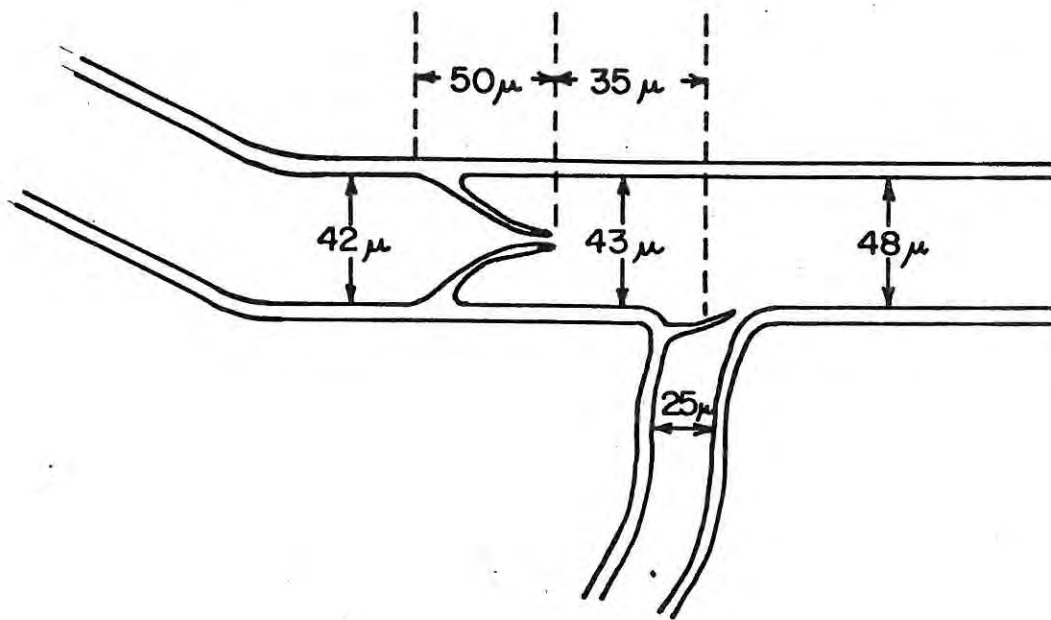


Figure 6.3. Details of region in the vicinity of junction of vessel segments and valve structure.

with the subclavian and another a few centimeters above the clavicle. Even in those cases where there is no evidence of valves in collecting vessels (e.g., innominate, common iliac, and hypogastric veins), the feeding vessels do have in them valves at their orifices. The subclavian vein itself has at least one valve which is most often located just before it joins with the external jugular vein. The internal mammary vein and its feeding vessels also have valves. The veins of the lower and upper limbs (especially the deep veins) are quite abundant with valves which are for the most part of the bicuspid type in the larger order vessels, and a combination of unicuspid and bicuspid in the smaller feeding vessels. However, as is the case with the wing, the unicuspid type is dominant in the smaller feeding vessels.

B. General Characteristics of Dynamics

Using figure 6.2 as a reference, some general characteristics of the post capillary dynamics may be described. In figure 6.2 (adjacent to vessel segments S_3 , S_4 , S_5 , and S_8) are boxed-in numbers which indicate the measured maximum and minimum inside diameters of these vessel segments which were undergoing venomotion. To illustrate the kind of flow dynamics that these are associated with, the activity in the vessel segments S_4 , S_8 , and S_9 is described. During part of the venomotion cycle, there is zero flow in S_4 . During this time, the diameter is about 63 microns. A slight dilation is then observed (diameter increases to 68 microns) associated with a slight forward flow of blood (toward valve X_2). When valve X_2 is fully closed, this slight forward flow does not pass through X_2 , but on occasion a small

amount trickles through. In either case, however, following the dilation to 68 microns there is an intense contraction of S_4 , reducing the diameter to 35 microns, and associated with a large forward flow into S_9 . The outflow from S_4 most often precipitates a dilation of S_9 followed by a contraction of S_9 . The contraction shuts off valve X_2 and allows outflow from segment S_8 , which has been shut off when there was inflow from segment S_4 .

Sometimes one has the distinct impression that the closure of valve X_2 occurs not due to the contraction of segment S_9 , but rather due to the closure of the distal valve (valve X_1). Thus, when this pattern is predominant, there is a rapid dilation of S_9 in the vicinity of valve X_1 (occurring after S_9 contracts). The dilation in S_9 is followed by dilation of S_4 in the vicinity of the valve. When this occurs, segment S_8 is cut off briefly. These kinds of dynamics are typical of the active post capillary vessels and will receive in depth treatment in Section IV.

To further illustrate the general character of these dynamics, we must "magnify" the region marked B in figure 6.1, as shown in figure 6.4. Note that the segment and valve designations in the figure (e.g., S_1 , S_2 , X_1 , X_2 , etc.) do not represent segments and valves similarly designated in other figures. The boxed-in numbers adjacent to the vessel segments designated as S_1 , S_2 and S_3 are observed diameters of these vessels in microns. In figure 6.4 is a further magnified version of the boxed-in region designated as D (located between valves X_3 and X_4).

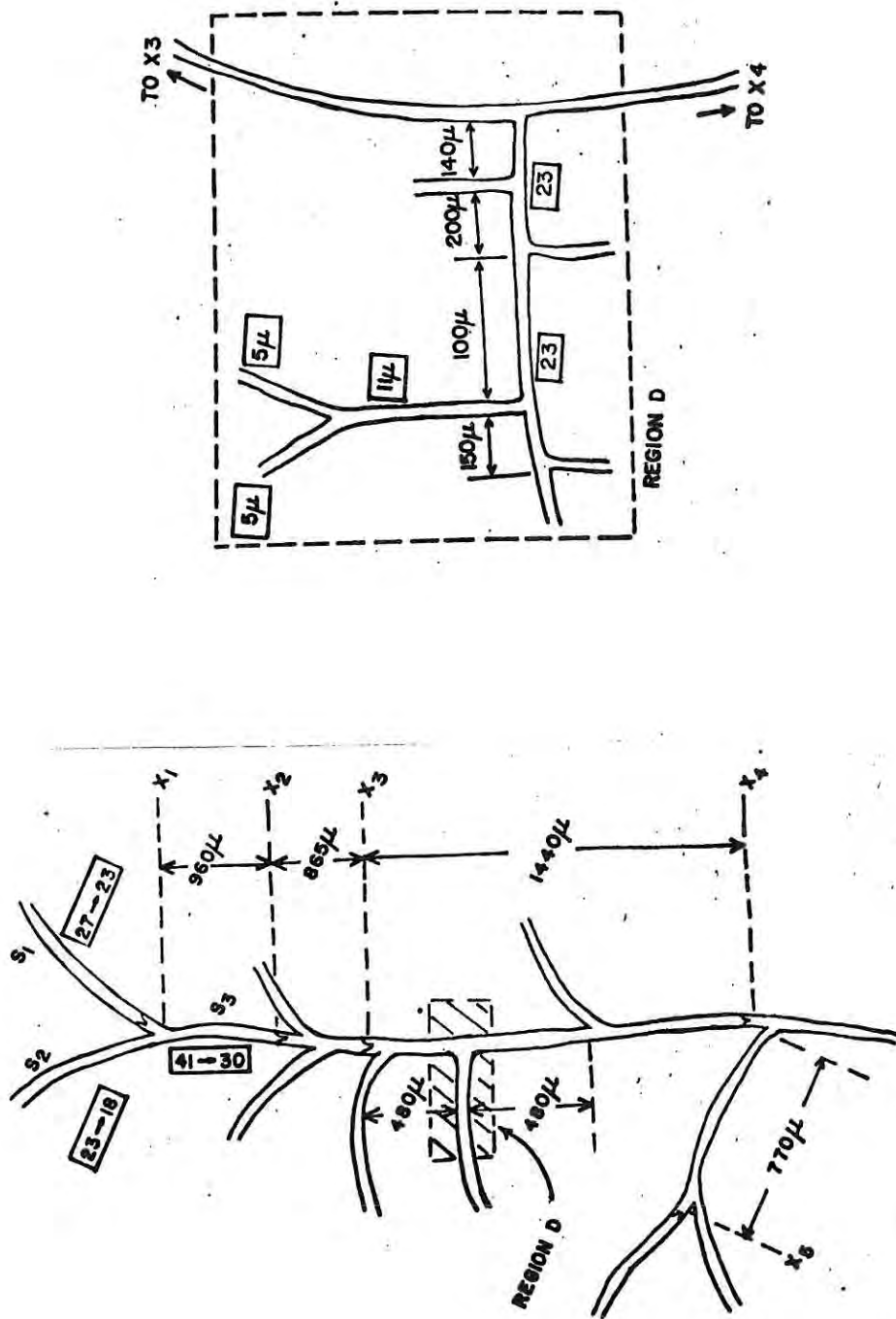


Figure 6.4. Region B of figure 6.1 expanded. x 's denote valve positions. Boxed in numbers adjacent to vessel segments (s) denote maximum and minimum diameters in microns.

It may be noted from figure 6.4 that the valve locations, when they are present, are again slightly upstream from the points of entry of the feeding vessels. As described before, the feeding vessels may or may not have valve-like structures at their exit ends. In vessel segment S_2 , no valve in the vicinity of the union was observed.

With respect to the dynamics, the outflows from S_1 and S_2 , for example, were observed to be synchronous at certain times and asynchronous at others. That is, the flow could be increasing and decreasing in both of them at the same time (synchronous), or flow could be increasing in one of them and decreasing in the other at the same time (asynchronous). The explanations of these different dynamical patterns will be presented in Section IV.

In figure 6.5 is illustrated a magnified version of region C of figure 6.1. The two pathways of the loop are designated as pathway A and pathway B. The position of the valves is again designated by the symbol S. In pathway A, the inflowing branches are designated as A_1 , A_2 , and so on in increasing numbers away from the downstream valve in pathway A. Similar designations could be given to pathway B, but, since there will not be the need to reference them in the following discussion, they are not labeled. The numbers that are boxed-in again give representative vessel diameters in microns. The numbers that are not boxed-in give the distance between inflowing vessels in microns. For example, the distance between A_1 and A_2 is 600 microns, the distance between A_2 and A_3 is 70 microns, between A_7 and the entry of the "bridge" segment is 620 microns, and so on.

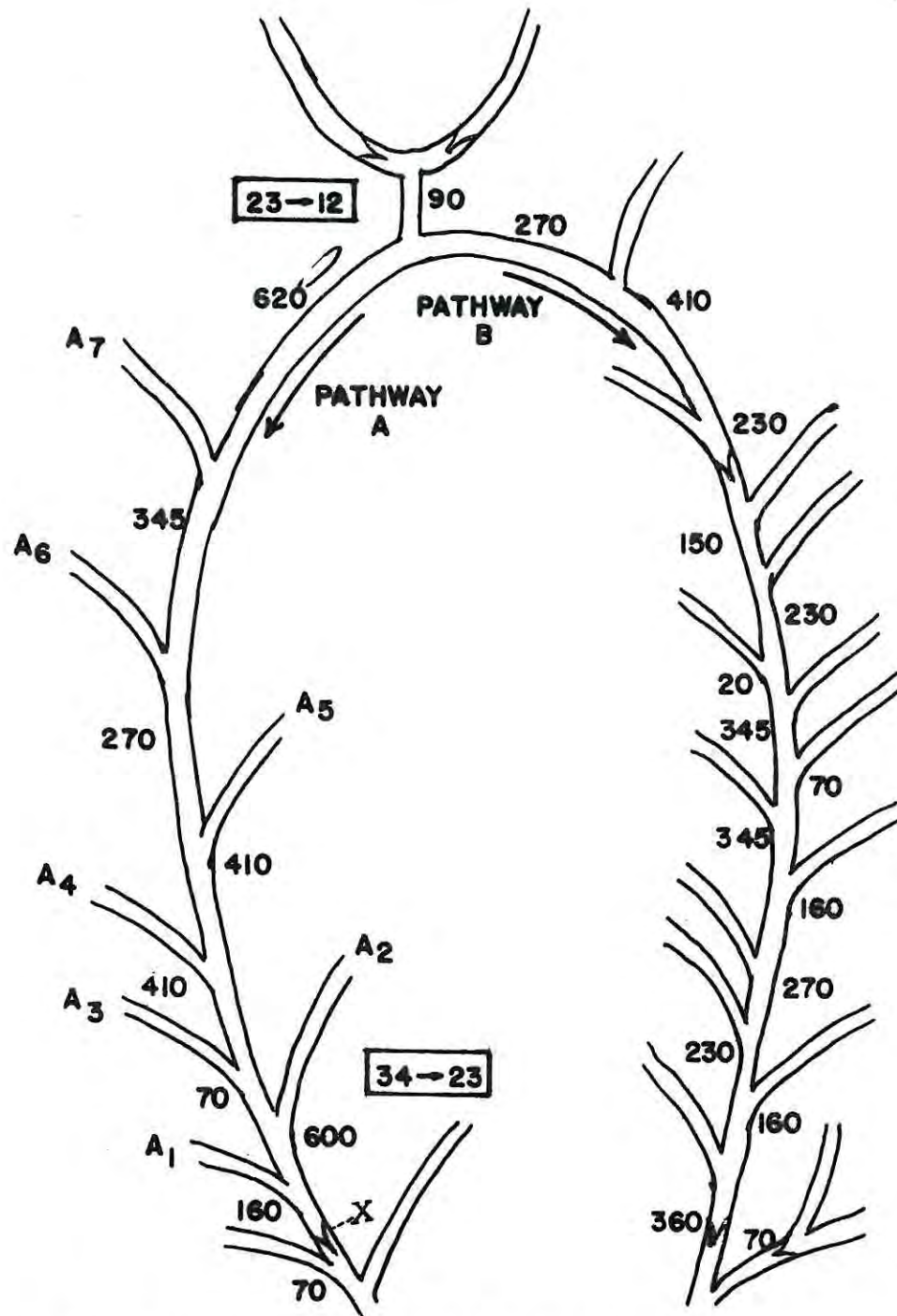


Figure 6.5. Expanded view of region marked C in figure 6.1. Boxed in numbers indicate maximum and minimum rhythmic vessel diameters in microns. Unboxed numbers indicate distance between inflowing branches in microns.

To describe the typical dynamics which are observed, valve X is used as a reference. Contraction of the vessel segment upstream from valve X causes valve X to open (if it had been slightly open, it is caused to open fully). Inflows from the feeding vessel segments (A_1 , A_2 , etc.) which had been occurring while the valve was closed now abruptly stop. The valve stays open for a certain length of time (e.g., one to four seconds) and then closes (this can occur for a number of reasons, as will be discussed in Section IV). Upon closure of valve X, flow again enters pathway A from its feeding vessels. At site A_1 , the incoming flow is directed toward valve X and is also directed upstream (in the direction of A_2). Similarly, there is inflow from the other feeding vessels. During this inflow time the diameter of the collecting pathway A continues to increase. While this is occurring, flow through the common pathway (the 90 micron "bridge") at the junctions of pathway A and pathway B is either zero or is passing into segment B. Very often, the inflow from the feeding vessels in the vicinity of the "bridge" (A_6 and A_7) is seen to move upstream toward the "bridge" and to enter pathway B during this phase. After a certain time (e.g., two to six seconds), vessel segment A again contracts, and the cycle repeats itself with the same characteristics.

This completes the general overview of the topological characteristics as depicted in figure 6.1 and the dynamics within this region. We now turn more specifically toward examining the details of these dynamic pressures.

III. Method of Recording Dynamics

A. Microscopic Observation of Microvessels

In figure 6.6 the basic arrangement for observing the microvessels is shown. The method is the same as described by Wiedeman (1967). The animal is placed on a small transparent plexi-glass board with one of the wings extended. The animal is awake and is confined within a cylindrical chamber with air intake ports. After a brief period of excitement the animal relaxes and for most of the time remains perfectly still. The wing is transilluminated and the microvasculature observed with magnifications up to 1200 diameters. Because of the thinness of the wing, the light intensities required for observation are small and do not, under normal circumstances, create any significant heating. Depending on the particular experimental protocol, the observations are made by direct microscopic viewing (American Optical Company, Microstar with trinocular head), filming using a 16 mm cine camera (BoloX), or using a closed circuit television system (Panasonic). The TV system has a monitor for immediate viewing and a video tape recorder for simultaneous recording and later playback. The microscope has a trinocular head which permits direct viewing with simultaneous filming or video recording. The TV camera resolution is 600 lines horizontal and 350 lines vertical, and the recorder resolution is 300 lines.

B. Measurement of Dimensions

Vessel diameters and lengths are measured either by direct viewing using a calibrated micrometer eyepiece or by

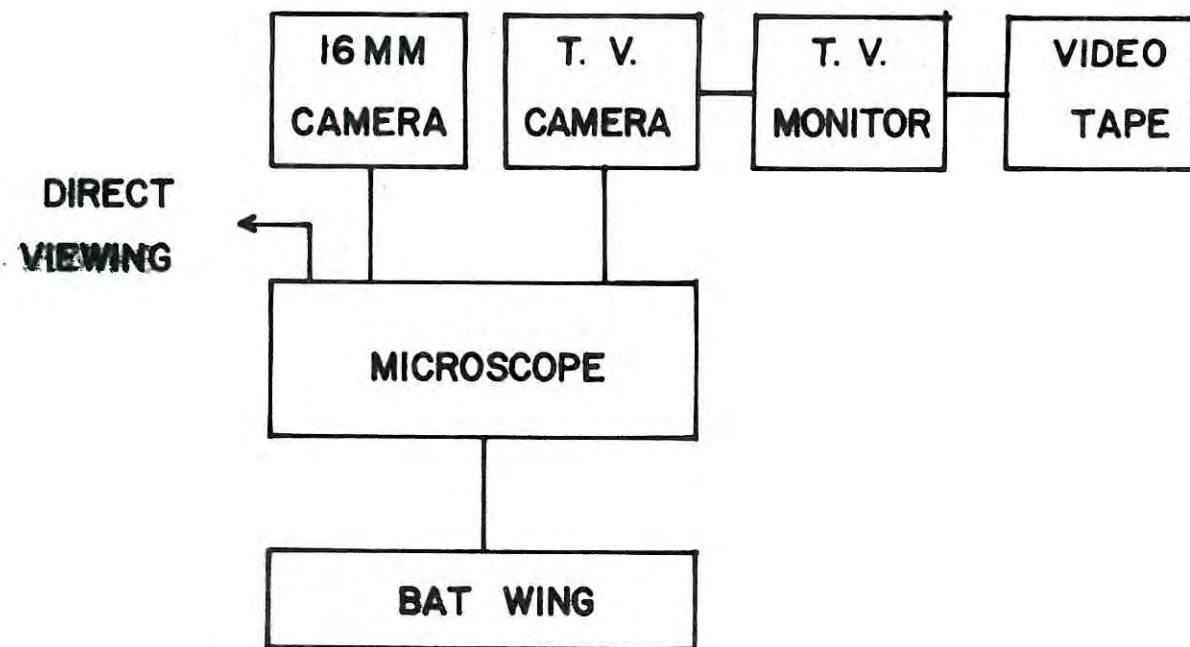


Figure 6.6. Schematic representation of basic experimental setup.

calibrating the video image on the television monitor.

In figure 6.7 the basic method of recording micro-vascular dynamics is illustrated. Photoconductive cells are placed in proximity to the vessel image on the TV monitor screen to record changes in diameter. The conductivity of these sensors is a function of the amount of light received by the active surface. The sensors are incorporated as part of an electrical bridge circuit, so that an electrical voltage is developed which is proportional to the change in light intensity received by the sensor. This voltage is amplified, filtered, and then displayed on a strip chart recorder and/or storage oscilloscope. The system designed and built by the author is so constructed that decreases in received light intensity will result in an upward deflection on the recording apparatus.

C. Operation of Sensors

To illustrate the operation of the sensing system, reference is made to figure 6.8. In figure (a) the schematized vessel image is shown in its fully dilated condition, and in (b) the same vessel is shown contracted. The quantities T_j and T_o represent the optical transmissibility of the region through the vessel lumen and through the region outside the vessel, respectively. Because of the presence of erythrocytes, T_o is greater than T_j . Thus, when the vessel goes from the dilated state to the contracted state, the amount of light falling on the sensor surface increases. This results in an increase in the electrical conductivity of the sensor (Clairex, C1704L), and after its conversion to an electrical voltage

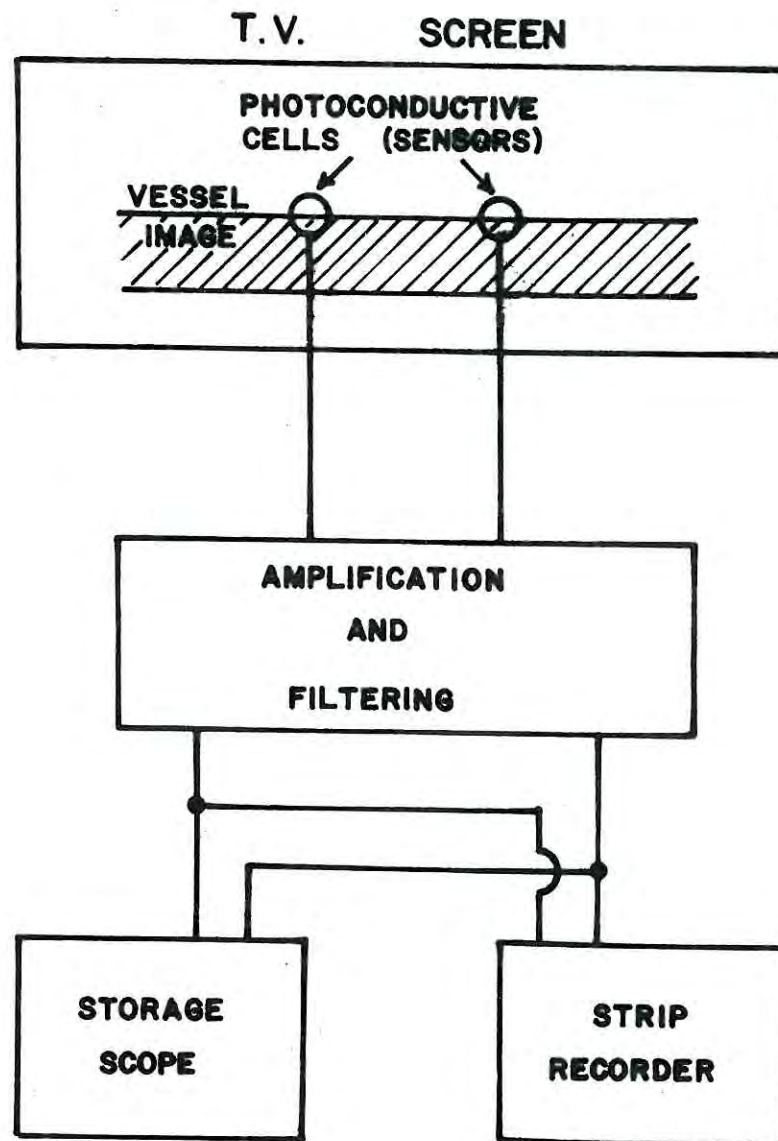


Figure 6.7. Method of recording vessel dynamics.

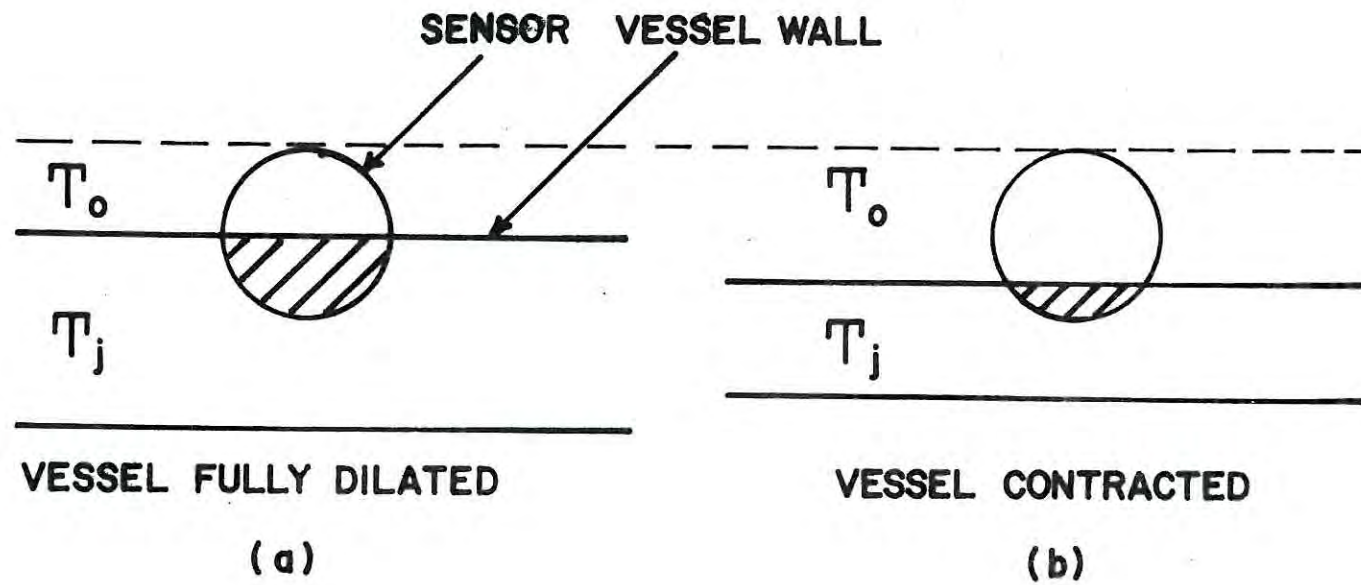
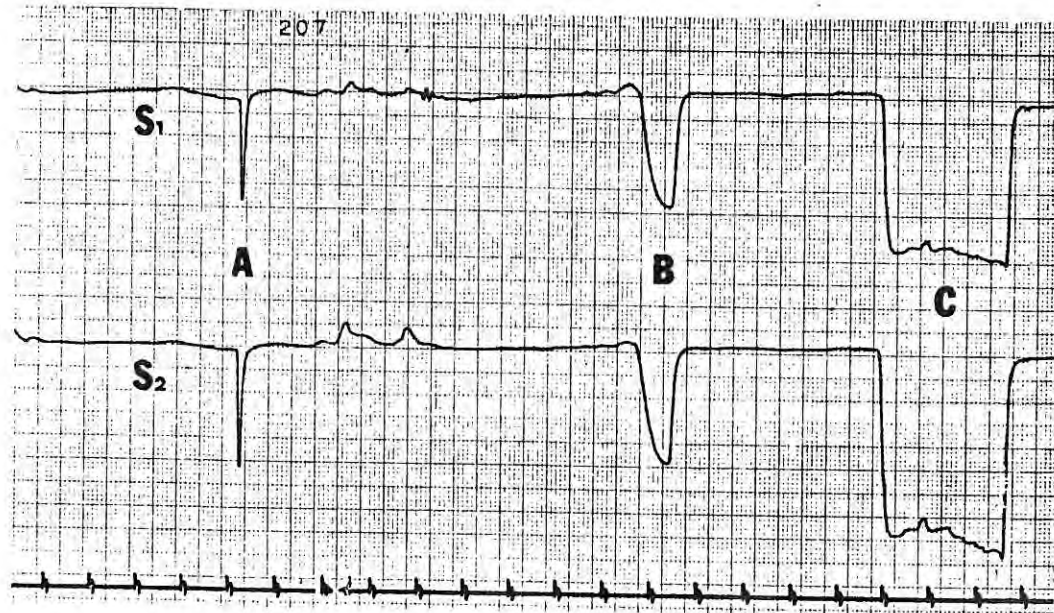


Figure 6.8. Illustrating sensor operation.

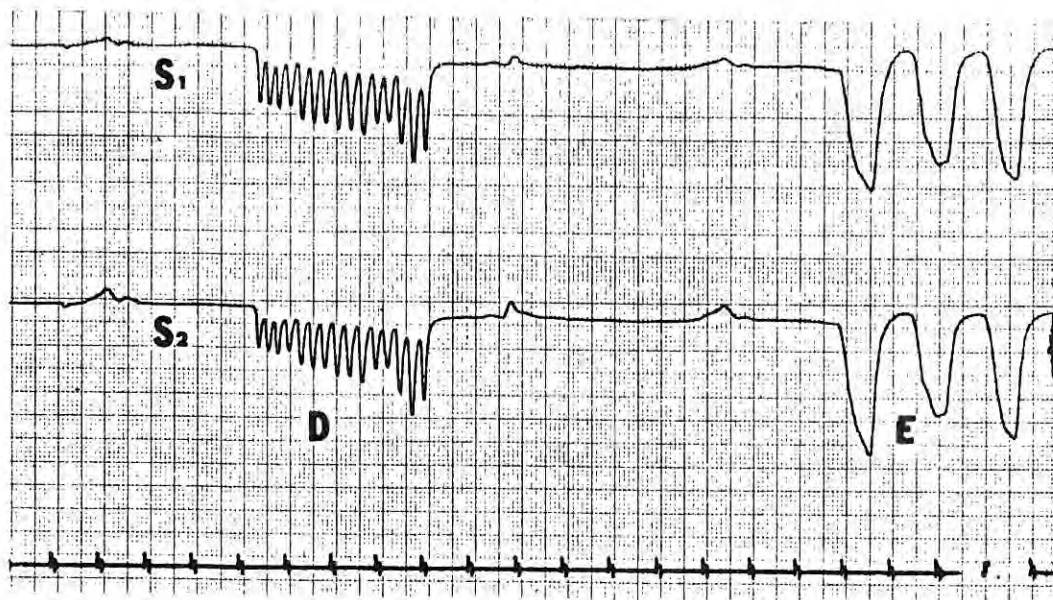
results in a downward deflection on the recording apparatus. Conversely, dilation results in an upward deflection. The system as shown is not calibrated to give absolute values of diameter (due to nonlinearity in the sensing system), but rather changes in diameters. Measurements of diameters are made directly, using calibrated micrometer eyepieces.

D. Dynamic Characteristics of Instrumentation

In order to insure that the sensors had dynamically similar characteristics, their dynamic responses were evaluated simultaneously. An animal was prepared for observation in the standard fashion. Two sensors were placed adjacent to each other over the same vessel segment. To obtain a variety of dynamic perturbations, the microscope substage was used to alter the position of the vessel image while maintaining the sensors fixed. In this way, rhythmic and transient dynamics could be used. In figure 6.9(a) examples of the dynamic responses of two sensors are shown. The first response is essentially the impulse response, and the third response is essentially the unit step response. The similarity of the dynamic characteristics is evident. In figure 6.9(b) the high and low frequency responses are shown. Again the similarity of the dynamic characteristics of the measuring system is clear.



(a)



(b)

Fig. 6.9. Dynamic response of photosensing system. S_1 & S_2 are the outputs of photosensors one and two respectively. In (a) the dynamic response for transient type perturbations is shown. A is the impulse response and C the unit step response. B is somewhere in between. In (b) the dynamic response to high (D) and low (E) frequency rhythmic variations is shown. Note similarity of each channel's response in all cases. Time marks at two second intervals.

IV. Results and Analysis of Normal Post Capillary Dynamics

A. Results

In figure 6.10 is shown a portion of the vascular region studied in a typical experiment. The locations of the sensors are indicated by the vertical arrows separated by 140 microns along segment S_3 . The upstream sensor is located 100 microns from the upstream valve site.

In figure 6.11 are shown sample tracings of one venomotion cycle as recorded from the sensors. The top tracing corresponds to the downstream diameter and the bottom to the upstream diameter. The fundamental period is 3.4 seconds. Careful observation of the flow pattern reveals the following dynamic picture. Using figure 6.10 as reference and starting with the relaxation phase of S_3 , the following events occur. Note that for brevity in the descriptions to follow a vessel segment will be referred to as S_i . Thus, S_2 for example may be read as vessel segment S_2 , and so on. The dilation of S_3 causes a small separation between the unicuspid valve X_1 and the opposite wall of S_1 . Flow from S_1 begins to enter S_3 through this opening, causing its volume to increase. In figure 6.11 this is first recorded as an increase in diameter beginning at point A. The time that elapses between the initial dilation upstream (point A) and the measured dilation at the downstream recording site (point B) depends on the flow pulse velocity and is calculated to be 1.5 cm sec^{-1} . Flow continues to enter S_3 , and the diameter continues to increase. S_2 then contracts and

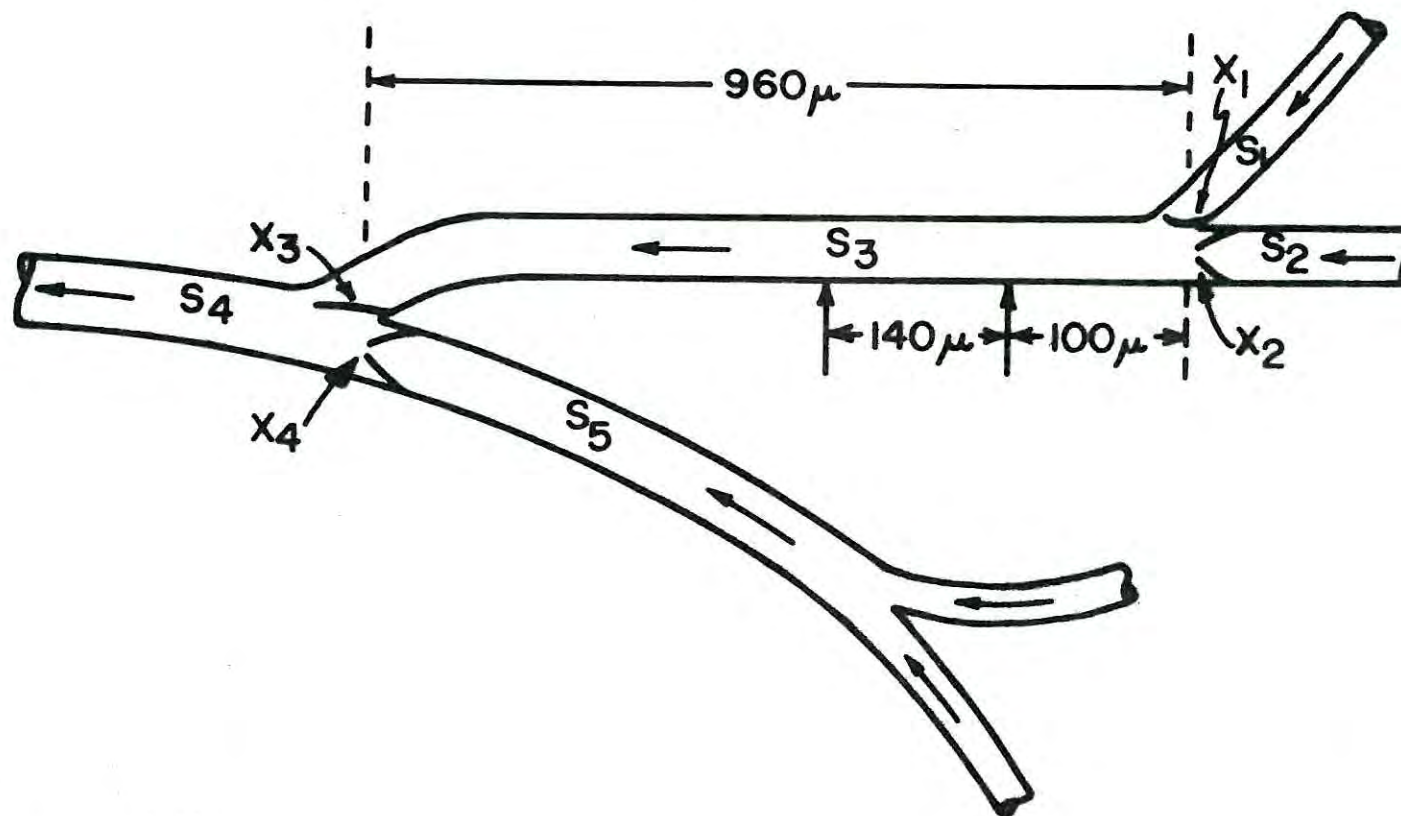


Figure 6.10 Vascular region studied in a typical experiment. Sensor positions indicated by vertical arrows along vessel segment S_3 .

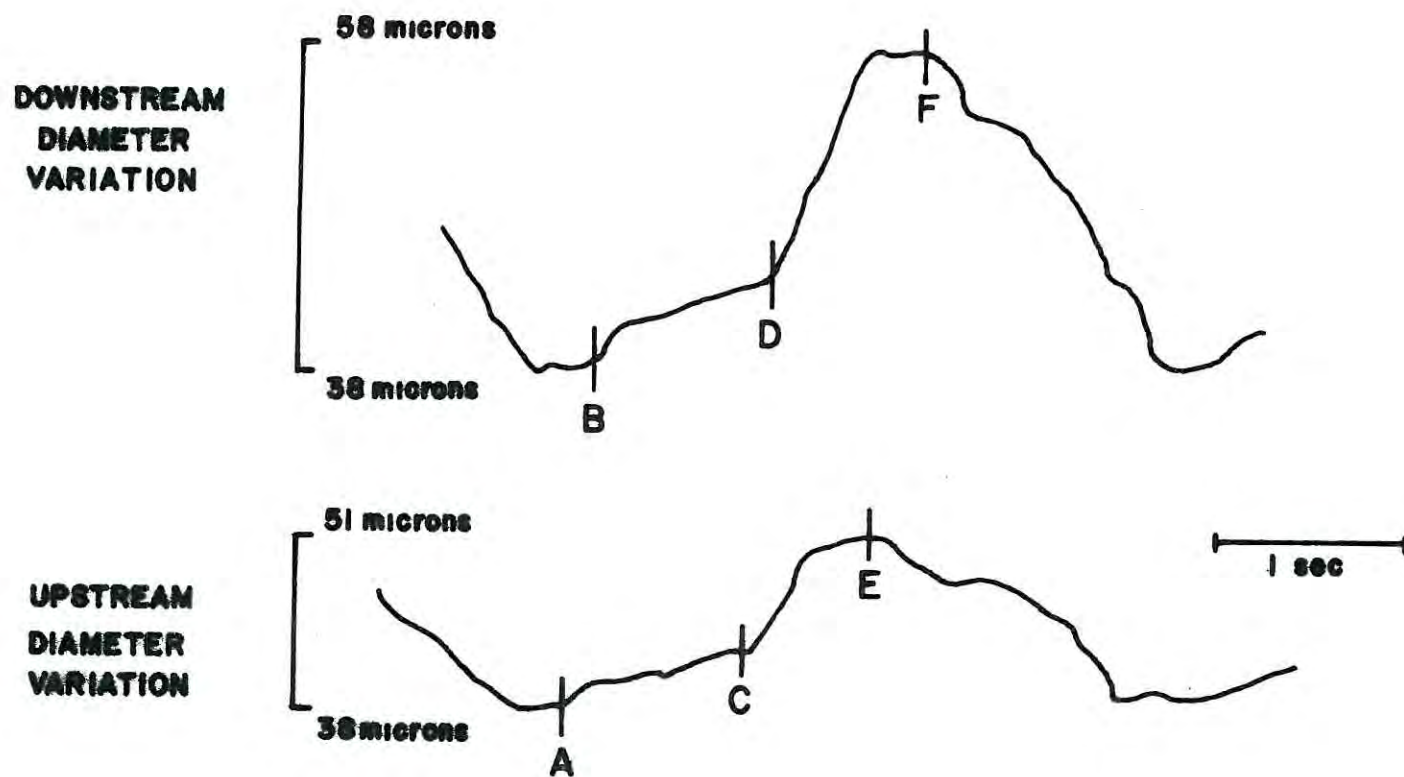


Figure 6.11. Diameter variation associated with venomotion. Recordings obtained as shown in figure 6.10. See text for description.

produces additional flow into S_3 with resultant vessel dilations beginning first upstream (point C), then downstream (point D). The combination of the dilation produced by the incoming fluid and the contraction itself has the additional effect in this instance of opening further valve X_1 . While the above sequence of events took place, flow in S_4 occurred via S_5 , and valve X_3 was closed. There then occurred a contraction of S_3 . The contraction registered first at the upstream sensing site (point E), and then downstream (point F). The effect of this contraction was to close both upstream valves (X_1 and X_2) and partially open the downstream one (X_3). With the opening of valve X_3 and resultant flow from segment S_3 , the bicuspid valve X_4 in S_5 was observed to swing shut. Valve X_3 swung open further, and the volume of S_3 continued to decrease as it continued to decrease in diameter.

In figures 6.12 and 6.13 are reproductions of recordings obtained at sites similar to those from which figure 6.11 was recorded. The diameter variations shown in figures 6.12 and 6.13 were obtained from the site located just downstream from valve X_3 in figure 6.2. This figure is repeated here for convenience. The separation between the sensors was 165 microns along segment S_4 . Note that the segment and valve notation is the same in figures 6.2 and 6.10, but it refers to different valves and segments. Thus, S_4 of figure 6.2 is not the same as S_4 of figure 6.10, and so on.

Considering first figure 6.12, the dynamic pattern occurring during the recording time was as follows. At point A S_4

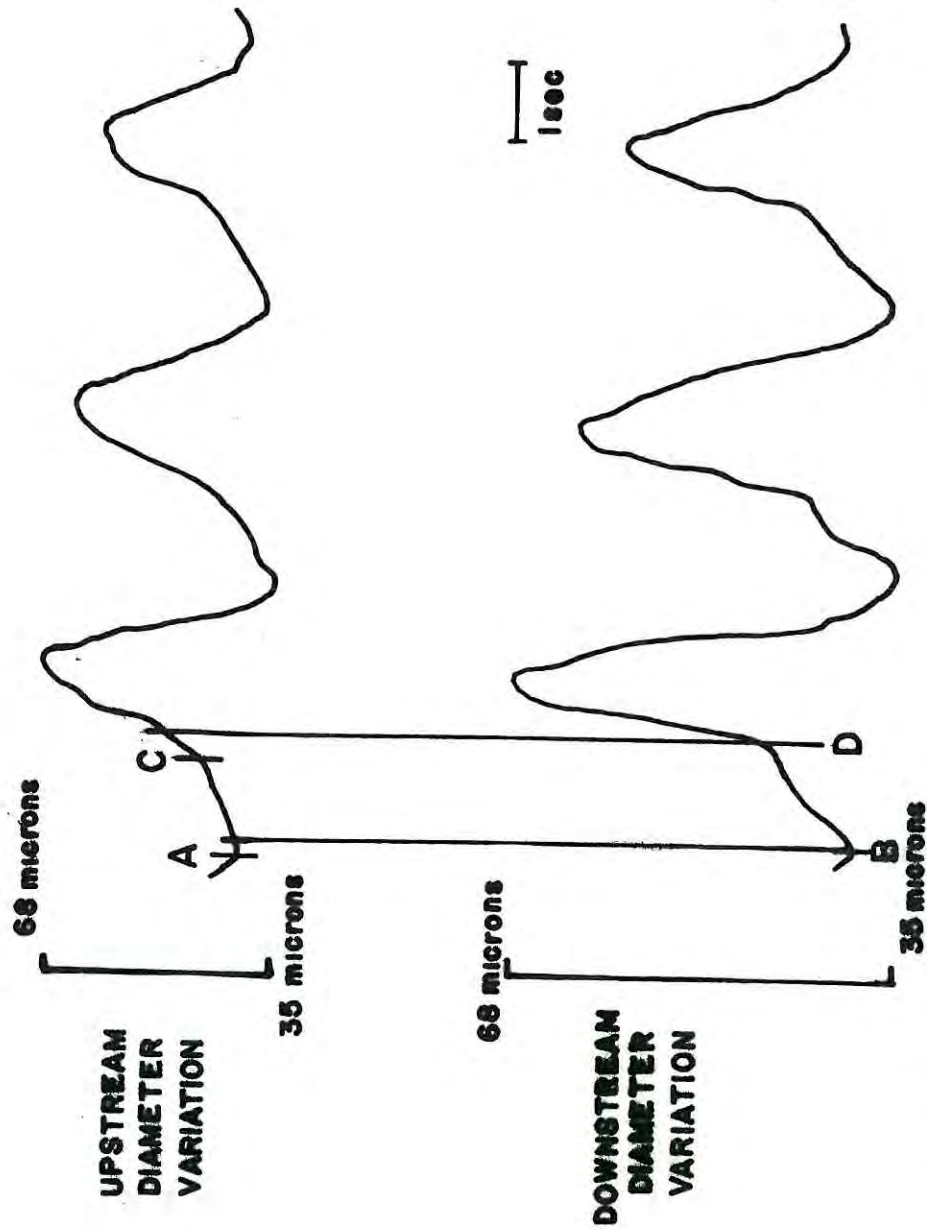


Figure 6.12. Pattern of diameter variation in small vein. Upstream and downstream sites separated by 165 microns. See text for discussion.

begins to dilate. Because the observation site is in the proximity of S_5 the dominant filling recorded here is emanating from this segment (side branch inflow is occurring as well). There is a 200 msec delay, after which (point B) the downstream site is observed to begin dilating. At point C there is a rapid filling phase corresponding to the contraction of segment S_3 . Again the influx causes dilation first at the upstream site, followed by the downstream site (point D). The precise start of contraction of S_4 following this rapid dilation is not discernible, but the result is the ejection of its contents. This basic pattern is seen to repeat itself in subsequent cycles.

In figure 6.13 the first cycle shown has characteristics similar to those in figure 6.12, and the points A, B, C, and D have the significance just described. However, although the second cycle in this particular sequence begins in the same way (upstream beginning its slow dilation phase first at point E), there is seen a rapid dilation phase occurring first downstream (point F), followed by a strong contraction (point G). This pattern has been observed to occur under two different circumstances. One is when the downstream valve has been partially open during the dilation phase and then suddenly closes. The second most common way is when there is a sudden burst of flow which enters the collecting segment downstream from the observation site. The first process thus depends on downstream valve action and the second on downstream inflow (which depends on upstream conditions in another circuit).

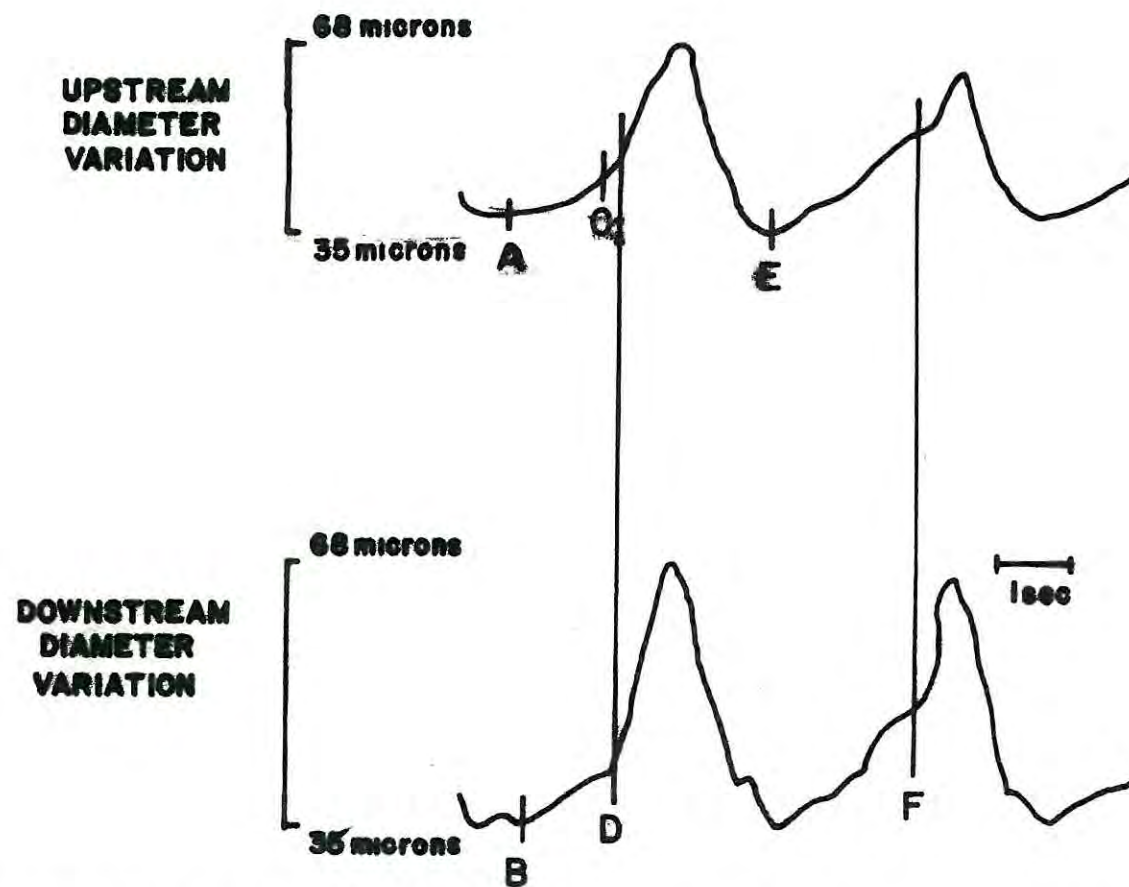


Figure 6.13. Changing pattern of venomotion. Diameter variations are recorded at the same sites as in figure 6.12. See text for discussion.

The dynamic patterns shown thus far are rhythmic, but, as has been shown, the time courses of adjacent cycles need not be the same. In the discussion of the general dynamics (Section II-B) there was mention of synchronous and asynchronous venomotion. If one records the dynamics across rather than between valved points, the independent activity of these regions may be examined. When individual vessel segments are acting both as independent effectors sensitive to conditions within a given segment while simultaneously being influenced by nonuniform or time varying upstream and downstream conditions, then the dynamics are typical of those shown in figures 6.14 through 6.16. The diameter variations are recorded at positions as shown in the figures. In figures 6.14 and 6.15, though a rhythmicity exists, cycle to cycle characteristics may be quite variable. To illustrate the degree of this variability, we show in figure 6.16, for example, that one segment (D_1) may contract and produce forward flow, while the other feeding segment is either contracting (point A), almost unchanging in diameter (point B), or dilating (point C). These asynchronous patterns may shift to become those recorded from precisely the same region but at a different time shown in figures 6.17a and 6.17b.

B. Discussion and Analysis

The preceding results show that the dynamic patterns of venomotion as characterized by diameter variation and associated flow are variable. This variability is evidenced both at the same site at different times and at different sites at the same time.

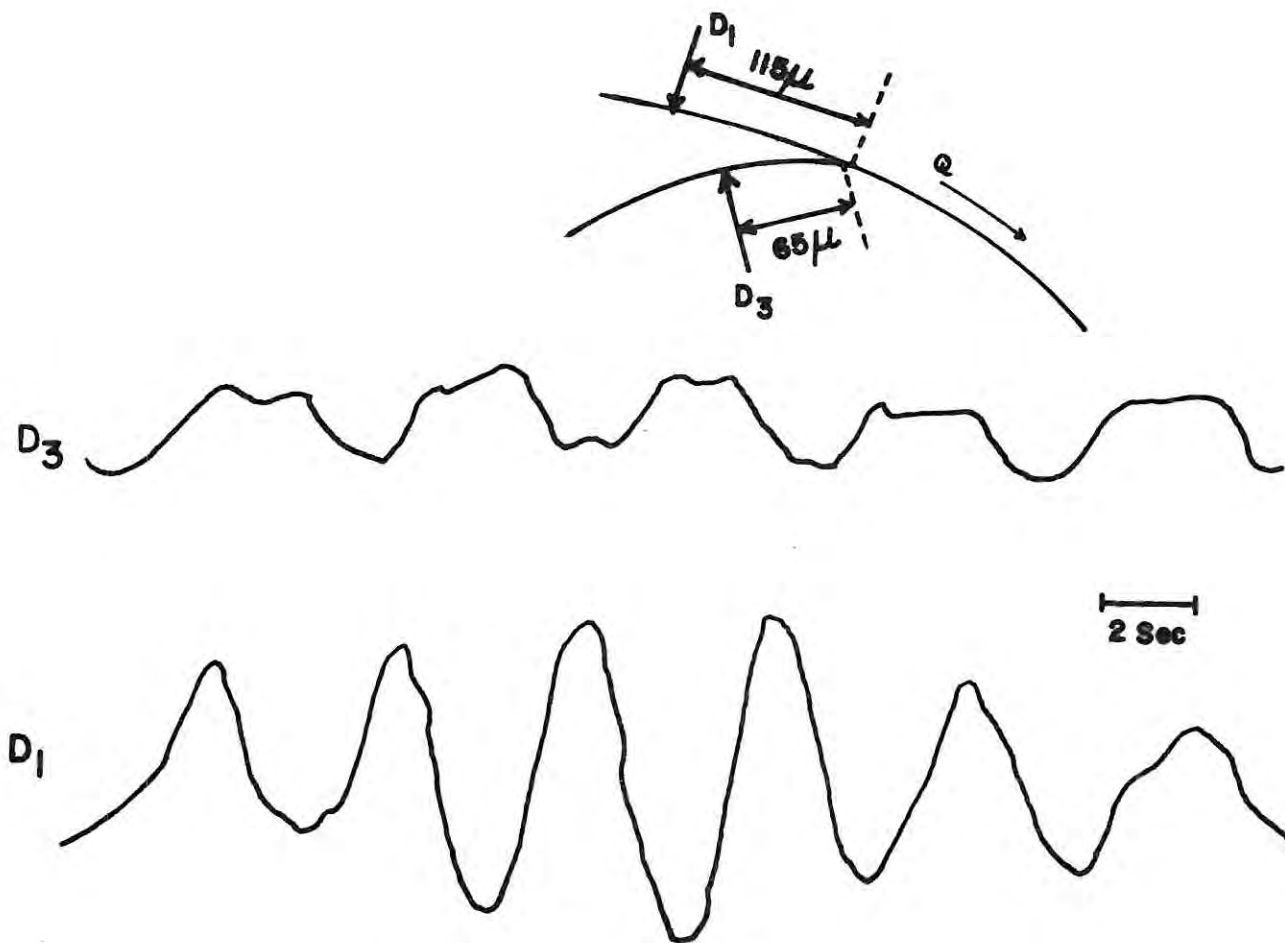
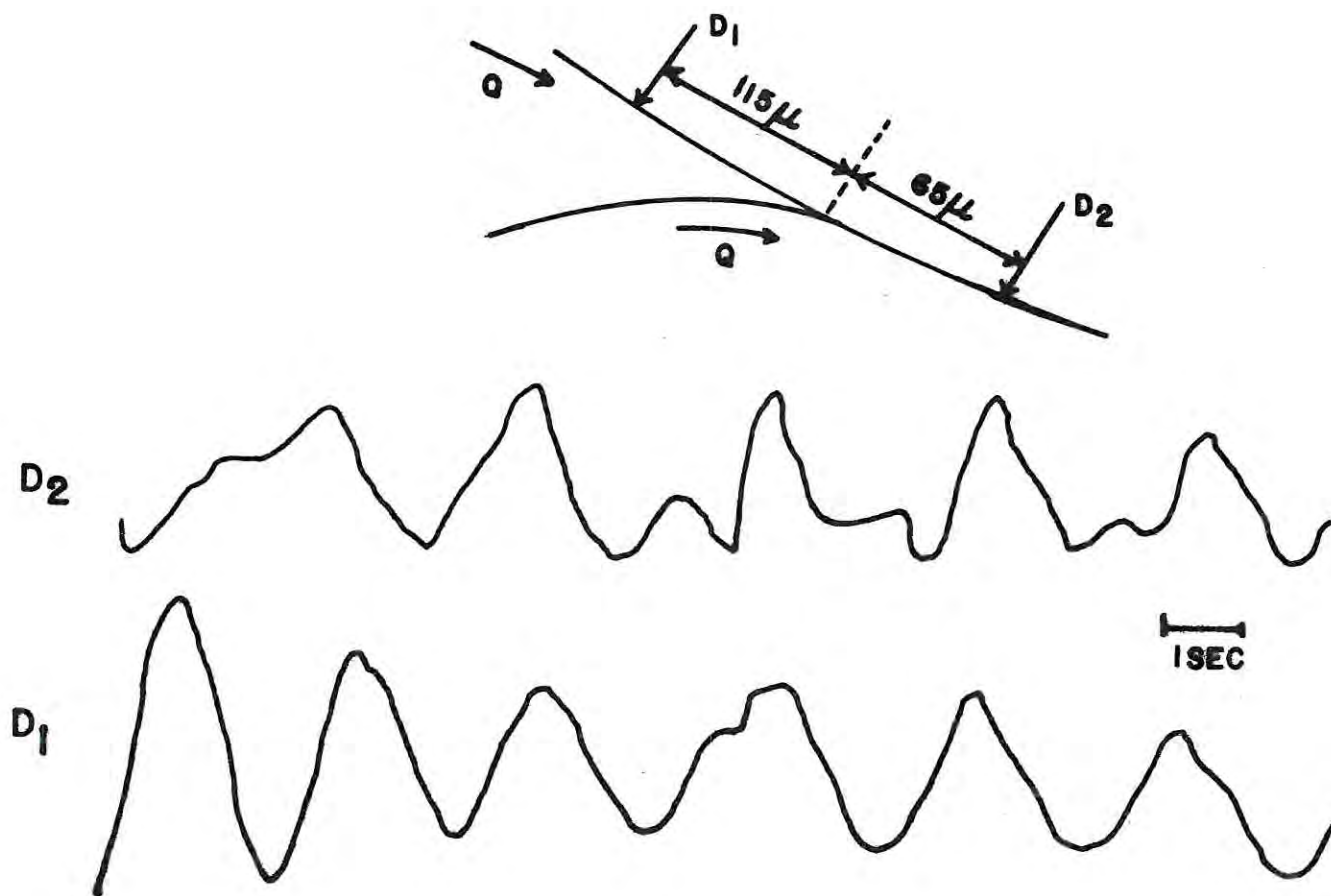


Figure 6.14. Cycle to cycle variability of rhythmic diameter changes. D_1 and D_3 are the diameter changes as measured at the sites shown in the inserted figure. Q is the normal flow direction.



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Figure 6.15. Asynchronous venomotion proximal and distal to valve site.

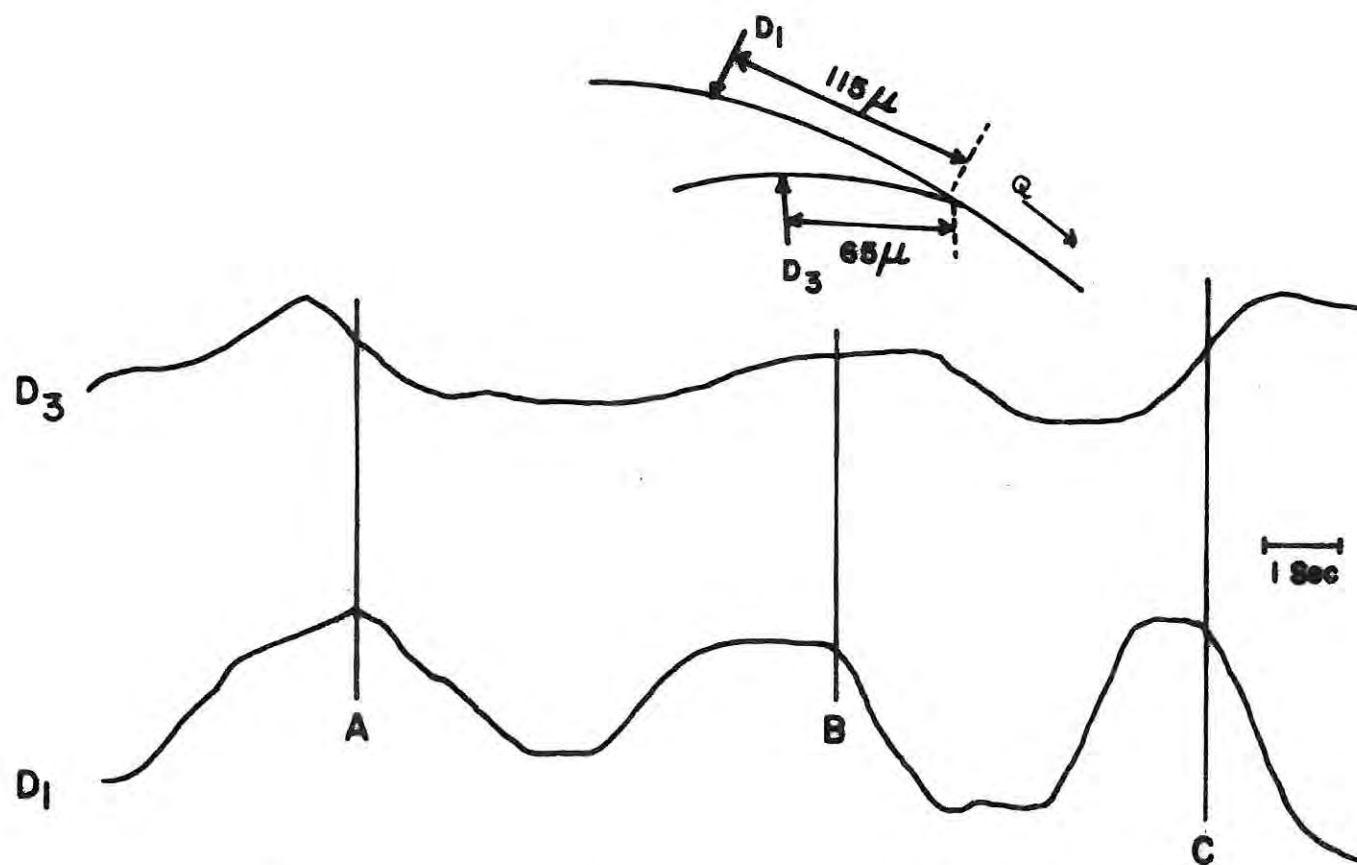


Figure 6.16. Asynchronous venomotion. D_1 and D_3 are diameter changes as measured at the sites shown in the inserted figure. Q is the normal flow direction. D_1 is seen to contract while D_3 is decreasing (Point A), while D_3 is relatively constant (Point B) and while D_3 is increasing (Point C).

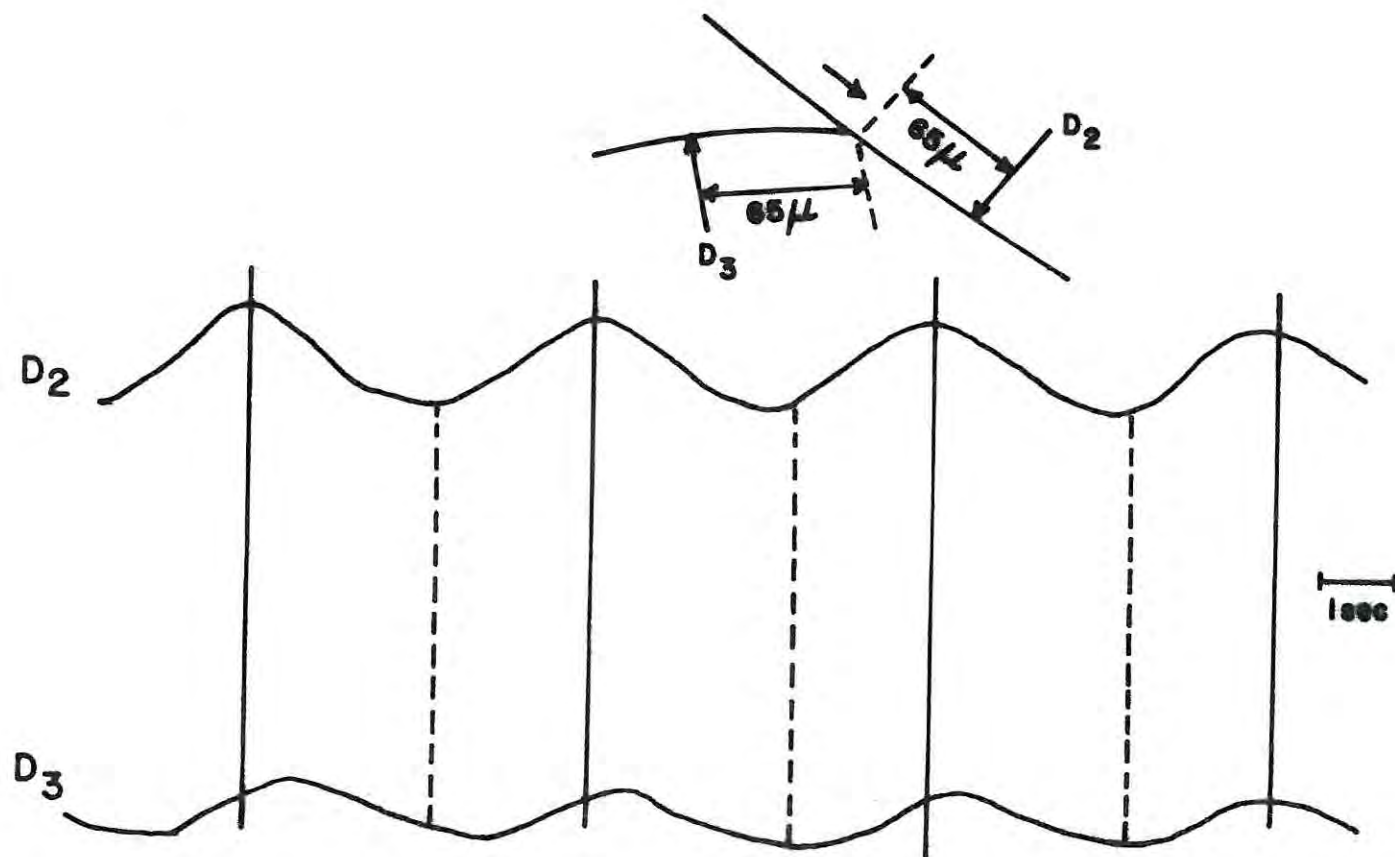


Figure 6.17a. Synchronous venomotion between collecting and feeding vessels. D_2 and D_3 are diameter variations measured at the sites shown in the inserted figure.

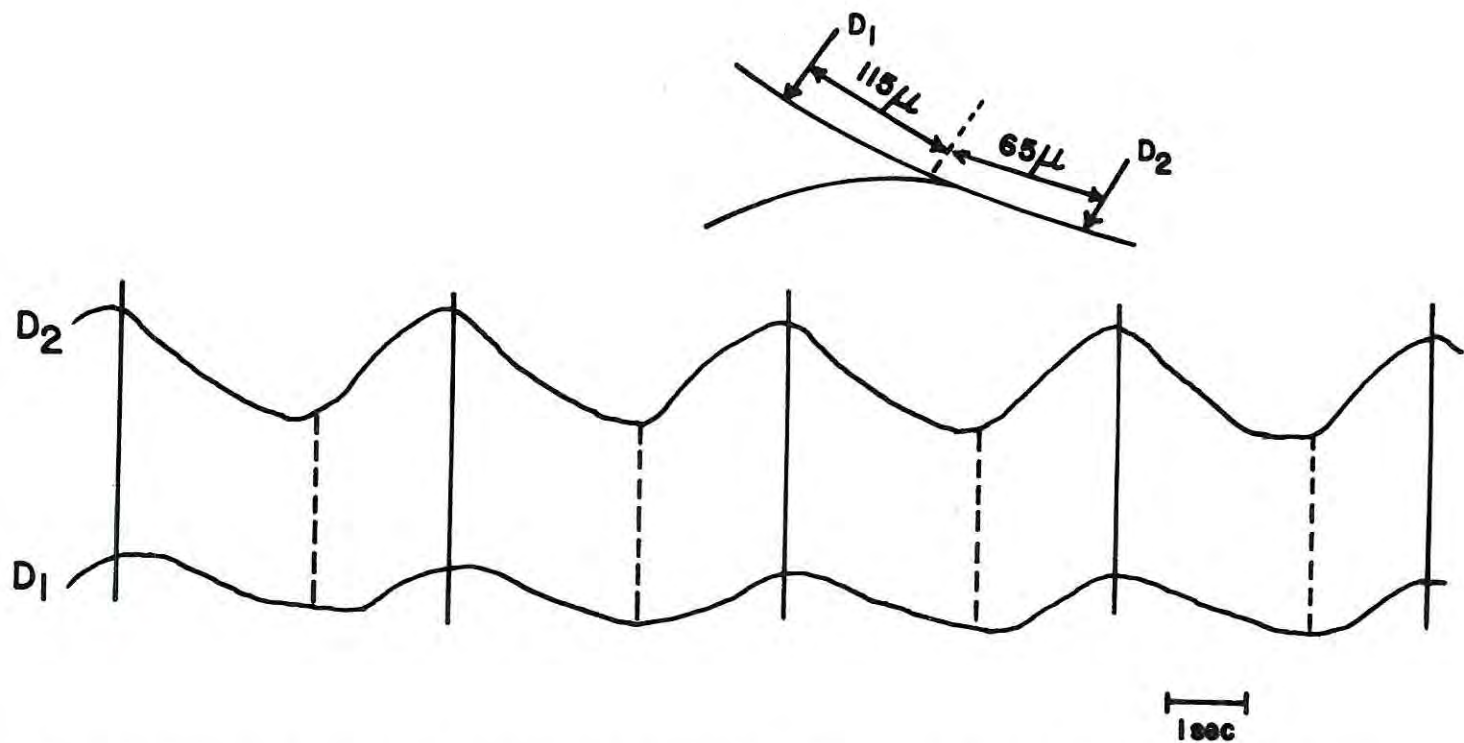


Figure 6.17b. Synchronous venomotion proximal and distal to valve site. D_1 and D_2 are diameter changes as measured at sites shown in the inserted figure.

In spite of this variability, there exists an underlying basic rhythmicity which can vary in the details of the observed time course of diameter and flow, but by careful observations and analysis of any particular set of dynamic events they may be interpreted in terms of the interplay between hemodynamics, valve action, and the active and passive characteristics of the venous vessels.

The general overriding characteristics of the dynamics of the venomotion process and the factors which influence these dynamics are now discussed with the aid of figure 6.18.

Contraction of S_3 may close valve X_1 by deformation and X_2 by pressure difference. That is, contraction of S_3 moves the wall surface (marked P_1) in such a fashion as to reduce the opening between the tip of valve X_1 and the wall. This results in a diminished flow out of S_1 and may entirely stop flow there, depending on the pressure in S_1 and S_3 . When this is the mode, then outflow from S_1 and S_2 go together. That is, contraction of S_3 reduces or stops both flows, and dilation of both ensues. When this is followed by a contracting S_2 the valve X_2 is opened by pressure developed by the contraction, and the valve X_1 is opened by deformation. This occurs as the result of S_2 diameter decrease, which then causes the wall region denoted as P_2 to exert a pulling force on the entire proximal wall segment of S_1 . This action creates an opening between the distal wall (P_1) and the valve tip (X_1).

The initial contraction of S_3 stops inflow from the side branches. When the vessel begins to relax, inflow from the side

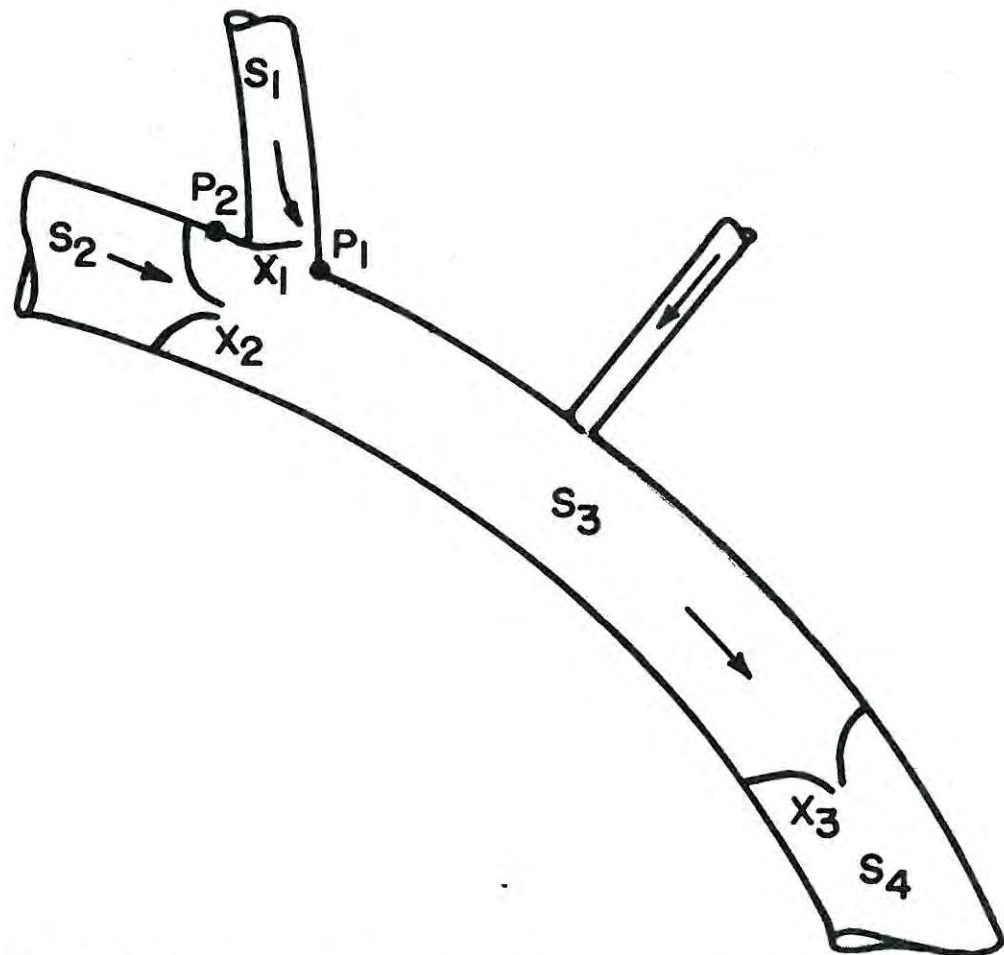


Figure 6.18. Typical segment of post capillary vasculature used as reference to describe dynamics. See text for discussion.

branches occurs. If the relaxation phase precedes the closure of the downstream valve (X_3), then the inflow from side branches in the vicinity of the valve is initially more vigorous. The dynamics described above may for convenience be termed Mode A.

A second general mode of dynamics may exist (Mode B). This mode is characterized by outflow from both S_1 and S_2 when S_3 contracts. At first glance this pattern appears to be inconsistent with the mode already described. However, by careful observation of the state of each of the contributors to the dynamic pattern, it is found not to be. When this mode is operative, S_1 , S_2 , and S_3 are found initially to be dilated, usually with a small flow entering S_3 from S_1 . Valves X_2 and X_1 are open, but the downstream valve X_3 is closed. The contraction of S_3 seems to open the valve X_3 . The contraction may instantaneously reduce the orifice opening of valve X_2 , but is insufficient to hold it closed, and flow issues from S_2 into S_3 and from S_3 out through valve X_3 . The reduction in diameter in S_2 appears to follow a passive reduction, and as this progresses, valve X_1 is opened admitting flow from S_1 . The flow may be stopped in two ways. If S_3 contracts again before the downstream valve X_3 closes, then X_1 and X_2 will again be closed and Mode A dynamics are obtained. This occurs when the rate of inflow from S_2 and S_1 is sufficiently greater than the rate of outflow through X_3 to cause sufficient dilation of S_3 to trigger a contraction. On the other hand, if S_4 contracts (due to its expanded volume), then valve X_3 is closed (providing that S_4 contraction is strong enough), and the

main flow is again stopped, and Mode B dynamics continue. It is important to point out, however, that the bicuspid valves need not always be closed after contraction of the downstream segment; this clearly depends on the relative magnitudes of upstream pressure to contracting strength. We have observed these valves to swing shut from a fully wide open position, but have also seen the valve orifice to modulate between 18 microns when "open" and 10 microns when "closed". Thus, we see that flow out of a particular vessel segment occurs in a way which may be due to its own contraction (S_3 , Mode B) or somewhat passively (i.e., due to upstream pressure gradient with the aid of a downstream valve opening, as in S_2 when Mode B is operative).

The dynamics for the side branch feeding vessels are clearly interrelated to the activity at the major branch points and valve sites. To describe the typical dynamic patterns, the topology shown in figure 6.18 is used as a reference. A feeding vessel (having an unlabeled valve) is illustrated joining S_3 . Flow from the feeding side branches may occur when there is flow in their collecting vessel segment (S_3) or when there is no flow. Which occurs depends on the dominant dynamic mode of the collecting segment (i.e., Mode A or B) and the position of the feeding vessel with respect to the valve sites.

The predominant entry of flow from the feeding side branches occurs when the collecting vessel segment is dilating. Conversely, the branch inflow is most frequently observed to stop

or become significantly reduced when flow is entering its collecting segment due to inflow originating upstream from its entry site to the collecting vessel (i.e., when flow is entering S_3 from either S_1 or S_2).

The dilation phase may occur in two general ways. The most common follows the closure of the downstream valve. Most frequently the timing of this closure coincides with a point near the end of the contraction of the collecting segment (S_3) (at this time the developed pressure due to the contraction is presumably falling off rapidly). However, as has already been stated, a downstream contraction or a significant increase in pressure within the larger feeding vessels into the downstream segment (S_4) could cause valve closure at any point in the collecting segment's (S_3) venomotion cycle. In any case, the resultant valve closure is quickly associated with a dilation of the collecting segment.

The fluid volume entering S_3 in this state has in general three sources: the feeding branch vessels throughout the length of the collecting vessel; the large vessel in the vicinity of the upstream valve (S_1); and the upstream segment (S_2). If the closure of the downstream valve (X_3) occurred following the active contraction of S_3 , then upon the valve's closure the upstream valve had already been closed, and the predominant inflow into the collecting vessel is from the feeding side branches. The branches closest to the downstream valve (X_3) produce flow first and are followed progressively by inflow from the other side branches. A

dilation wave spreads upstream, and when it reaches the site of a large inflowing branch the wall distension opens its valve, and a more rapid dilation rate is observed as the inflow from this larger branch occurs. Finally either by distension or active contraction of the upstream segment (S_2) (precipitated by its own dilation), flow enters from the upstream segment causing a further rapid rise in the dilation of the collecting vessel. This final distension precipitates a contraction in the collecting vessel (S_3) which again, depending upon pressure upstream, may close the upstream valves, stop or significantly reduce side branch inflow, and produce flow into the downstream segment (S_4). The separate phases of this process (which are most clearly observable when the pressures in the side branches and upstream segments are not too high) are illustrated in figure 6.19. Three consecutive venomotion cycles characterized by the diameter variations at two longitudinally separated observation sites in a collecting segment (e.g., S_3 of figure 6.18) are shown. In cycle one the "filling" phase of the collecting segment is between points 1 and 6, in cycle two between points 7 and 12, and in cycle three between points 13 and 16. Downstream valve closure (e.g., X_4 of figure 6.18) occurs approximately at points 1, 7, and 13. During the interval between 1 and 3 there is filling of the collecting vessel from the side branches. The dilation delay between the downstream and upstream sensor may be noted in each of the cycles. At point 3 there is rapid increase in diameter which in this case was due to flow influx from an upstream large feeding vessel and an

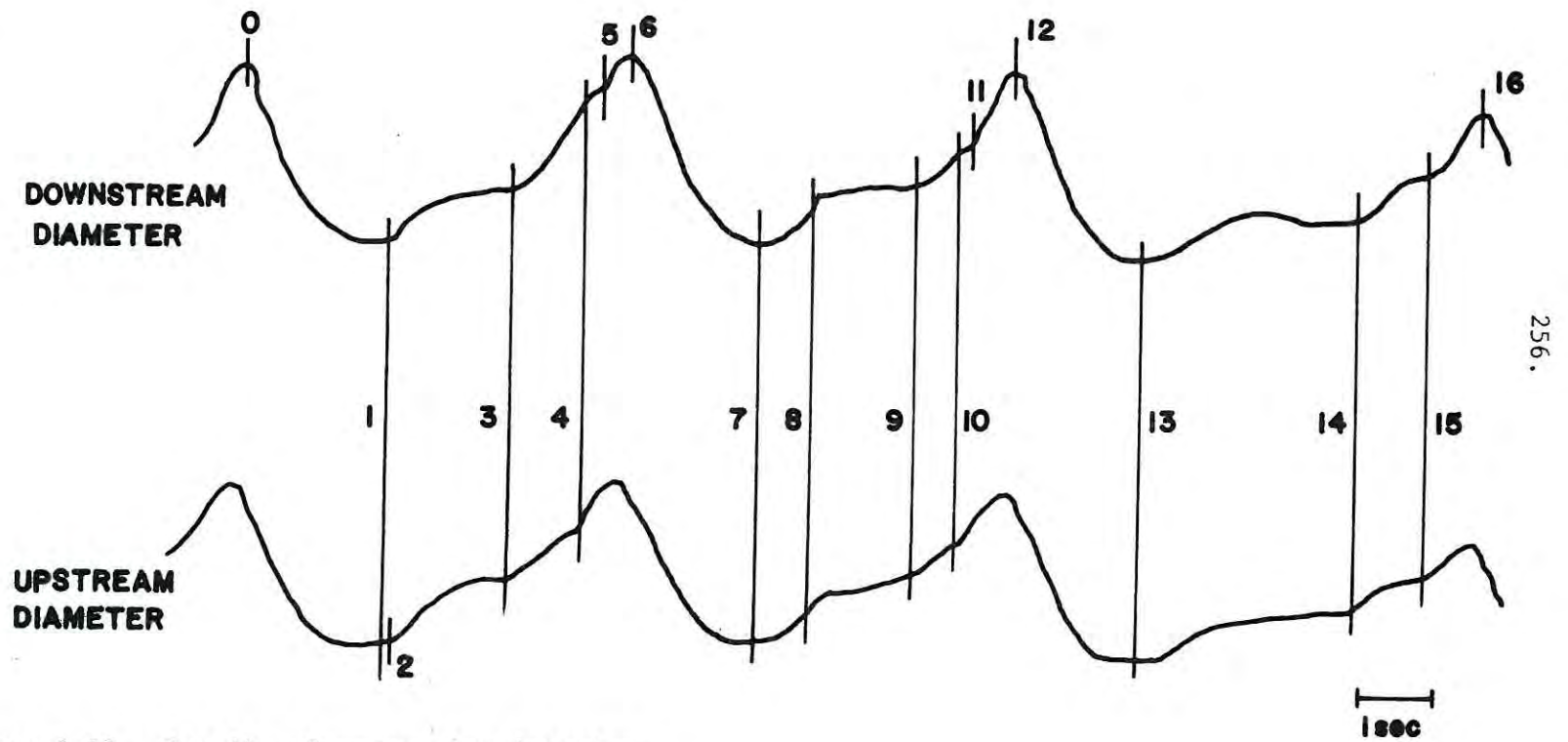


Figure 6.19. Details of venomotion dynamics.

increase in the rate of inflow from the feeding side branches. Whether this is precipitated by a relaxation of the contractile state of muscle of the collecting segment or by the nonlinear characteristic of the opening valves with increasing distension was not determined. At point 4 the upstream segment contracted producing an accelerated dilation occurring first upstream and spreading downstream (point 5). Point 6 marks the beginning of the contraction phase. Similar relationships may be seen in the other cycles. It is worth noting that in the third cycle illustrated (points 12 through 16) the filling phase is longer than in the two previous cycles. The result of this is a decreased fundamental period, i.e., $T_{0-6} = 5.2$ sec, $T_{6-12} = 5.2$ sec, $T_{12-16} = 6.2$ sec, which occurs with no significant change in the contraction phase.

A second general way in which dilation of the collecting segment (S_3) may occur is due to upstream flow entry while the collecting vessel's downstream valve (X_3) is open. It may be open due to a prior contraction of the collecting vessel segment (S_3) or due to conditions downstream from the valve (e.g., in S_4). In either case the entry of upstream flow will (when the rate of entry exceeds the rate of outflow) cause dilation of the collecting segment (S_3). If this inflow occurs while the collecting segment is in a contracting or contracted state, the induced dilation may result in outflow from the side branches in the vicinity of the downstream valve. The extent of outflow is determined by two conflicting factors. On the one hand, the pressure in the collecting

vessel is rising due to the upstream flow. On the other hand, the resultant distension has the tendency to partially distend the feeding vessels, which results in an opening of unicuspid valve at its entrance. On occasion flow is observed to enter from a feeding vessel, depending on the pressure upstream in the feeding vessel circuit.

V. Effect of Thermal Perturbations on Dynamics

The evidence which has been presented in Sections III and IV suggests that the post capillary vasculature is endowed with intrinsic, hemodynamic control properties. This control is manifested as a rhythmical variation of vessel diameter having fundamental oscillatory periods ranging from eight to two seconds. A principal characteristic associated with alterations in frequency is the change in the duration of the filling phase of collecting vessel segments. One of the factors influencing the filling rate is the rate of inflow from the feeding vessels, which, as has been pointed out, depends on the state of contraction of the collecting vessel, its intravascular pressure, and the state of the various valves.

Examination of the hemodynamic changes in effects of venomotion frequency using the Microvascular Model has shown that the rate of fall of intravascular pressure following contraction increases with increasing frequency, whereas the rate of rise of contraction induced pressure remains relatively constant (c.f., figures 5.10 and 5.12). Further, it was found that due to the valves, this is associated with an increase in the average outflow (c.f., figure 5.6). These hemodynamic predictions suggest that where venomotion frequency is increased, the rate of diameter dilation will be increased, whereas the rate of diameter decrease will remain relatively unchanged. Further, for any given value state, the branch inflow would be expected to increase for any perturbation which causes the pressures in the upstream circuits to increase. To test

this hypothesis, two forms of perturbation were used: heating of the local vasculature (results presented in this section), and pressure elevation on the arterial side (results presented in Section VI).

In figure 6.20 is shown the diameter recording and the typical response to heating produced by opening the microscope diaphragm. Under normal conditions the light intensity is maintained below the threshold, which may cause any significant local heating. Opening of the diaphragm fully results in more intense heat, which radiates over a wider area. The resulting decrease in the fundamental period of oscillation is seen to be rapid and significant. For the particular case illustrated in figure 6.20, the average fundamental period prior to the increase in light intensity (the average of the previous ten cycles) is 3.1 seconds. This value is somewhat smaller than the average values most often recorded in control states. The average period for the first 10 cycles after the light intensity increase is 1.9 seconds, and for the second 10 cycles is 1.7 seconds. After returning the light intensity to the control value, the measured period averaged over the first 10 cycles in the recovery phase is 2.7 seconds.

The decrease in the period is principally due to a reduction in the duration of the filling phase. This would occur is the increased light intensity caused arteriole dilation and hence an increase in the pressure in venule side branch circuits. However, it is alternatively possible that, given the presence of pacemaker type muscle in the collecting vessels, the heating causes an increase

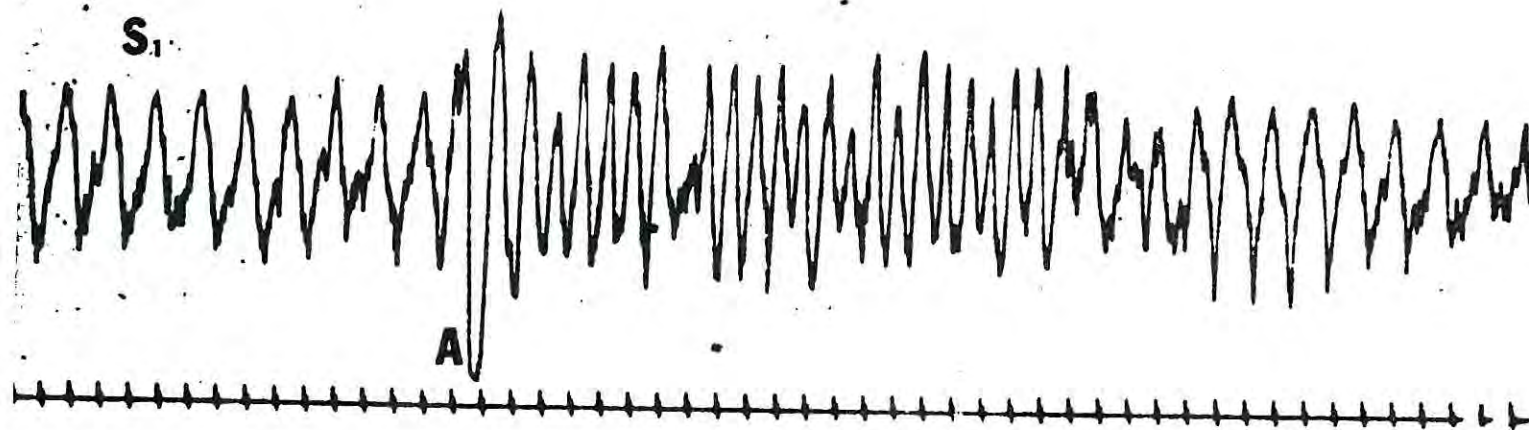


Fig.6.20.Effect of thermal perturbation on venomotion. Photosensor output (S_1) records pattern of diameter variation. Downward deflection denotes decrease in vessel diameter. Rapidly opening microscope diaphragm (at A) produces the thermal perturbation. Venomotion period rapidly decreases from control value of 3.1 seconds to 1.7 seconds. Pre-perturbation maximum diameter is 50 microns and minimum diameter is 36 microns. Post-perturbation maximum diameter is 54 microns and minimum diameter is 33 microns. Time marks are at two second intervals.

in the intrinsic contraction rate. However, if the latter possibility were dominant, an increase in rate accompanied by a significant decrease in both the mean and peak to peak diameter variation would be expected. This is, however, not observed. On the other hand, if the basic rhythm associated with venomotion is myogenically triggered, then an increase in the rate of filling will achieve a given threshold sooner, with a resulting increase in frequency. The observed response would suggest, then, that the increase in frequency observed with heating is secondary to upstream pressure elevation precipitated by arteriole dilation.

VI. Effect of Pressure Perturbations on Dynamics

Direct investigation of the effect of elevation of arterial pressure was carried out by cannulating a major artery in the manner described in Chapter Two, Section III. Pressure was elevated by injecting in a retrograde fashion a small quantity of buffered saline. This method also permitted the study of the transit characteristics of the injected bolus from artery to vein and local vascular regions in between (this aspect is discussed in Section VI-C). On occasion the tip of the microcannule was allowed to become plugged so that pressure could be transmitted from the cannula through the plugged tip without any saline injection.

Using this technique of arterial pressure elevation, the arteriole which is feeding the region of the post capillary vasculature under observation will be free of red cells for a period of time which corresponds to the time interval in which the induced perturbation pressure (by injection) exceeds the normal arterial pressure at the arteriole branch point (one to three seconds).

A. Arterial Effect

In figure 6.21 the physical arrangement on the arterial side is illustrated. The two sensors are placed over the center of the artery and separated by an axial distance of 350 microns. In figure 6.22 a typical response as recorded at these sites is shown. The bottom tracing denotes the initiation of the pressure increase by injection into the microcannula. Increasing the pressure in the microcannula above that in the artery produces retrograde

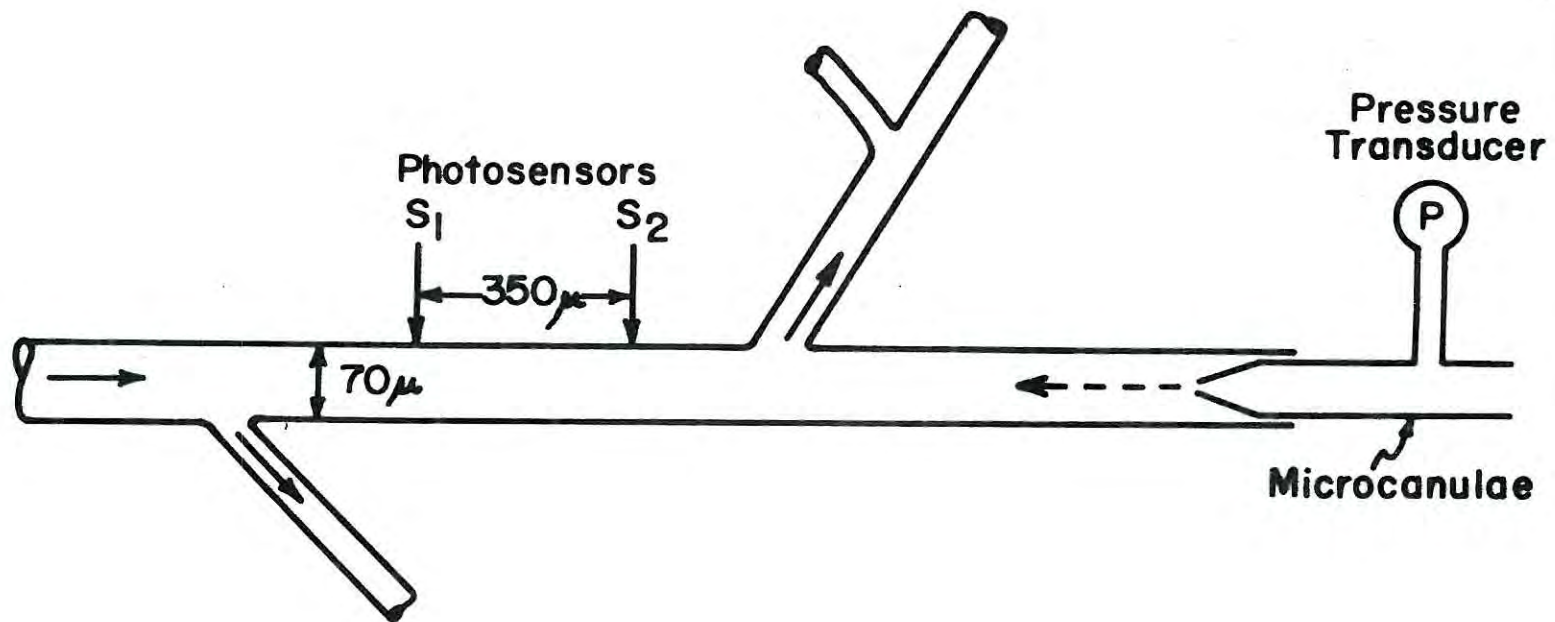


Figure 6.21. Method of producing and recording arterial perturbation.

flow in the direction indicated by the dotted arrow in figure 6.21. The region in the vicinity of the sensors becomes increasingly transparent, since the red cells which are normally flowing are forced upstream. The arrival of this clear plasma bolus is seen in figure 6.22 to occur first at S_2 , but quickly appears at S_1 . The time delay depends on the pressure exerted, and in this case the measured velocity is approximately 1.88 cm/sec.

As the perturbation pressure falls and becomes less than the normal arterial pressure, the direction of flow in the vicinity of the sensors reverses itself (returns to the normal direction). Normal blood now first enters the sensor zone S_1 , causing the lumen opacity to return toward normal. The returning flow then arrives in the zone of sensor S_2 , with a delay which is proportional to the initial velocity of the returning flow. On occasion, the individual contribution of each arterial pulse in the returning flow may be seen, as shown in figure 6.23. Each small discrete increment in the S_2 tracing during the return flow phase corresponds to the effect of the arterial pulse (rate about 300/minute).

In figure 6.24 the bolus pattern is illustrated as monitored in a branch of the artery (sensor separation 350 microns, vessel diameter 48 microns). In the arteriole, because of the larger velocity, the delay in recovery at the two axial sites is much reduced in comparison to the larger vessels. However, on occasion even in these branches the pulsatile components of the

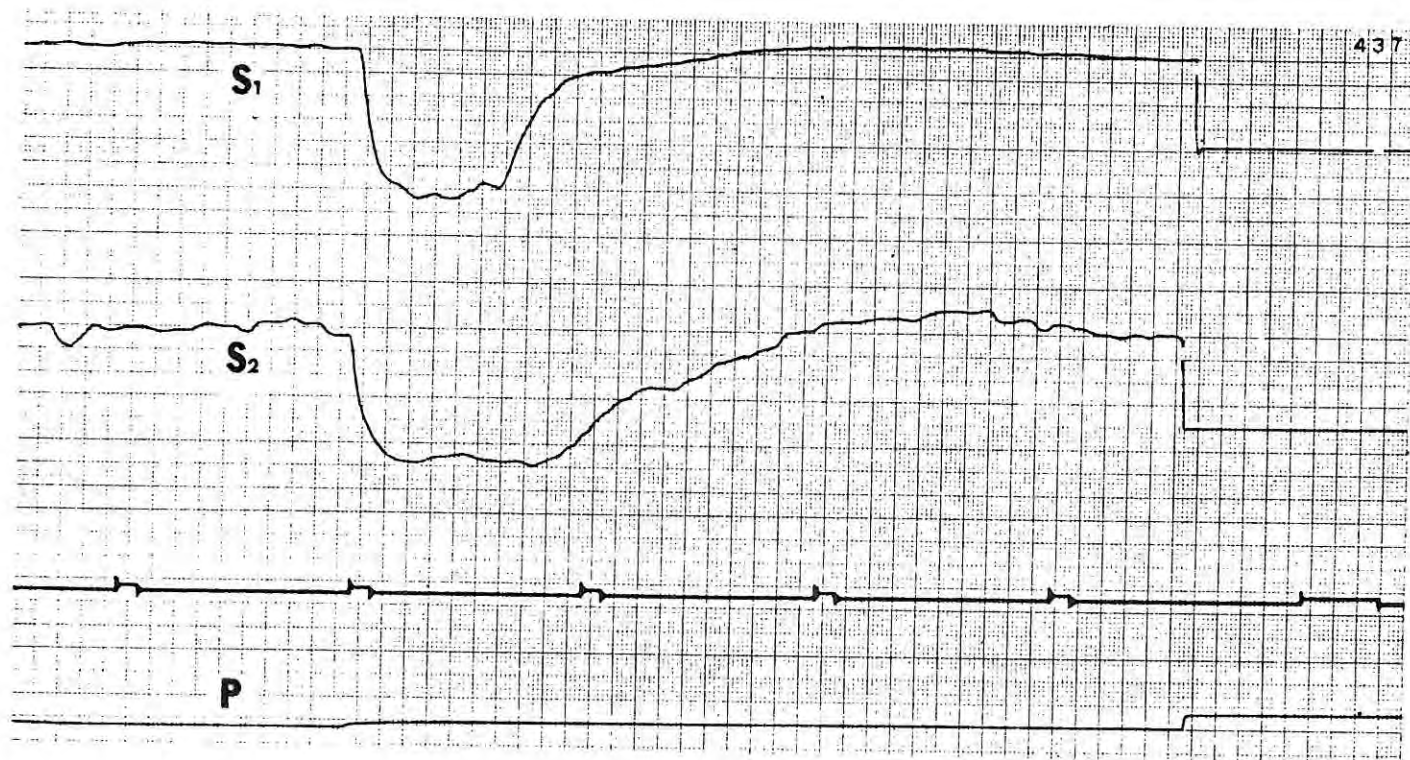


Fig. 6.22. Flow pattern in cannulated artery resulting from arterial pressure perturbation sensor locations (S_1 & S_2) correspond to those shown in the previous figure. Time marks are at two second intervals. The initial rise in the cannula pressure (P) denotes start of perturbation. Decrease in sensor output corresponds to decrease in vessel opacity.

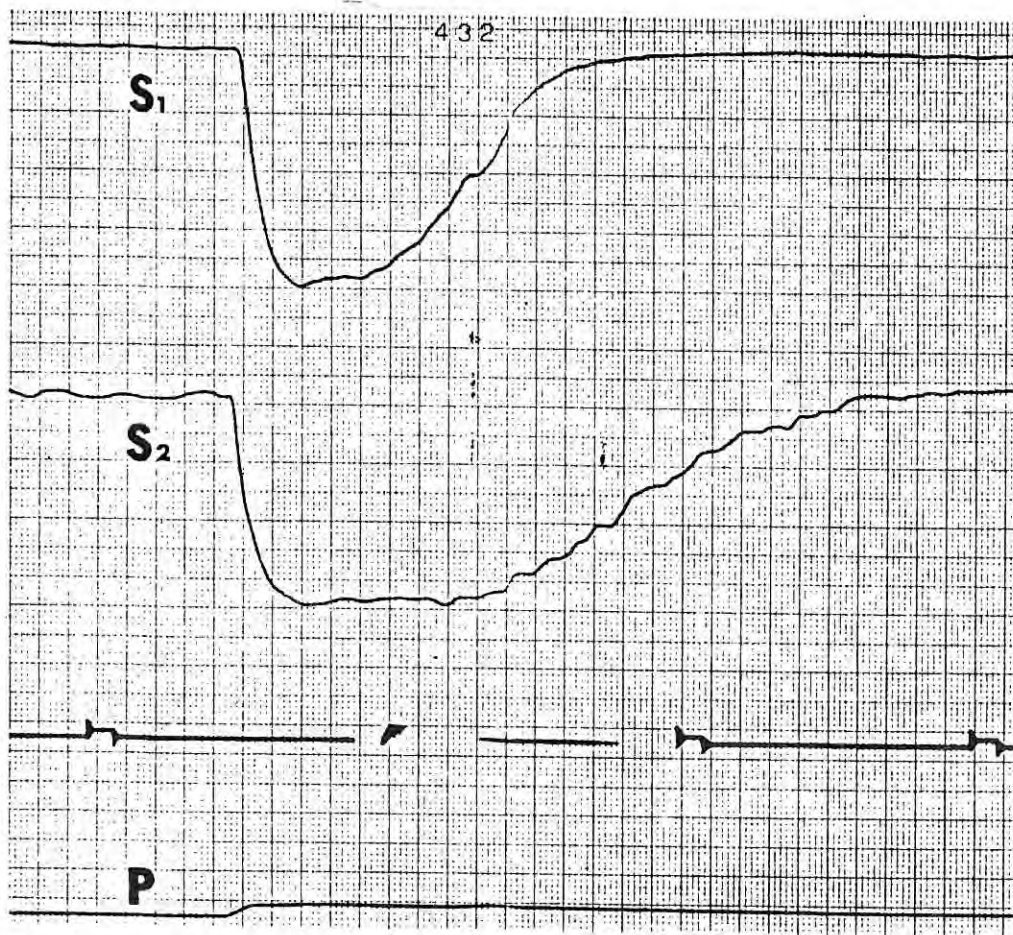


Fig. 6.23. Effect of arterial pulse on recovery phase of flow perturbation. The individual contribution of each pulse is clearly seen on the ascending limb of sensor 2 output. Heart rate 300 per minute. Time mark intervals are two seconds.

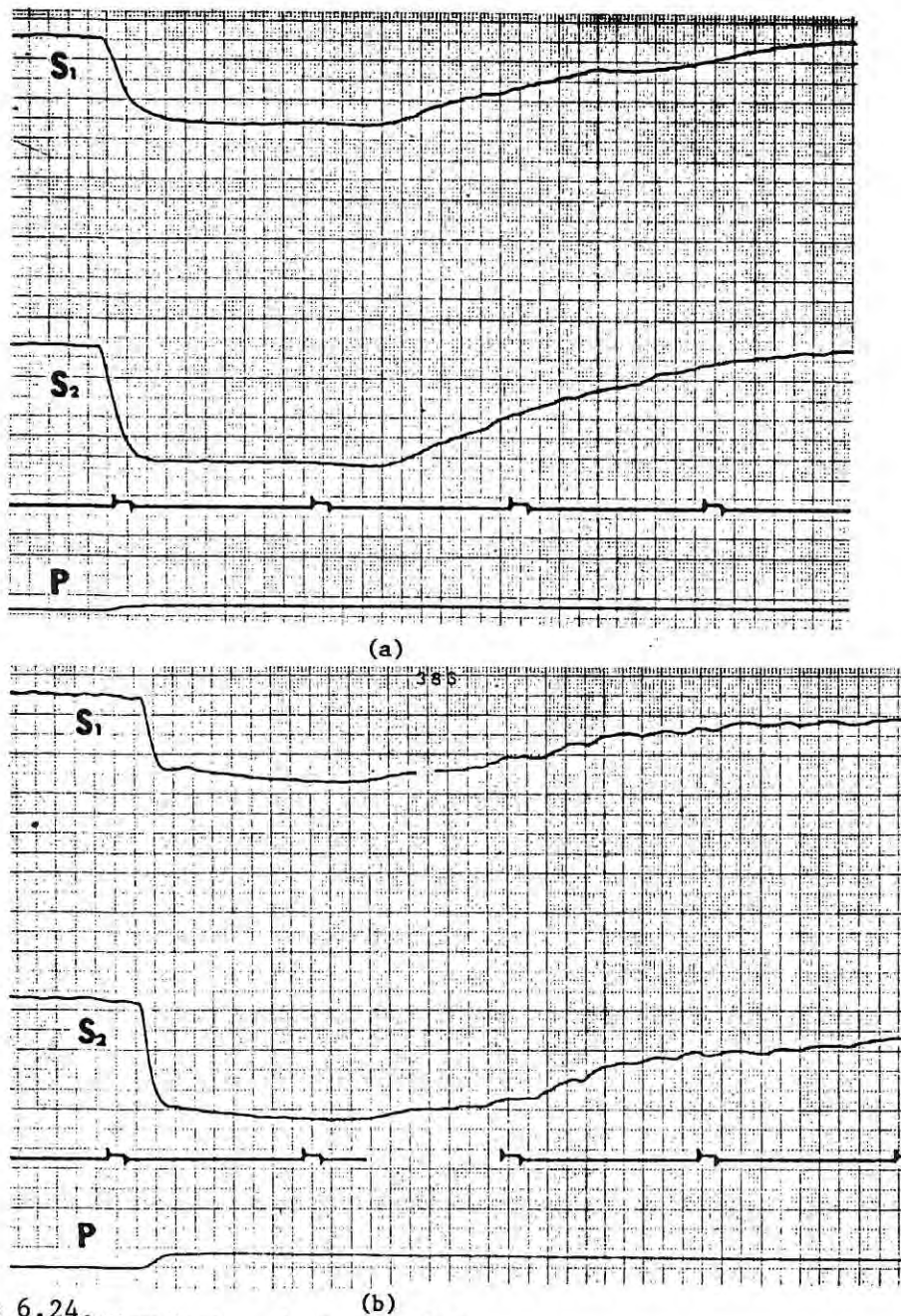


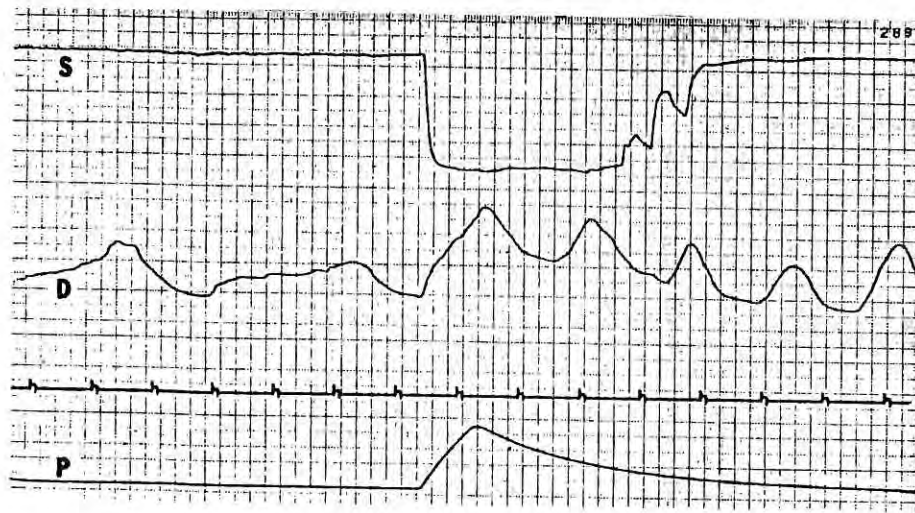
Figure 6.24. Flow Pattern in Branch of Cannulated Vessel Due to Pressure Perturbation. Time marks at two second intervals. Downward deflection of sensor outputs (S_1 & S_2) denote decreasing vessel opacity. Initial rise in cannula pressure (P) denotes perturbation start. In (a) standard pattern is seen. In (b) effect of arterial pulse on recovery phase is clearly seen on ascending limbs of sensor outputs.

recovery phase are observable, as shown in figure 6.24b.

The relationship between the duration of the arteriolar bolus and its manifestation at the collecting venule is illustrated in figure 6.25. The mechanisms associated with the increase in venomotion rate are as described in Section B below. However, as can be seen, the duration of maximal diameter elevation in the post capillary vessel is related to the duration of the arteriolar bolus. This result is to be expected, since the duration of the arteriolar bolus corresponds to the time that the arteriolar pressure is elevated above the normal arterial pressure.

B. Post Capillary Effect

In figure 6.26 are shown the diameter variation (d) and flow pattern (S) recorded in a small venous vessel before and after pressure elevation on the arterial side (P). Downward deflection of the flow recording corresponds to increasing flow. In (a) it may be seen that in this example the arterial perturbation arrives at the venous segment under observation while that segment is contracting. The elevated pressure associated with arrival of the perturbation causes the vessel to dilate even though in the contracting state, whereas the flow produced by this contraction continues. When the vessel relaxes the diameter is forced to a larger value than in the control, due to the now elevated intravascular pressure. The rapid dilation is followed by a contraction, but due to the elevated pressure in the feeding circuits the filling phase is considerably more rapid than prior to the perturbation,



(a)



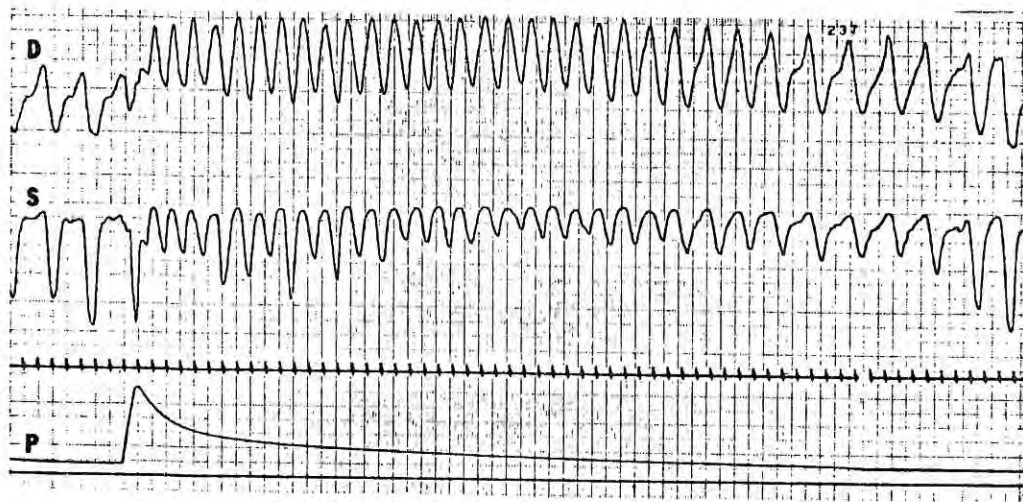
(b)

Fig.6.25. Effect of arterial perturbation duration on post capillary dynamics. S is arterial sensor output. Downward deflection denotes decreasing vessel opacity. D is venule diameter in relative units. Downward deflection denotes vessel diameter decrease. Upward deflection of arterial

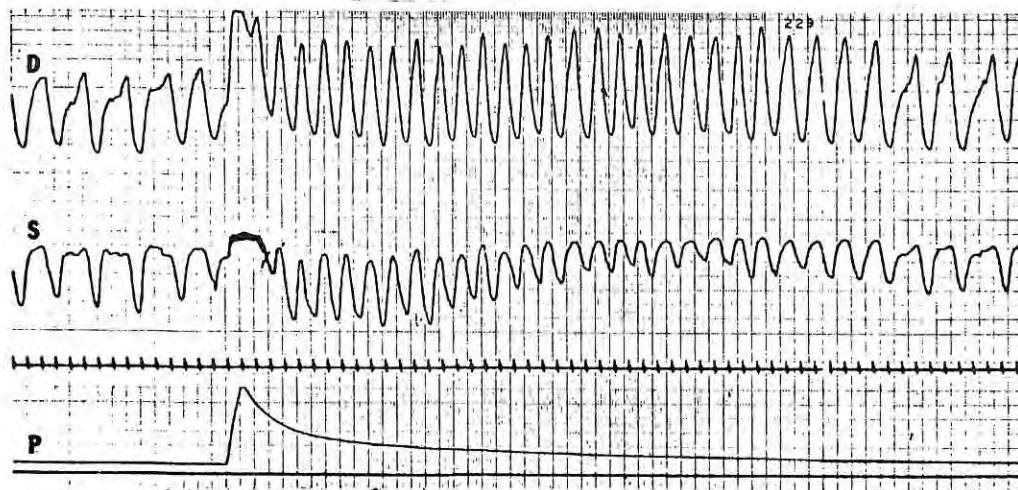
whereas there is not a significant change in the time course of the contracting phase. The average period in the control state is 5.8 seconds and 3.1 seconds after the perturbation, an increase in frequency by almost a factor of two!

In part (b) of figure 6.26 the effect of a pressure elevation becomes manifest in the venule while it is dilating. Comparison with the results shown in part (a) shows that the initial dilation caused by the pressure elevation is larger here. However, when the vessel relaxes the total change in diameter from the control level is the same in both cases.

Another difference in response related to the state of the vessel at the time of the arrival of the pressure perturbation is the time required for the pressure elevation to manifest itself in the venous segment. In figure 6.26 (b) this delay is about 400 msec, whereas in figure 6.26 (a) this delay is about 800 msec. To understand how this time delay difference comes about, the sequence of events starting with the initial elevation of arterial pressure needs to be considered. The pressure wave arrives at the vessel segment under observation via the side branch feeding vessels. The propagation time of the pressure wave is small (20-40 msec), and for many purposes may be neglected. However, if the wave arrives when the feeding vessel exit valve is closed, there will be a delay in the manifestation of this pressure within the collecting segment associated with the opening of this valve. Once the valve is opened, side branch inflow will occur, and vessel dilation will



(a)



(b)

Fig.6.26.Effect of arterial pressure perturbation on venomotion and small vein flow pattern. D is small vein diameter in relative units. Downward deflection denotes decreasing diameter. S is the sensor output which records the opacity of the vessel lumen and is representative of the rhythmic flow pattern. Downward deflection denotes increasing flow. Upward deflection of the arterial cannulae pressure (P) denotes start of perturbation. Time marks are at two second intervals. In (a) perturbation arrives at venous vessel under observation while it is contracting and in (b) while it is dilating. See text for explanation.

result. The time required for a typical side branch valve to fully open in normal operation has been measured to range from 200 to 300 msec.

In addition to this valve delay, there is the time required for the side branch inflow to arrive at the measuring site. That is, vessel dilation can only occur in the presence of a net increase in inflow. If the perturbation arrives while the collecting segment's downstream valve is open (as is the case when it arrives while the vessel is contracting), then the pressure wave associated with the side branch valve opening propagates in a manner similar to a diffusional process. The associated net inflow serves to dilate the vessel and will be observed at the measuring site at a time depending on the velocity of the inflow (see Section C for mathematical analysis). On the other hand, if the perturbation arrives at an open side branch valve and closed downstream valve [as is the case in figure 6.26 (b)], then valve delay is eliminated, and in addition the pressure wave exerts a compressional effect on the relatively stagnant volume in the collecting segment causing dilation first at sites close to the downstream valve. These factors account for the difference in observed initial or transient response. However, the similarity of the sustained response, that is, the frequency elevation in the two types of cases, is quite clear.

The initial phase of the response is more clearly seen using an expanded time scale, as shown in figure 6.27, which records the diameter variations at two closely separated axial sites on the

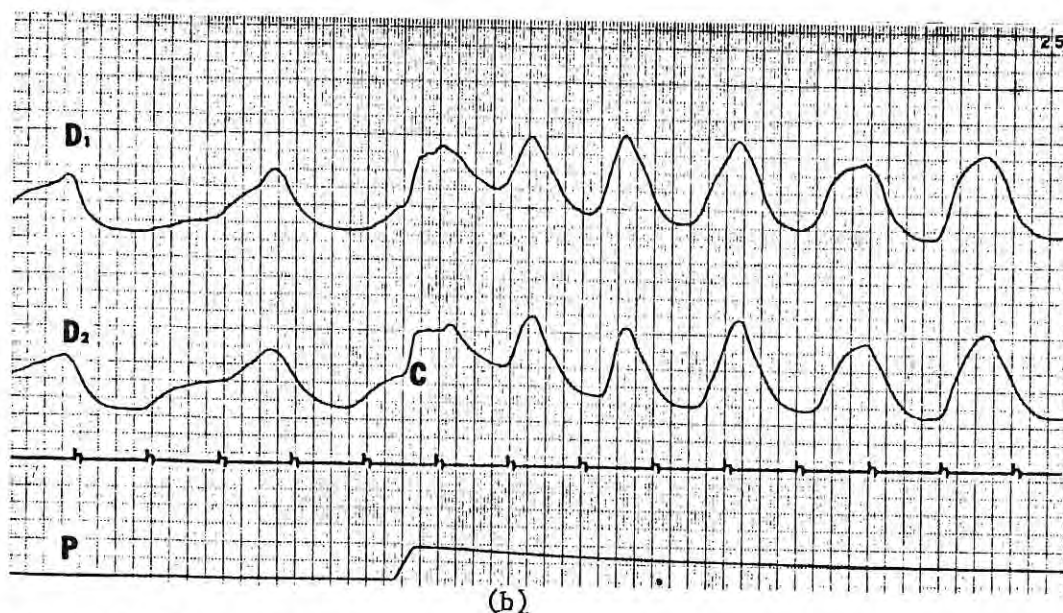
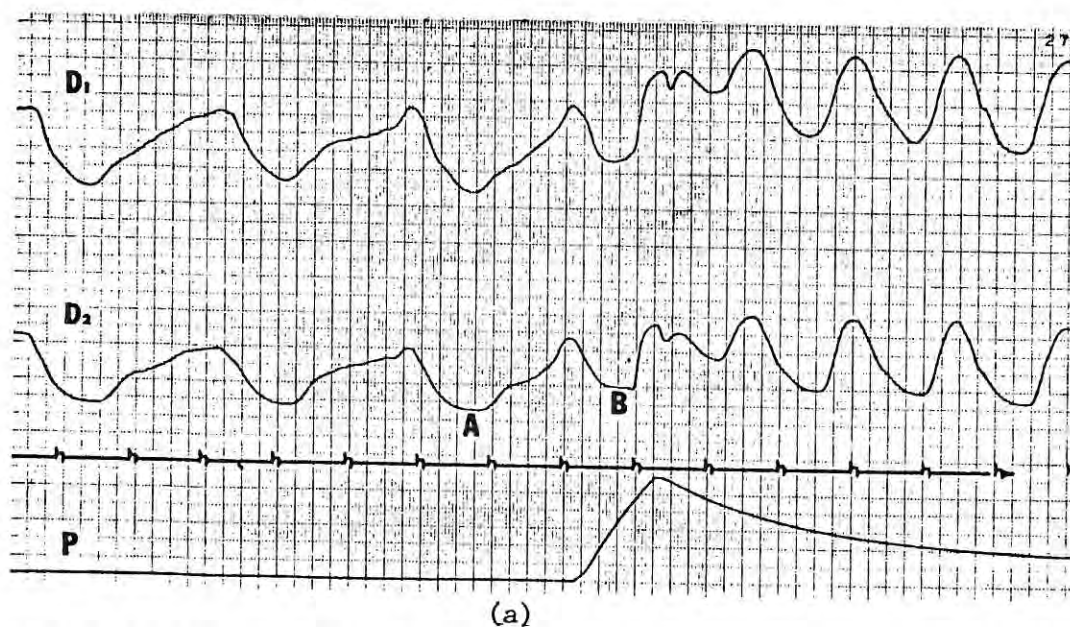


Figure 6.27. Initial response of venomotion to arterial pressure perturbation. D_1 and D_2 are diameter variations of small vein as recorded by closely spaced photosensors. Downward deflection denotes decreasing diameter. Upward deflection of cannulae pressure (P) denotes start of arterial perturbation. Time marks are at two second intervals. In (a) perturbation arrives while the vessel is contracting. Note that the contraction following arrival of perturbation produces less diameter reduction (c.f. A with B). In (b) perturbation arrives while vessel is relaxing and produces rapid vessel dilation (point C).

same vessel segment. In figure 6.27(a), the perturbation arrives while the segment is contracting. The initial effect is a reduction in the amount of diameter decrease associated with the contraction (c.f., Points A and B). The two opposing forces acting on the vessel wall (i.e., muscle contraction and the pressure perturbation) reach a short-lived equilibrium in which the vessel diameter remains essentially constant. Upon relaxation of the muscle, the pressure dominates, and a significant dilation results. This is followed with a contraction which achieves only a small reduction in vessel diameter, being quickly overcome by the distending pressure. In (b) of this figure, the perturbation arrives while the vessel is in a relaxing state. The initial effect of the perturbation is rapid dilation (Point C). In both cases, we again note that the increase in frequency after the transient effects is primarily associated with a reduction in the duration of the "filling" phase.

In summary: The frequency of venomotion will increase when the pressure in the vascular circuits feeding the rhythmically active post capillary vessels increases. Pressure increase may be due to normally occurring changes in terminal arteriole and pre capillary sphincter diameter, as was shown by the Microvascular Model results, or by induced pressure increases, as has been shown experimentally. The elevation in frequency is associated with a more rapid reduction in post contraction

intravascular pressure, as was shown by the Microvascular Model, which together with the elevated pressure in the feeding circuits results in a reduction in the filling phase duration. This reduction is manifested in a more rapid dilation of the vessel diameter, which initiates the next contraction. The duration of the elevated frequency is proportional to the duration of the pressure perturbation, and, as shown by the Model, is associated with an increased venous outflow.

C. Bolus Transit Time

The transit time of an injected indicator (as measured by the time delay between injection at one vascular site and recovery at another) has long been used as one method of characterizing the nature of the vasculature which lies between. It is the purpose of this section to describe the way in which the vascular topology and post capillary dynamics may significantly influence the transit time through a vascular bed.

Using the method of arterial injection previously described (Section VI-A), there is generated an initial pressure perturbation. In addition to the influence on the dynamic activity associated with the pressure perturbations, the bolus itself disperses throughout the vasculature as it is carried with the flow through a multiplicity of pathways. By tracking the pathway of the dispersed bolus, information relating to its transit time through different vascular regions may be obtained. To do this

the sensors are placed over the center of the vessels in order to detect the appearance and velocity of the perturbation.

In figure 6.28 the typical characteristics associated with the bolus transit time are illustrated. The top tracing (S_1) is the output of a sensor placed in the center of an arteriole, and S_2 is the output of a sensor placed in the center of a venule supplied by that arteriole. The bottom tracing (P) indicates the initiation of the injection and pressure elevation on the arterial side. The pressure elevation is timed so that the pressure wave arrives at the venous segment at a point in the venomotion cycle (point A) corresponding to vessel relaxation. The measured transit time from small artery to small vein depends on the amount of excess pressure caused by the arterial perturbation. In figure 6.29 this effect is illustrated. In part a of this figure the basic sequence is as follows. The start of the arterial perturbation is designated as Y. The arrival of the perturbation at the venous observation site is quite rapid, resulting in an influx of red cells and an increase in vessel opacity (point A). The arrival of the bolus is detected by the rapid decrease in opacity and is recorded as a downward deflection (point B). As the bolus passes by the sensor, the opacity of the vessel again begins to increase. However, possibly in response to the elevated volume and pressure, the vessel segment is observed to contract (point C). The contraction is insufficient to close the upstream and feed vessel

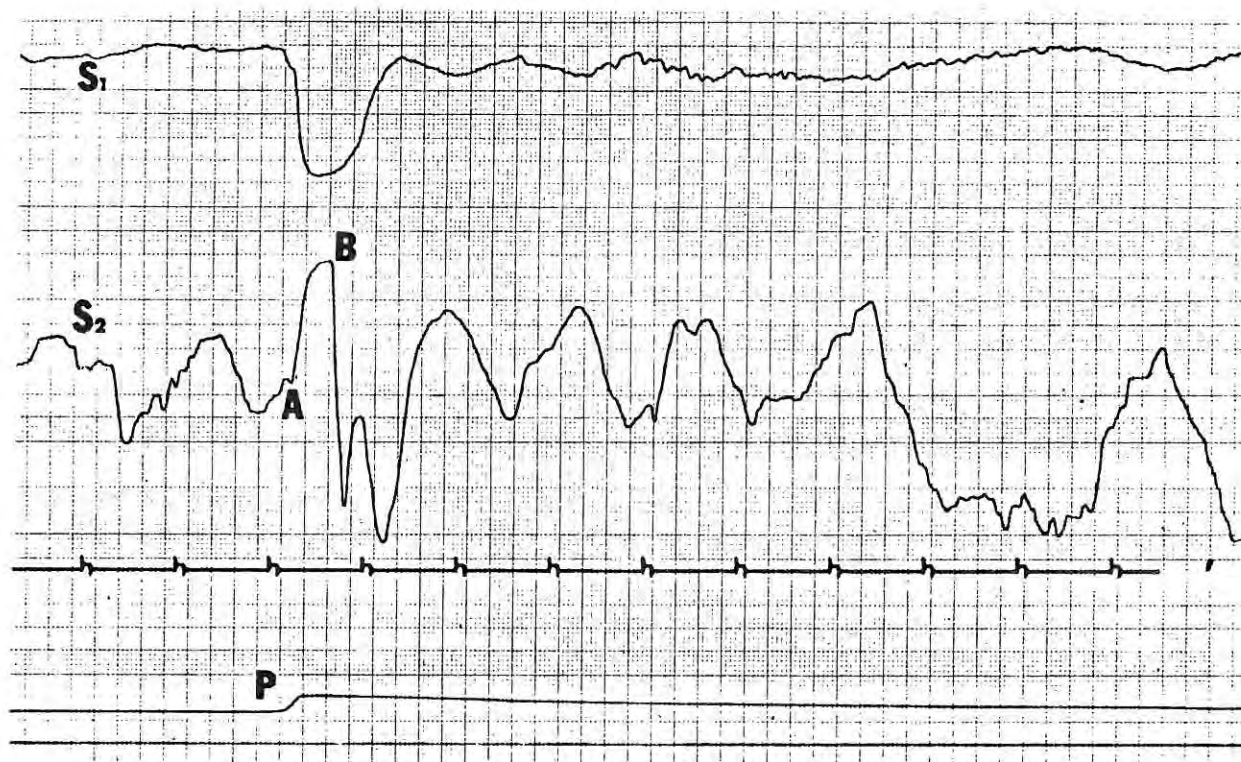


Figure 6.28. Typical characteristics of arteriole-venule transit time. S_1 is output of arteriole photo sensor which records passage of arterial bolus. Downward deflection denotes decreasing vessel opacity. S_2 is output of venous photo sensor. The rhythmic flow pattern in the active venous vessel is seen as well as the arrival of the pressure perturbation (Point A) and bolus (Point B). The upward deflection of the arterial microcannule pressure (P) denotes initiation of the perturbation. Time marks at two second intervals.

valves due to the still elevated pressure in these circuits. Because of this, the influx is only transiently reduced (points D and E). Finally, as the upstream pressure falls toward control values, a subsequent contraction succeeds in shutting off further inflow, and the volume within the segment is accelerated downstream, which is denoted by the large downward deflection (point F). The measured bolus transit time (point Y to point B) is 120 msec.

In figure 6.29b, in which less excess pressure was used (as indicated by the decrease in the initial recovery time of the arterial vessel), the transit time (Y to G) is 720 msec, and the secondary contraction (point H) is more effective in accelerating the flow and reducing the vessel blood volume. As shown in part c, use of a smaller perturbation results in a still longer transit time (800 msec, Y to J) and a secondary contraction (point K).

Using small perturbations, the measured transit time should approach that which represents the normal circulation time. Recorded in this way, the mean transit time from small artery to small vein is 940 msec (5 animals with 5 measurements in each animal).

The transit time measurements even when localized to a small region of the vasculature as in the present case still reflect the end result of a multiplicity of factors. The nature of the complexities associated with transit time measurements in

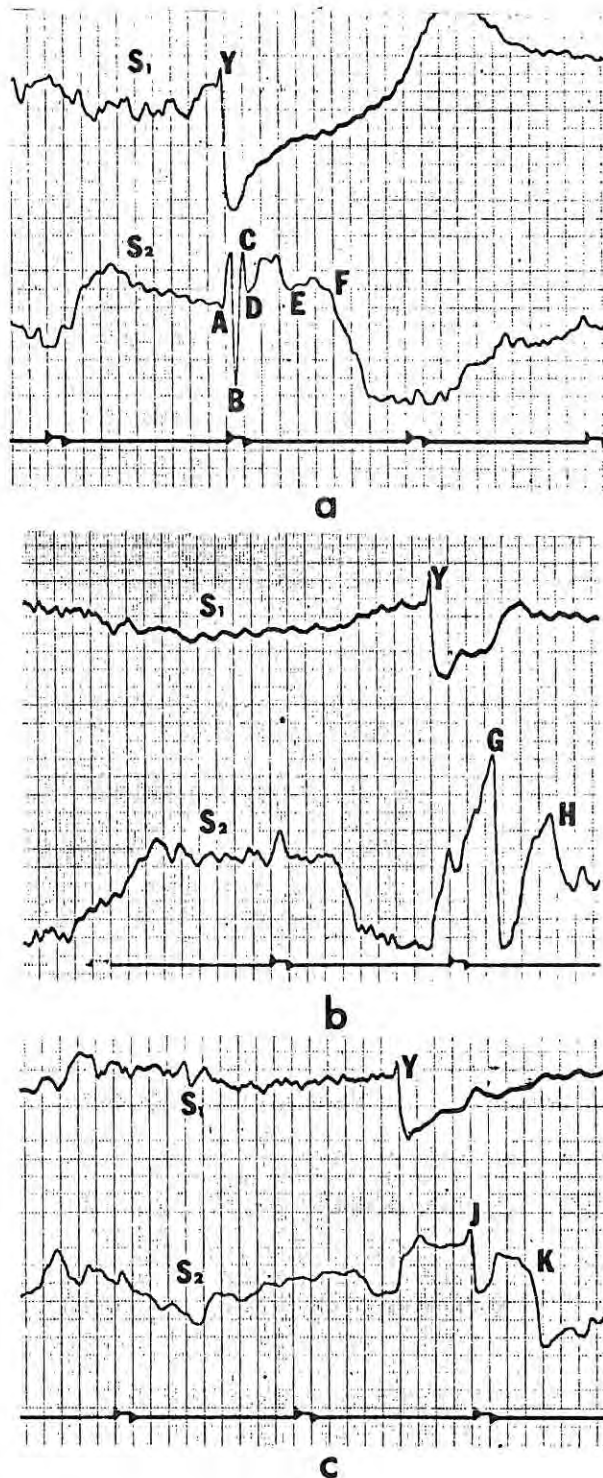
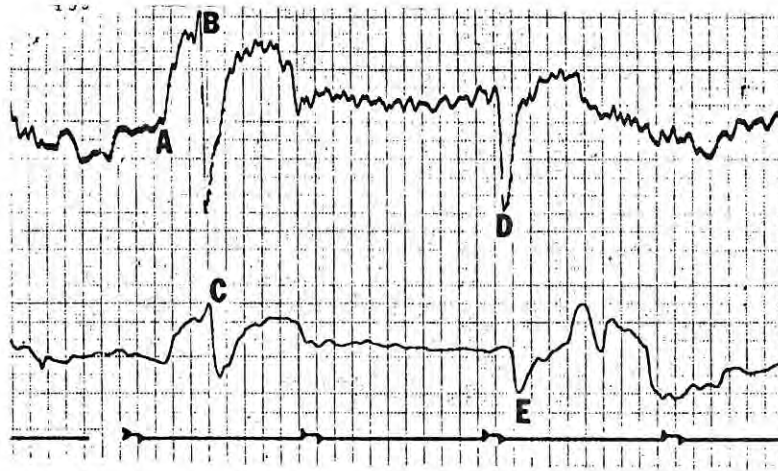


Figure 6.29. Variation in arterial-venous transit time. S_1 and S_2 are respectively the arterial and venous photo sensor outputs. Downward deflection denotes decreasing vessel opacity. Start of bolus is denoted as Y, and first appearance at venous site is at B, G and C. Time marks at two second intervals. Transit times in (a), (b) and (c) are 120, 720 and 800 msec respectively. See text for discussion.

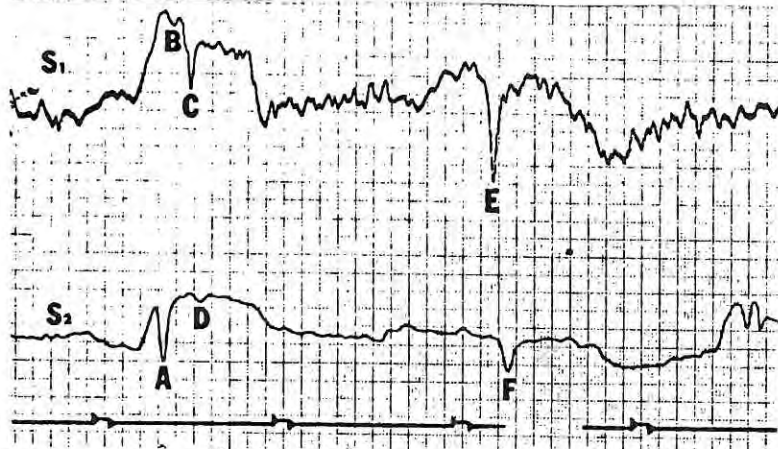
general becomes apparent during attempts to measure the proportion of the total time associated with a particular vessel type. To determine the transit time which is due to the small vein or venule, the sensors are placed axially in the vessels of interest. Typical recordings made in this way are shown in figure 6.30. The sensor S_1 is located 330 microns upstream from the sensor S_2 . S_1 amplitude scale is magnified to show the fluctuation in the normal red blood cell flow due to passage of clumps of erythrocytes by the sensor. In 6.30(a) the total transit time as measured from the arrival of the pressure perturbation (point A) to the initial appearance of the bolus at the downstream site (point B) is 500 msec. The bolus time delay between the measuring sites (B to C) is 80 msec. A secondary flow pulse (D) propagating from upstream to downstream with a time delay (D to E) of 160 msec may also be noted due to normal venous activity.

In figure 6.30(b) is shown a second recording at exactly the same site as in part (a). It can be seen that there is a bolus which appears first at the downstream site (point A) and progresses upstream. It almost reaches the upstream sensor in this case, resulting in a small downward deflection in the recording (point B). This is followed by a bolus first appearing upstream (point C) and then downstream (D). After a period of about three seconds a flow pulse due to the rhythmic activity is seen to originate upstream (point E) and progress downstream (point F). In figure 6.29(c), the bolus is first observed at the downstream

(a)



(b)



(c)

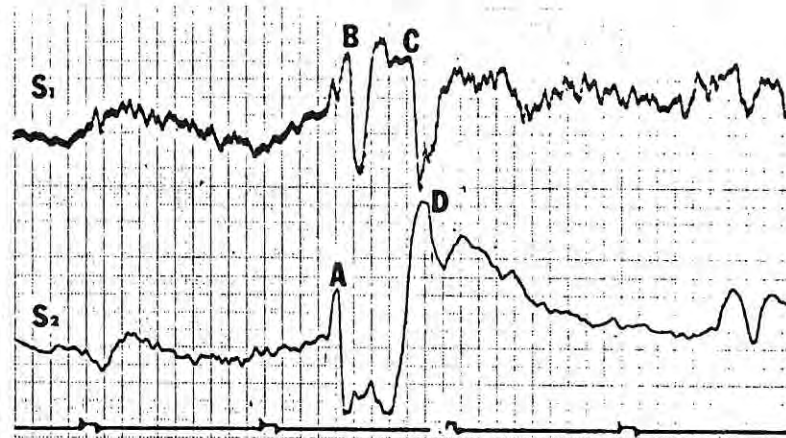


Figure 6.30. Variability in bolus flow pathways in postcapillary vessels. S₁ and S₂ record upstream (u.s.) and downstream (d.s.) flow patterns, respectively in small vein. Axial separation is 330 microns. Downward deflection denotes decreasing vessel opacity. Time marks at two second intervals. In (a) d.s. appears first (B) followed by d.s. (C). In (b) d.s. bolus appears first (A). In (c) bolus of longer duration appears first d.s. (A) followed by appearance u.s.(B). See text for further discussion.

site (point A) and propagates upstream (point B). The duration of the downstream bolus is about 700 msec, as compared with about 150 msec in part (b) of the figure. The initial bolus observation is again followed by an upstream originating bolus (point C) which is observed at the downstream site (point D) 200 msec after its upstream appearance.

An explanation of these different patterns recorded at the same sites and due to perturbations initiated at the same arterial site may be provided by considering the interaction between vascular topology and valve presence. In figure 6.31 is a schematic representation of the vascular topology relevant to this discussion. The numbers in parentheses correspond to the vessel orders as used in the Topological Model (figure 2.3). The sensors (S_1 and S_2) are positioned to record the dynamics in a small vein. The normal flow direction is indicated by the solid arrows outside the vessels. Under the assumption that the terminal arteriole states of both feeding pathways are similar, the bolus arrives at the downstream segment of the collecting small vein first (point b). If when it arrives the valve (designated by x) is open or is opened by the arriving bolus, then this bolus is not seen by the sensors and follows the pathway a-b-x. The sensors will record the bolus associated with the pathway c-d-b, and this corresponds to the recording of figure 6.29a. If, on the other hand, the valve is closed and remains so, the bolus which arrives via the pathway a-b may move upstream passing sensor S_2 , as was shown

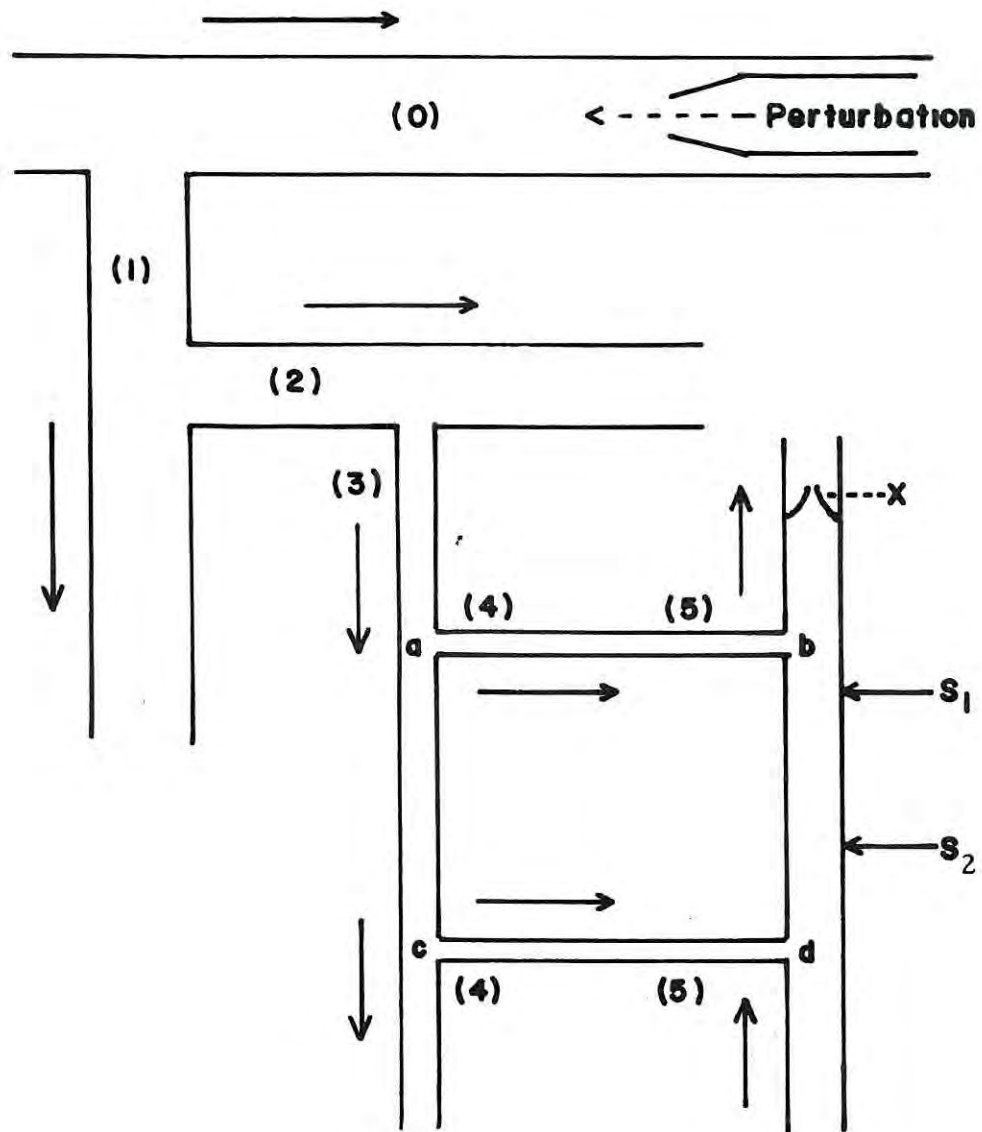


Fig. 6.31. Diagrammatic Representation of Bolus Pathways to Illustrate and Explain Experimental Findings. Numbers in parentheses are the vessel branching orders as defined by the Topological Model (Figure 2.3). Arrows show the normal flow direction. The sensors S_1 and S_2 are positioned along a small vein. See text for discussion.

in figure 6.29b, and sometimes passing S_1 , as was shown in figure 6.29c. The increased volume precipitates a segmental contraction opening the valve with concomitant inflow from the upstream feeding vessel and then the appearance of the upstream originating bolus.

CHAPTER SEVEN... DISCUSSION AND CONCLUSIONS

The measurement of pressure and flow in a large artery supplying a vascular bed permits the calculation of the vascular impedance to flow associated with the entire region distal to the measuring site. The low frequency limit value of the impedance is the vascular resistance and is the quantity which determines the mean value of pressure required to provide a flow sufficient to meet the needs of the dependent vascular bed being measured or studied. The derived value of vascular resistance at any instant reflects the composite properties of an array of inter-connected blood vessels, their physical and chemical environment, and the blood itself.

One problem which has been attacked in the preceding chapters is that of characterizing the microvasculature in a way which permits vascular bed resistance to be predicted based on knowledge of the properties and behavior of the microvasculature.

Using the wing vasculature of the small brown bat as an experimental preparation and as a prototype of a self contained vascular bed, it has been shown (Chapter Two) that by representing the dimensional and topological features of the real vascular bed in an appropriately idealized form, together with theoretical fluid dynamic formulations, it is indeed possible to predict the vascular bed resistance in the normal resting state with good accuracy. The idealized representation termed the Topological Model predicted vascular resistance values that were indistinguishable from measured values obtained by the author and as calculated from data available in the

literature (Wells, 1969).

Using the Topological Model, it was also possible to determine the resistance distribution throughout the vasculature (Table 2.2). However, with the available instrumentation, resistance could only be determined at one level, and thus these predicted values have not been directly confirmed. Indirect confirmation of the predicted resistance distribution, however, is obtained when the predicted results are used as part of a Microvascular Model, to be described below, and the resistance pressure distribution through the vasculature evaluated (figure 4.10).

As presently formulated, the Topological Model is strictly applicable to the bat wing. One aspect of the significance is that it represents an initial and basic framework for developing a functional Microvascular Model, as was shown in Chapter Four, and this will be elaborated upon below.

Another aspect of its significance is that it represents a characterization method potentially applicable to other vascular beds, providing that appropriate specific refinements are incorporated. Its major advantage in this respect is that the effects of changes in dimensions of individual vessel orders as they relate to changes in vascular bed resistance may be incorporated and evaluated. Thus, it provides the required framework for incorporating non-uniform systems and local control acting on the several vessel orders comprising the microvasculature and for evaluating the composite and separate significance of these controls on changing vascular

resistance.

Such control represents a parametric change in the dimensional and physical properties of identifiable vessels, which in turn alter vascular bed resistance and resistance distribution. Such controls are not implicitly incorporated in the Topological Model, as that was not the purpose. However, in order to test its range of applicability in this regard, the Topological Model was used as a reference vasculature, from which it was attempted to predict changes in blood pressure accompanying hypertension induced changes in vessel morphology (Friedman, 1971). For a number of reasons (Chapter Two, Sections IV and V), the predicted pressure rise was greater than that which was measured (31% rise measured and 44% predicted, see Table 2.6). This result and the discussion of Chapter Two thus emphasize the care required, as well as the factors to be considered, in extrapolating from a single vascular bed to whole body vascular behavior.

The distributed nature of the model allows it to be utilized to determine the impedance characteristics throughout the vascular bed as a function of frequency. Further, the input impedance of this model represents the terminating impedance to the distributing large arteries and would thus determine the reflection properties of the arterial vasculature.

The microvascular resistive or peripheral load characteristic is but one of the functional properties of this region of the circulation, as discussed in Chapter One, Section I. A second general

problem area with which this dissertation deals is the microcirculation itself. Specifically, an attempt has been made to clarify and quantify the hemodynamic and functional significance and interaction of dynamic processes in the pre capillary (vasomotion), capillary (filtration) and post capillary (venomotion) vascular regions.

To examine some of the basic properties of venomotion, an analytical model was developed (Chapter Three). Theoretical expressions for flow, pressure, and volume, as well as quantities determinable from these (resistance and transit time) were derived and results compared to those obtained from non-rhythmic vessels. As argued in Section IV of Chapter Three, the rhythmic property of these vessels implies a smaller vascular conductance and blood volume, as compared with non-rhythmic reference vessels having in vivo characteristics and upon which are imposed the same pressure gradient.

Thus, the effect of increasing contraction amplitude at a fixed venomotion frequency is to decrease both conductance (figures 3.9 and 3.12) and volume (figure 3.10) of these post capillary vessels in a non-linear fashion. Changes in relative contraction amplitude, for example .2 to .3, can shift 15% of the venous blood volume into the active circulation with essentially no change in the transit time of these vessels (figure 3.11). A similar change in volume produced by a maintained contraction would result in about a two-fold increase in transit time. The significance of the constancy of transit time in the rhythmically active vessels is obscure, but may

be related to heat transfer in the wing vasculature.

Investigation of the effects of both variable viscosity (figures 3.13, 3.14 and 3.15) and non-zero blood yield stress (figures 3.18, 3.19 and 3.20) showed these factors not to be significant with respect to the basic venomotion properties and resultant hemodynamics (figures 3.17, 3.20, 3.21 and 3.22). In addition, the analysis produced an equation (equation 3.52) which may serve to link viscosity to vessel hematocrit and which has the advantage over other available equations of being derived, rather than empirically obtained.

These rheological results and the previously derived hemodynamic equations were utilized together with the basic framework of the Topological Model (figure 2.3) to develop a detailed Microvascular Model (figure 4.10) for the purpose of studying in more depth the properties of the microcirculation and to supplement experimental studies undertaken for the same purpose (Chapter Six). The overall structure of the model satisfied the simultaneous conditions of representing the essential microvascular features being studied and the characteristics of the microvasculature (Chapter Four, Sections I and II) and included a detailed representation of the venomotion process, capillary filtration, and pre capillary sphincter dynamics.

Solution of the model equations showed that the resultant distribution of mean pressure throughout the microvasculature was similar to that obtained experimentally from mesentery and cremaster preparations (Zweifach, 1971; Intaglietta, 1970; Richardson and Zweifach, 1970) and was fully consistent with more limited data in

the bat wing (Wiederhielm, 1968; Nicoll, 1969). The arterial to venous phase shift was within two degrees of that measured in the cat omentum (Intaglietta et al., 1971) but predicted a pressure transmission ratio of .03, as compared with a value for the omentum of .05. The difference in attenuation properties may be due to the fact that in the omentum so called preferential channels which do not pass through the true capillaries are present. Such a topology would be expected to attenuate the arterial pulse less than a vascular bed in which no such channels are present, as is the case in the bat wing (Wiedeman, 1963).

Extensive results obtained from the Microvascular Model (Chapter Five), together with experimental findings of Chapters One and Six and data from the literature, form the basis of the following discussion and conclusion having a bearing on a number of microcirculatory questions of long standing.

As one proceeds from the main artery entering the wing toward the capillary the vascular resistance increases (see for example figures 2.3, 4.10 and Table 2.2). The normal spontaneous variations in diameter of terminal arterioles, pre capillary sphincters, muscular venules and small veins have little effect on the resistance seen looking into the vascular bed, but appear to play a significant role in the distribution of flow within the microvasculature.

The spontaneous diameter changes associated with the terminal arterioles and pre capillary sphincters (vasomotion) produce a modulation of the pressure and flow in the capillary networks (e.g.,

figure 5.17). This modulation due to vasomotion has several effects. Decrease in diameter is associated with a drop in the pressure at the arterial end of the capillary by an amount which depends on the amount of diameter change. For the diameter changes most frequently observed experimentally, the capillary pressure is reduced from a value of about 40 mmHg to a value close to the venous pressure (10 to 15 mmHg). This means that the contraction phase of vasomotion reduces the capillary pressure to a value below the commonly accepted normally occurring value of plasma osmotic pressure (25 mmHg). The implication of this is that the contraction phase of vasomotion is associated with capillary re-absorption over the entire capillary length for normally occurring arterial pressures. Thus, the classical picture of a rather steady filtration on the arterial side of the capillary and re-absorption on the venous side does not appear applicable on two counts. First, the process is anything but steady, since the capillary dynamics occur in what appears to be an almost random fashion (Wiedeman, 1966). Secondly, confinement of the filtration-re-absorption process to anatomic positions of the capillary does not conform to the predicted hydrodynamic pressures required for such to be the case.

In view of the predicted filtration dynamics and their relationship to pre capillary sphincter state, one may speculate that sphincter control (i.e., how long will the sphincter remain contracted, and when will it contract again?) is at least in part determined by the values of significant tissue quantities which are

modified by the sphincter dynamics. For a number of reasons, as argued in Section IV-D of Chapter Four, tissue pressure was evaluated as one such significant quantity. Increasing the arterial pressure in the Microvascular Model resulted in a non-linear increase in the fraction of time that the pre capillary sphincters were closed (see figure 5.20). Comparison with in vivo data obtained in the bat wing (Wiedeman, 1966) showed that the results predicted by the Model were in excellent quantitative agreement. In addition, the Model results showed that this mode of control simultaneously resulted in an auto-regulation of the average capillary flow.

Study of the post capillary microvasculature has yielded evidence which indicates that, in addition to the pre capillary dynamics, the rhythmic diameter variation of the muscular venules and small veins (termed venomotion) plays a significant role in determining the flow and pressure distribution in the microcirculation. Though the fundamental mechanisms controlling venomotion have not as yet been fully explained, the responses of these post capillary vessels to pressure perturbations (Chapter Six, Section VI) and the presence of substantial vascular smooth muscle in the walls of these vessels (Rhodin, 1967; Wiedeman, 1972) clearly suggest that there is a substantial myogenic component involved. The persistence of venomotion in the denervated preparation as observed by this author and as documented previously (Wiedeman, 1968) further supports a local mechanism associated with an active contraction. Whether the myogenic response is stimulated by pressure

per se or by vessel distension is not clear. However, detailed examination of the characteristic properties of venomotion has shown that elevations in frequency secondary to pressure elevation stimuli are produced by an increase in the rate of distension with only an increase in the vessel maximum diameter but no significant change in the time course of the contraction phase (see for example figures 6.26 and 6.27). Venomotion frequency returns to pre-perturbation levels as the vessel diameter returns toward its normal value. However, since the period of elevated frequency persists well after the initial pressure perturbation has dissipated (up to two minutes), it appears that the response is to elevated vascular volume. These results, as well as those obtained from thermal perturbations (see for example Section V of Chapter Six), would suggest and favor a stimulus mode due to a triggered active contraction associated with vessel distension and rate of distension as the normal venomotion mode.

The functional significance of venomotion has been studied using the Microvascular Model and experiments. Recorded diameter variations have shown that contraction may reduce the inside diameter by as much as 50% (see for example figures 6.12 and 6.13) but is generally in the range of 10 to 30%. This contraction is associated with an increase in segmental vascular resistance and vessel wall thickness and a decrease in vascular compliance (see for example figure 5.2). The contraction causes the instantaneous pressure within these vessels to rise by an amount which depends on the

absolute value of the venous pressure existing prior to the contraction and on the strength of contraction with a range from six to ten mmHg (see figures 5.3, 5.4 and Table 5.2). These values represent a significant increase in the venule and small vein pressure in view of the normally occurring mean pressure levels in these post capillary vessels (10 to 15 mmHg). The pressure elevations due to contraction as predicted by the Model results are consistent with measured values in the bat wing (Wiederhielm, 1967). In the absence of an imposed pressure gradient, uniform contraction and subsequent relaxation phase of venomotion are associated with a forward and retrograde flow, respectively, and an average flow approaching zero. However, when the presence of the valves is taken into account, the average flow production approaches that which is estimated to be present in these vessels in vivo (see for example figure 5.6), and the general pattern of hemodynamics is altered.

The general pattern of interaction between capillary flow and venous activity is seen both in the Model and experimental studies. Contraction of the collecting venous vessels and the associated pressure rise reduce the capillary outflow for the duration of the contraction, followed by acceleration of that flow during vessel relaxation. The net effect is to produce a capillary and venule hemodynamic pattern which is in part controlled by post capillary activity, which is itself spatially and temporally variable. The modulated hemodynamic pattern resulting from this activity serves to permit each capillary pathway to have an appropriate duration

of active flow in a manner analogous to a time sharing or sampling process. Valve presence and dynamics and the specific post capillary vascular topology aid are significant to this general hemodynamic property, as argued in Sections I and II of Chapter Six. Further, because the dynamics themselves are sensitive to pressure in the feeding vessels, it appears that pressure within individual capillary pathways may alter the collecting vessels' dynamic pattern (see for example figure 6.27). This would imply a "fingertip" control mechanism and may represent an intrinsic microvascular control process.

Indeed, the experimental results (see for example figure 6.26) have shown that there are dramatic changes in the frequency and time course of venomotion which are correlated with changes in feeding vessel pressure. Increases in pressure, for example, led to increases in venomotion frequency and reduction in the relaxation phase with little change in the contraction characteristic. Studies with the Model in which changes in frequency were simulated indicate that increases in frequency (all other parameters constant) are associated with reductions in intravascular pressure and increases in small vein outflow.

Since the observations of Jones (1851), the term peristalsis has been used in connection with some of the dynamic modes of small vessel contraction. Comparisons have been made, for example, with the type of segmental contraction observed in the small intestine. A number of theoretical analyses (Shapiro, 1968; Fung, 1969) have

been carried out on peristaltic type motion, principally in connection with ureter hydrodynamics. In these analyses, the assumed peristaltic motion is taken as a continuous progressive wave. Thus, in effect, the wave moves in only one direction of flow, and it is further assumed to be independent of realistic proximal and distal boundary conditions. The role of the so called peristaltic character frequently associated with active contraction of microvessels appears to be minimal. Simulation of this process shows that its contribution to active flow is small compared to the combination of segmentally uniform contraction and valve presence. In vessel regions lying between two consecutive bicuspid valves (a vessel segment), the experimental results (e.g., figures 6.11 and 6.13) have shown that there are indeed diameter variations which are axially out of phase. The phase difference is most apparent during the dilation part of the venomotion cycle. Casual observation of such vessel segments might give the impression that part of the vessel is actively contracted, while an adjacent part is relaxed. This then may lead to the conclusion that peristaltic type motion similar in character to that present, for example, in the intestines is present. However, when one carefully examines and analyzes the hemodynamics associated with this activity (see for example Sections IV and V of Chapter Six and figure 6.19), it is found that the phase lag corresponds to that associated with the time required for inflowing blood to fill a vessel segment having a closed or partially closed downstream valve. The flow patterns

predicted by the Model have a striking similarity to the experimentally determined pattern of diameter variation during the segmental filling phase (c.f., figure 5.13 with figures 6.11 and 6.13). This filling may thus cause a dilation wave to progress toward or away from the valve site (e.g., figure 6.30), depending on pressure conditions in the feeding vessels. Thus, intrasegmental peristaltic pumping in the sense seen in the intestine and ureter, for example, appears not to play any significant hemodynamic role in the post capillary vessels under normal conditions.

There is, however, a possibility that under appropriate conditions intrasegmental phase delays associated with the contraction part of venomotion do result in alterations in the hemodynamic pattern. As simulated on the Model, an interaction between venomotion frequency and active contraction propagation delay results in an attenuation of the ordinarily time varying character of the hemodynamic variables (e.g., figures 5.8 and 5.12). This effect is strongest at the highest observed venomotion frequency which occurs secondary to pressure elevation. Under conditions of elevated pressure in the vessels feeding the active vessels the flow is observed to be in fact more continuous than in the control state. Thus, rather than the flow stopping and starting with successive contractions, there are instead relative increases and decreases in venule and small vein outflow. The resulting time variation associated with the flow thus bears a resemblance to that which is predicted by the simulation as an interaction between

venomotion frequency and contraction propagation delay.

Intrasegmental phase delays associated with the contraction part of the venomotion cycle have not been unambiguously identified experimentally. There is, however, substantial evidence that spontaneously active vessels similar in character to those seen in the bat wing are endowed with a nexus, a site of close proximity of adjacent smooth muscle membranes (Barr et al., 1968; Somlyo and Somlyo, 1968). It is suggested that these nexes provide a low resistance path for intercellular propagation of action potentials. Funaki (1966) measured an action potential propagation velocity in the rat portal vein of 1.7 cm sec^{-1} . If similar velocities are present in the bat wing venous vessels, the required resolution to detect the associated intrasegmental mechanical deformation may have prevented our detecting them. However, if the five consecutive segments of the Model are taken to represent five consecutive vascular segment, then the contraction delay associated with consecutive segments is the time required for the outflow of the upstream segment and inflowing major branches to dilate the collecting segment. The measured time for this process to occur in the animal is 1200 msec. This represents an integer multiple of the 400 msec delay which, when used in the model, predicts the frequency-contraction interaction. Thus, the reduction in the pulsatility of the hemodynamics predicted by the Model is supported by these experimental observations. However, the precise nature of this interaction requires, and indeed merits, more intensive study

directed specifically at this question.

Further aspects of interaction between pre and post capillary dynamics have been illustrated. The amount of control exercised by post capillary dynamics depends on the state of the pre capillary sphincter supplying the dependent capillary region. In the sphincter dilated phase, the effect of normally occurring venomotion on capillary flow is about the same in magnitude (but different in time course) as that produced by the pulsatile arterial pressure (see for example figure 5.15). The most dramatic effects on capillary flow, however, are related to alterations in the pre capillary sphincter state (e.g., figure 5.17). However, when the sphincter is in its contracted state, the modulation in capillary flow (expressed as a percentage of the maximum capillary flow associated with the sphincter state) due to venomotion may be 50% or larger (see for example figure 5.21). Thus, it appears that under normal conditions the significance of venomotion with respect to capillary flow modulation waxes and wanes with alternate contraction and dilation phases of vasomotion. From this, it follows that increases in relative contraction time of the sphincter (e.g., figure 5.20) would assign to the post capillary vasculature and associated dynamics (as described in Sections IV, V, and VI of Chapter Six) an increasingly significant role as a determinant of capillary flow distribution and as a factor in venous circulation. One may speculate, then, that physiological conditions which tend to augment the constrictor

phase of vasomotion will simultaneously increase both the local and system circulatory importance of the post capillary vasculature.

Systemic hypertension is a pathological condition which, according to the present results, should augment the constrictor phase of vasomotion. This implies that vascular and cellular changes concomitant with, or as a sequel to, hypertension are, to a large extent, dependent on the functional capacity and integrity of the post capillary microvasculature. Contrastingly, systemic hypotension due to hemorrhage or accompanying myocardial infarction would tend to increase the dilation phase and reduce the dynamic component of vasomotion. This reduction represents a diminution of a control component to which the capillary and post capillary microvasculature are sensitive. The so called state of irreversibility of shock may, therefore, be associated with the expected decrease in venomotion accompanying the loss of sufficient dynamic or triggering input from the pre capillary vasculature. The new concepts which have evolved from the present work regarding the pre and post capillary interaction, the pressure dependent control range of vasomotion, and the dynamic aspects of capillary exchange should pave the way for a deeper insight into the vascular aspects of these pathological conditions. In addition the overall Microvascular Model and conceptual framework of the microcirculation should provide the basis for extending our understanding of numerous aspects of vascular function and microvascular hemodynamics in both health and disease.

Appendix A...Variable Viscosity and Non-Newtonian Effects

I. Introduction

In the equations developed in section III-B of Chapter Three, the viscosity of the blood within the rhythmic vessels was assumed constant and the rheological behavior was assumed to be Newtonian. For several reasons it is important to test the validity of these assumptions. Concerning the assumption of constant viscosity, the author has observed marked increases in red blood cell concentration within the rhythmic vessels associated with vessel diameter increase. Further in vitro studies on the flow behavior of blood (Cokely, 1971) have indicated that the concentration in a fed vessel depends on the ratio of the fed vessel diameter to the source vessel diameter. Since this ratio is a function of time during venomotion, it would appear that the erythrocyte concentration and hence the viscosity in the rhythmic vessels would be variable. In addition to the variable viscosity, there is evidence that blood deviates from Newtonian behavior at low shear rates. Much of this evidence (Merrill, 1969) comes from viscometric measurements which show that unless the shear stress in the blood exceeds a certain positive threshold, the rate of shear will be zero. This threshold stress is referred to as the yield stress (τ_y). The implication of this fluid behavior is that in order to have non-zero flow, say in a cylindrical vessel as we are here concerned with, the imposed pressure gradient must exceed a certain positive value.

In order to investigate the possible effect and hemodynamic significance of these factors, a detailed analysis has been carried out and is presented in this appendix.

Briefly the procedure used to analyze the significance of variable viscosity consists of four aspects.

First an expression for the viscosity of blood as a function of the hematocrit of the rhythmic vessel is obtained. Secondly, the hematocrit within the rhythmic vessel is expressed as a function of the time varying vessel diameter. The third part consists of expressing the resistance of the rhythmic vessels in terms of these two quantities. This analysis is carried out in detail for the Q Model with the assumption that all parameters are independent of venomotion frequency. The final part consists of evaluating the effect of variable viscosity by comparing the resistance obtained when variable viscosity effects are included with the resistance associated with pure time dependence (η Constant) and the reference vessels described in Section III-A of Chapter Three.

The procedure for evaluating the effect and significance of the non-Newtonian behavior on rhythmic vessel dynamics consists also of four parts. First, an expression is developed for the apparent viscosity in terms of the classical Newtonian viscosity, yield stress, and wall shear stress. Secondly, expressions are written for yield stress and wall shear stress in a form which are applicable to the time varying diameter vessels. Again it is assumed that the parameters are frequency independent. In the third part of the analysis, the results

of the previous two parts are combined to examine the yield stress and wall shear dependence on rhythmic vessel dynamics and to evaluate the amount by which the apparent viscosity deviates from the Newtonian case. In the fourth and final part, the non-Newtonian and variable viscosity factors are incorporated into the pressure flow equations for the general analytical model and the extent to which resistance pressure and flow in the rhythmic vessel are affected is evaluated.

For the convenience of the reader, a list of symbols and definitions used in this appendix are provided below. Other symbols will be defined as needed.

- η is the viscosity of whole blood
- η_p is the viscosity of plasma
- H is the hematocrit within the rhythmic vessel
- H_s is the hematocrit within the vessels feeding the rhythmic vessel
- β is the relative contraction amplitude
- α is a constant derived from empirical flow studies
- $R(t, \eta)$ is the resistance of the rhythmic vessel as a function of time and viscosity. As defined previously Roman numerals denote mode of diameter variation to which equations apply
- τ_w is the shear stress at the wall of the rhythmic vessel
- τ_y is the yield stress of the blood
- η_a is the apparent viscosity of the blood defined as the ratio of shear stress to velocity gradient
- $R(t, \eta, \tau_y)$ is the resistance of the rhythmic vessel as a function of time, viscosity, and yield stress
- $R(t)$ is the resistance of the rhythmic vessel purely as a function of time (viscosity assumed constant and yield stress zero)
- R_r is the resistance of the reference vessels with no time variation.

II. Viscosity in Terms of Red Blood Cell Concentration

A. Approach

To relate viscosity to the concentration blood is viewed as being composed of two distinct phases. The red cells are taken as an included phase in plasma which is taken as the suspending phase. Use is made of a result due to Christenson (1969) who expresses the complex shear modulus of a heterogeneous structure, G^* , in terms of the complex moduli of its constituents. Making use of the following definitions applicable to the blood suspension, Christenson's result may be expressed as in equation A.1 below.

G^* is the complex shear modulus of the suspension

G_s^* is the complex shear modulus of the suspending phase

G_i^* is the complex modulus of the included phase

σ_s^* is the Poisson's ratio of the suspending phase

c is the volume concentration of the included phase

$$(A.1) \quad \frac{G^*}{G_s^*} = 1 + \frac{15(1-\sigma_s^*) \left(\frac{G_i^*}{G_s^*} \right) c}{7-5\sigma_s^* + 2(4-5\sigma_s^*) \left[\frac{G_i^*}{G_s^*} - \left(\frac{G_i^*}{G_s^*} - 1 \right) c \right]}$$

The approach used in the following analysis is to first treat the red cell as a spherical structure with a membrane enclosing a hemoglobin solution. For this heterogeneous structure, the hemoglobin is taken as the included phase with shear modulus G_i and the membrane with shear modulus G_m . An effective shear modulus G_e is then determined for the cell. This effective shear modulus is then

used to characterize the cell which is then treated as the included phase in the suspending plasma with shear modulus G_p .

B. Details of Analysis

The red cell radius and membrane thickness are taken as four and .1 microns respectively. Since the membrane volume is small compared to the included phase (hemoglobin), the shear modulus of the composite structure (cell and membrane) may be given by a reduced version (Christenson, 1969) of equation A.1 as in equation A.2. In equation A.2, the real parts of the complex moduli are neglected with respect to the imaginary parts, and hence the asterisk notation is here discarded. Subscripts c, m, and b correspond to the cell, membrane, and hemoglobin respectively.

$$(A.2) \frac{G_c}{G_m} = 1 - \frac{\left(1 - \frac{G_m}{G_b}\right) \left[7 - 5\sigma_m + 2(4 - 5\sigma_m) \frac{G_b}{G_m}\right]}{15(1 - \sigma_m)} (1 - c)$$

The numerical value for G_m is obtained by assuming $\sigma_m = .5$ and expressing $G_m = \frac{E_m}{2(1 + \sigma_m)}$ in which E_m is the elastic modulus of the membrane.

Katchalsky (1966) estimates $E_m = 2.4 \times 10^7$ dynes cm^{-2} which is close to the value of 3×10^7 obtained by Mela (1967) for the egg cell. The value used here is chosen conservatively as 3×10^7 dynes cm^{-2} .

Heilbrunn (1967) has estimated the shear modulus of sea urchin cytoplasm to be $3 - 4 \times 10^{-2}$ Poise and that of undiluted hemoglobin suspension at 6×10^{-2} . The latter value is the one used in this

analysis. Below are summarized the numerical values applicable for the calculation of G_c .

$$G_m = 1 \times 10^7 \text{ Poise}$$

$$G_b = 6 \times 10^{-2} \text{ Poise}$$

$$\sigma_m = .5$$

$$c = .93$$

$$1-c = .07$$

Using these values in eq. A.2 leads to an effective cell shear modulus of 4.2 Poise.

To obtain the viscosity of the suspension (η) we make use of the fact that for sinusoidal angular frequency ω , the imaginary part of G^* in equation A.1, is given by $\omega\eta$ so that upon substitution of the numerical value of G_c , we finally obtain eq. A.3 in which η_p is the plasma viscosity.

$$(A.3) \dots \quad \eta = \eta_p \left(1 + 2.5 \frac{c}{1-c} \right)$$

Equation A.3 thus gives the relationship between the viscosity of the blood suspension and the red cell concentration. It is interesting to note that eq. A.3 contains Einstein's result (1906) as a special case. He considered the case of extremely dilute suspensions. To show the equivalency of the two expressions, we expand eq. A.3 as in eq. A.4.

$$(A.4) \dots \quad \eta = \eta_p \left[1 + 2.5c \left(1 + c + c^2 + c^3 + \dots \right) \right]$$

For the case considered by Einstein $C \ll 1$. Thus retaining only the zero order term of the expansion in eq. A.4, we obtain:

$$(A.5) \dots \quad \eta = \eta_0 (1 + 2.5C)$$

which is precisely the result he obtained.

In figure A.1, equation A.3 is plotted and compared to experimental data and to the result of Vand, who empirically modified Einstein's result by the addition of a 2nd order term with an empirical coefficient.

The advantage of equation A.3 is that not only does it fit the experimental data quite well, even in vessels as small as 40 micron diameter as were used by Bugliarello, but that it was derived, rather than empirically fitted. To be consistent with the bulk of physiological usage, the term hematocrit with symbol H will be substituted for red cell volume concentration in subsequent discussions.

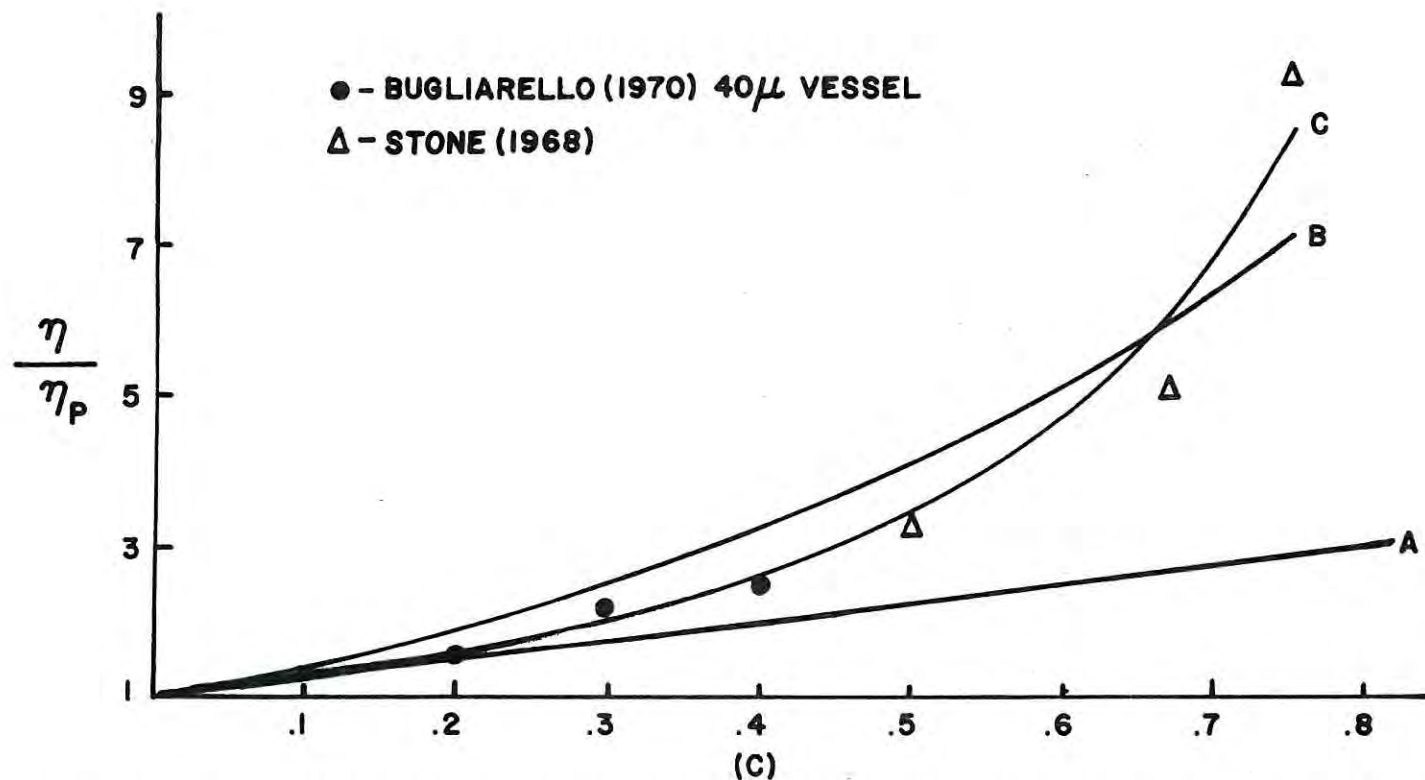


Fig. A.1. Blood viscosity (η) relative to plasma viscosity (η_p) as a function of red blood cell concentration (c). Curve A is a plot of Einstein's result for dilute suspensions. Curve B is a plot of Vand's empirical extension of Einstein's result to include 2nd order term. Curve C is a plot of the result derived by the Author. Circles indicate experimental data of Bugliarello (1970) obtained in 40μ diameter vessels. Triangles are experimental data from Stone (1968).

III. Hematocrit as Function of Diameter of Vessel

A. Assumptions

To develop an expression for the hematocrit within the active vessel (H) as a function of the instantaneous vessel diameter (D) it is assumed that:

- (1) Venules which supply the active vessel under study serve as a blood reservoir in that they contain a volume large compared with the active vessel.
- (2) The composite venule volume is contained in an equivalent vessel having a constant diameter, D_g , equal to the maximum diameter of the active vessel.
- (3) The variation of the hematocrit within the equivalent source (H_g) is small with respect to the variation associated with the active vessel.
- (4) Only changes in active vessel hematocrit due directly to changes in diameter are considered in the analysis.

B. Requirements on the Form of the Function

- (1) The form of the expression linking H to D must satisfy the condition that the hematocrit in the active vessel be equal to that in the adjacent source vessel when their diameters are equal.
- (2) And the requirement based on in vitro experimental data that when the diameter of the source is larger than the active vessel, the hematocrit is a function of the diameter ratio.

C. Phenomenological Equation

A phenomenological relationship which is consistent with the above assumptions and restrictions, and which satisfied the data of Cokely (1972) and others, is given by eq. A.6.

$$(A.6) \dots H = \left[\frac{D}{D_s} + \alpha D \left(1 - \frac{D}{D_s} \right) \right] H_s$$

The value of the parameter α is obtained from the data of Cokely (1972) and is equal to $2.5 \times 10^2 \text{ cm}^{-1}$.

D. Expansion to Include Mode of Diameter Variation

Using the fact that D and D_s in eq. A.6 are given by:

$$(A.7) \dots D = D_0 C (1 + \beta \cos x)$$

$$(A.8) \dots D_s = D_0 C (1 + \beta)$$

together with:

$$(A.9) \dots H = \frac{D C \alpha D_s + D - \alpha D^2}{D_s} H_s$$

yields:

$$(A.10) \dots H = \frac{H_s}{1+\beta} \left[D_o C (1+\beta) \alpha + 1 \right] (1+\beta \cos X) - \alpha D_o (1 + \cos X)^2$$

Substitution of equation A.10 into equation A.3 with H for c, provides an expression which relates the relative viscosity in the active vessel to the single variable of interest, the diameter of the active vessel. For analytical purposes, it is however more convenient to use the expanded form of equation (A.3) given in equation (A.4). Expressed in terms of relative viscosity η_r and H, equation (A.4) may be written as equation A.11.

$$(A.11) \dots \eta_r = 1 + 2.5(H + H^2 + H^3 + H^4 + \dots) = 1 + 2.5 f(H)$$

Substituting eq. A.10 into eq. A.11 together with the following definitions yields for $f(H)$ the expression given by eq. A.12 below.

$$A = D_o C (1+\beta) \alpha$$

$$B = \alpha D_o$$

$$S = 1 + \beta \cos X$$

$$G = H_s C (1+\beta)^{-1}$$

$$\begin{aligned}
 (A.12) \dots f(H) &= SCA - BSJG + S^2CA^2 - 2ABS + B^2S^2JG^2 \\
 &\quad + S^3CA^3 - 3A^2BS + 3AB^2S^2 - B^3S^3JG^3 \\
 &\quad + S^4CA^4 - 4A^3BS + 6A^2B^2S^2 - 4AB^3S^3 + B^4S^4JG^4 \\
 &= f_1 + f_2 + f_3 + f_4
 \end{aligned}$$

In equation A.12 terms from eq. A.11 above fourth order have been neglected. Using equation A.12, equation A.11 may now be written in the compact form:

$$(A.13) \dots \eta = \eta_0 \left[1 + 2.5(f_1 + f_2 + f_3 + f_4) \right]$$

in which the f's are defined by the consecutive terms of eq. A.12. Equation A.13 represents the analytical relationship describing vessel viscosity in terms of relative contraction amplitude of the rhythmic vessel which implicitly includes the effect of hematocrit variation.

IV. Active Vessel Resistance

A. General Form of Equation

The average axial pressure difference is different from the average vessel resistance only by a multiplying constant. It is more convenient to express the results to follow in terms of this average resistance.

Since the viscosity is no longer to be considered constant, the instantaneous axial pressure difference is written as:

$$(A.14) \dots \Delta P(t) = K_1 Q_0 \eta D^{-4}(t)$$

$$K_1 = 128 \ell / \pi$$

From eq. A.14 we have by definition:

$$(A.15) \dots R(t, \eta) = K_1 \eta D^{-4}(t) = K_1 \eta D_0^{-4} S^{-4}$$

Equation A.15 is the form of the resistance function for model Q.

B. Mode I and II average resistance and comparison equations

1. Mode I

Substituting eq. A.13 into eq. A.15 yields eq. A.16, which is the relationship between active vessel resistance and all pertinent parameters for Mode I variation.

$$(A\ 16) \dots R(L, \eta) = K \cdot \eta \rho D o^{-4} \left\{ S^{-4} + 2.5 \left[\begin{aligned} &S^{-2}(A-BS)G + S^{-2}(A^2 - 2ABS + B^2S)G^2 \\ &+ S(A^3 - 3A^2BS + 3AB^2S^2 - B^3S^3)G^3 \\ &+ (A^4 - 4A^3BS + 6A^2B^2S^2 - 4AB^3S^3 + B^4S^4)G^4 \end{aligned} \right] \right\}$$

In order to determine the average resistance, it is necessary to obtain the time average of the instantaneous relationship given by eq. A.16. It is noted that there are two general forms of integrals contained or required by eq. A.16. These are given below.

$$I_X = \int \frac{dx}{(1 + \beta \cos x)^n} \quad I_Y = \int (1 + \beta \cos x)^n dx \quad n=1, 2, 3, 4$$

We proceed by expanding form Y integrand and integrating term by term

For form X, we make use of the following relationships:

$$\frac{1}{2\pi} \int_0^{2\pi} \frac{dx}{S} = \frac{2}{\sqrt{1-\beta^2}} \operatorname{tg}^{-1} \left[\frac{\operatorname{tg}(\frac{x}{2}) + \beta}{-\sqrt{1-\beta^2}} \right] \equiv I_1$$

$$\frac{1}{2\pi} \int_0^{2\pi} \frac{dx}{S^2} = \frac{\beta \cos x}{(1-\beta^2)S} + \frac{1}{(1-\beta^2)} \int \frac{dx}{S} \equiv I_2$$

$$\frac{1}{2\pi} \int_0^{2\pi} \frac{dx}{S^3} = \frac{\beta \cos x}{2(1-\beta^2)S^2} + \frac{3}{2(1-\beta^2)} \int \frac{dx}{S^2} - \frac{1}{2(1-\beta^2)} \int \frac{dx}{S} \equiv I_3$$

$$\frac{1}{2\pi} \int_0^{2\pi} \frac{dx}{S^4} = \frac{\beta \cos x}{3(1-\beta^2)S^3} + \frac{5}{4(1-\beta^2)} \int \frac{dx}{S^3} - \frac{2}{3(1-\beta^2)} \int \frac{dx}{S^2} \equiv I_4$$

I_1 becomes improper at $x = \pi$. Upon evaluation at the limit values of 0 and 2π , we obtain:

$$I_1 = \frac{2}{\sqrt{1-\beta^2}} \left[\int_0^\pi \frac{dx}{S} + \int_\pi^{2\pi} \frac{dx}{S} \right]$$

and finally:

$$I_1 = \frac{2\pi}{\sqrt{1-\beta^2}}$$

$$I_2 = \frac{2\pi}{(1-\beta^2)(1-\beta^2)^{1/2}}$$

$$I_3 = \frac{3}{2(1-\beta^2)} \frac{2\pi}{(1-\beta^2)(1-\beta^2)^{1/2}} - \frac{2\pi}{2(1-\beta^2)(1-\beta^2)^{1/2}}$$

$$I_4 = \frac{5}{3(1-\beta^2)} \frac{3}{2(1-\beta^2)} \frac{2\pi}{(1-\beta^2)(1-\beta^2)^{1/2}} - \frac{5}{3(1-\beta^2)} \frac{2\pi}{2(1-\beta^2)(1-\beta^2)^{1/2}} - \frac{2}{3(1-\beta^2)} \frac{2\pi}{(1-\beta^2)(1-\beta^2)^{1/2}}$$

Dividing by 2π and multiplying through, we obtain, after simplification, the following values for the form X integrals:

$$I_1 = \frac{1}{(1-\beta^2)^{1/2}}$$

$$I_2 = \frac{1}{(1-\beta^2)^{3/2}}$$

$$I_3 = \frac{(1 + \frac{\beta^2}{2})}{(1-\beta^2)^{5/2}}$$

$$I_4 = \frac{(1 + \frac{3}{2}\beta^2)}{(1-\beta^2)^{7/2}}$$

For corresponding integrals of form Y, we have :

$$I_1^* = 1$$

$$I_2^* = (1 + \frac{1}{2}\beta^2)$$

$$I_3^* = (1 + \frac{3}{2}\beta^2)$$

$$I_4^* = (1 + 3\beta^2 + \frac{3}{8}\beta^4)$$

The time average of equation (A.16) may now be written as :

$$F_1 \equiv (AI_3 - BI_2)G$$

$$F_2 \equiv (A^2I_2 - 2ABI_1 + B^2)G^2$$

$$F_3 \equiv (A^3I_1 - 3A^2B + 3AB^2 - B^3I_2^*)G^3$$

$$F_4 \equiv (A^4 - 4A^3B + 6A^2B^2 - I_1^* - 4AB^3I_3^* + B^4I_4^*)G^4$$

$$(A.17) \dots \overline{R(t, \eta)}_I = K_1 \eta \rho D^{-4} \left\{ I_4 + 2.5 \left[F_1 G + F_2 G^2 + F_3 G^3 + F_4 G^4 \right] \right\}$$

To compare equation A.17 to the average resistance associated with a vessel whose diameter is constant and not subjected to the hemotocrit change, we write for the steady maximum and mean diameter vessels respectively:

$$(A.18) \dots (R_2)_I = K_1 \eta \rho D^{-4} (1+\beta)^{-4} \left[1 + 2.5 \frac{H_s}{1-H_s} \right]$$

$$(A.19) \dots (R_1)_I = (1+\beta)^4 (R_2)_I$$

Forming the ratio of (A.17) to (A.18 & A.19) yields the two comparison quantities given by equations (A.20a) and A.20b). These equations are analogous to equations (48) and (49) of Section III.

$$(A.20a) \dots \frac{\overline{R(t, \eta)_I}}{(R_2)_I} = \frac{(1 + \beta)^4}{(1 + 2.5 \frac{H_s}{1 - H_s})} \left\{ I_4 + 2.5 (F_1 G + F_2 G^2 + F_3 G^3 + F_4 G^4) \right\}$$

$$(A.20b) \dots \frac{\overline{R(t, \eta)_I}}{(R_1)_I} = (1 + \beta)^{-4} \frac{\overline{R(t, \eta)_I}}{(R_2)_I}$$

To compare equation (A.17) to the mean resistance of an active vessel not subject to the hematocrit variation, we first write:

$$(A.21) \dots \overline{R(t)_I} = \frac{1}{2\pi} \int_0^{2\pi} \frac{\kappa_1 dx}{D_0^4 (1 + \beta \sin x)^4} = \frac{\kappa}{D_0^4} \overline{I}_4$$

$$= \kappa_1 \eta_p D_0^{-4} \left(1 + 2.5 \frac{H_s}{1 - H_s} \right) \overline{I}_4$$

Forming the ratio of equation (A.17) to (A.21) gives the proper comparison which is given in equation (A.22).

$$(A.22) \dots \frac{\overline{R(t \tau)_I}}{\overline{R(t)_I}} = \frac{1 + 2.5 \left(\frac{GF_1 + G^2 F_2 + G^3 F_3 + G^4 F_4}{I_H} \right)}{1 + 2.5 \left(\frac{H_5}{1 - H_5} \right)}$$

2. Mode II

The next case of interest is that of the active vessel with constant maximum diameter. The equations corresponding to (A.7) and (A.8) are respectively (A.23) and A.24).

$$(A.23) \dots \begin{aligned} D &= D_m (1 - \beta) + \beta \cos X \\ &= D_m (1 - \beta) [1 + \phi \cos X] \\ &= D_m (1 - \beta) S\phi \end{aligned}$$

$$\phi \equiv \frac{\beta}{1 - \beta}$$

$$S\phi \equiv (1 + \phi \cos X)$$

$$(A.24) \dots D_s = D_m$$

The method for solution for the time mean resistance in this case is the same as that leading to equation (A.17). Thus we obtain for form X integrals:

$$I_1 = \frac{1}{(1 - \phi^2)^{1/2}}$$

$$I_2 = \frac{1}{(1 - \phi^2)^{3/2}}$$

$$I_3 = \frac{1 + \frac{1}{2} \phi^2}{(1 - \phi^2)^{5/2}}$$

$$I_4 = \frac{1 + \frac{3}{2} \phi^2}{(1 - \phi^2)^{7/2}}$$

For form Y integrals we obtain:

$$I_1^* = 1$$

$$I_2^* = \left(1 + \frac{\phi^2}{2} \right)$$

$$I_3^* = \left(1 + \frac{3}{2} \phi^2 \right)$$

$$I_4^* = \left(1 + 3\phi^2 + \frac{3}{8} \phi^4 \right)$$

We now note that the solution for Mode II, i.e. $\overline{R(t, \eta)}_{II}$, is obtainable from the solution $\overline{R(t, \eta)}_I$ given in equation (A.17). To accomplish this, we write for Mode II:

$$(A.25) \dots H_{II} = \left[(1 + \alpha D_m)(1 - \beta) S_\phi - \alpha D_m (1 - \beta)^2 S_\phi^2 \right] H_S$$

Comparison of equation (A.25) with (A.17) indicates that the following transformations in (A.17) are required.

$$(A.26) \dots \left\{ \begin{array}{lcl} H_s (1+\beta)^{-1} & \longrightarrow & H_s \\ A & \longrightarrow & (1+\alpha D_m)(1-\beta) \\ B & \longrightarrow & \alpha D_m (1-\beta)^2 \\ S & \longrightarrow & S\phi \\ I & \longrightarrow & I\phi \end{array} \right.$$

In addition, equation (A.16) requires the transformation $\bar{D} \rightarrow D_m$. The transformations given by equation (A.26) facilitate numerical evaluation of $\overline{R(t, \eta)}_x$. The Mode II equations are summarized below.

$$(A.27) \dots \overline{R(t, \eta)}_x = K_1 \eta_0 D_m^{-4} (1-\beta)^{-4} \left[I_4(\phi) + 2.5 F(\phi) \right]$$

$$(A.28) \dots \overline{R_1(t)}_x = K_1 \eta_0 D_m^{-4} (1-\beta)^{-4} \left[1 + 2.5 H_s (1-H_s)^{-1} \right] I_2(\phi)$$

$$(A.29) \dots (R_1)_x = K_1 \eta_0 D_m^{-4} (1-\beta)^{-4} \left[1 + 2.5 H_s (1-H_s)^{-1} \right]$$

$$(A.30) \dots (R_2) = K_1 \eta_0 D_m^{-4} \left[1 + 2.5 H_s (1-H_s)^{-1} \right]$$

$$(A.31) \dots \frac{\overline{R(t, \eta)}_{\pi}}{(R_1)_{\pi}} = \frac{I_4(\varphi) + 2.5 F(\varphi)}{1 + 2.5 H_5 (1 - H_5)^{-1}}$$

$$(A.32) \dots \frac{\overline{R(t, \eta)}_{\pi}}{(R_2)_{\pi}} = (1 - \beta)^{-1} \frac{I_4(\varphi) + 2.5 F(\varphi)}{1 + 2.5 H_5 (1 - H_5)^{-1}}$$

$$(A.33) \dots \frac{\overline{R(t, \eta)}_{\pi}}{\overline{R(E)}_{\pi}} = \frac{1 + 2.5 \left(\frac{F(\varphi)}{I_4(\varphi)} \right)}{1 + 2.5 \left(\frac{H_5}{1 - H_5} \right)}$$

V. Non-Newtonian Factors

A. Assumed Rheological Equation

In general form the functional relationship which may be used to characterize the rheological properties of a fluid is given by eq. A.34, in which $\dot{\gamma}$ is the shear rate (velocity gradient), and τ is the axially acting shear stress in the fluid.

$$(A.34) \dots \tau = f(\dot{\gamma})$$

When the shear stress is a linear function of the shear rate, then the specific form of eq. A.34 is that of eq. A.35, in which η is the Newtonian viscosity of the fluid or simply the viscosity.

$$(A.35) \dots \tau = \eta \dot{\gamma}$$

Equation A.35 is the proper relationship for characterizing a fluid to which Poiseuille's equation applies. Merrill (1969), Oka (1968), and others, recognizing that blood does not exhibit Newtonian behavior at least at low shear rates, have put forward empirical equations of the general form of eq. A.36 to account for blood's empirically observed behavior. Testing of this equation using viscometric methods has shown reasonable agreement between experimental results and equation predictions.

$$(A.36) \dots \tau = \eta \dot{\gamma} + 2(\eta \dot{\gamma} \tau_y) + \tau_y$$

B. Apparent Viscosity

Since viscosity per se applies strictly to a Newtonian fluid, it is necessary to formulate a quantity which carries the similar meaning for the non-Newtonian fluid. One such quantity called the apparent viscosity η_a may be obtained by forming the ratio of the shear stress to velocity gradient to obtain equation A.37.

$$(A.37) \dots \left(\frac{\tau}{\dot{\gamma}} \right) = \eta + 2 \left(\frac{\eta \tau_y}{\dot{\gamma}} \right)^{1/2} + \frac{\tau_y}{\dot{\gamma}} \equiv \eta_a$$

Equation A.37 thus defines apparent viscosity of the fluid in the following sense. If this fluid were placed in a standard viscometer from which a plot of shear rate (velocity gradient) vs. shear stress (related to pressure gradient) could be constructed, then the slope of the curve at any point may be interpreted as apparent viscosity in the sense that it has a shear stress/shear rate ratio, at this point, equal to that of a Newtonian fluid with viscosity η_a . From equation A.37 it may be seen that the apparent viscosity approaches the Newtonian viscosity as the ratio of yield stress to shear rate becomes small. Thus, for shear rates large with respect to the yield stress, equation A.37 predicts essentially Newtonian behavior which is characteristic of the flow properties of blood.

For purposes of latter comparison, it is convenient to express equation A.37 in a slightly different form. Using eq. A.36, the shear

rate term may be eliminated, and after rearrangement, eq. A.38 for the apparent viscosity is obtained.

$$(A.38) \dots \eta_a = \eta \left[1 + \frac{\left(\frac{\tau_y}{\tau} \right)^{1/2}}{1 - \left(\frac{\tau_y}{\tau} \right)^{1/2}} \right]^2$$

Equation A.38 represents a general form of the approval viscosity in terms of the yield stress of the fluid and the shear stress. The appropriate form for each of these quantities associated with the rhyimically active vessel now needs to be considered. This is necessary to examine the amount by which the apparent viscosity deviates from Newtonian viscosity in the active vessel and for latter use in formulation of the non-Newtonian pressure flow equations.

C. Parameters of Apparent Viscosity

1. Yield Stress as a Function of Hematocrit

As we discussed in the introduction, the hematocrit within the active vessel is not constant. The effects of these hematocrit changes with vessel diameter were investigated in depth in Section A-III. It was also pointed out that the yield stress was also a function of the local hematocrit. Thus, in order to develop a formulation of yield stress applicable to eq. A.38, the appropriate relationship must be used. Merrill has developed an empirical expression which relates yield stress to hematocrit as given by eq. A.39. In this equation K_y is a number which is dependent on the fibrinogen concentration, and H_0 is the value of hematocrit for

which no yield stresses can be experimentally measured. When hematocrit is expressed in decimal (rather than as %) K_y has a range of .6 to 1.2 for normal blood, and H_0 is approximately .04 to .08. In the present analysis, the middle range values are used for both quantities that is $K_y = .9$ and $H_0 = .06$.

$$(A.39) \dots \tau_y = K_y (H - H_0)^3$$

2. Average Axial Shear Stress

In cylindrical coordinates with v defined as the radial component of velocity and u as the axial component, the shear stress acting in the axial direction may be written in terms of the two velocity gradients as in eq. A.40.

$$(A.40) \dots \tau = \eta \left(\frac{\partial v}{\partial z} + \frac{\partial u}{\partial r} \right)$$

Since the dynamic motion of the wall is assumed to be axially uniform, the axial variation in the radial component of velocity may be neglected. Thus, to a first approximation, the velocity profile of the axial velocity component determines the radial dependence of shear stress.

For a fluid having the rheological description given by eq. A.36, Oka (1969) and others have shown that the velocity profile satisfies eq. A.41 below, in which p' is the axial pressure gradient, and r is the radial coordinate from the point of zero shear, and a is the vessel

radius.

$$(A.41) \dots u = \frac{p'}{4\eta} (a^2 - r^2) - \frac{4}{3} \frac{\sqrt{\tau_Y}}{\eta} \left(\frac{p'}{2}\right)^{1/2} (a^{3/2} - r^{3/2}) + \frac{\tau_Y}{\eta} (a - r)$$

Differentiating eq. A.41 with respect to r and multiplying by η yields the expression for the axial shear stress as a function of radial coordinate and other parameters given by eq. A.42.

$$(A.42) \dots \tau = \frac{r p'}{2} + \tau_Y - (2\tau_Y p' r)^{1/2}$$

It may be noted that as in the case of a Newtonian fluid, the largest shear stress occurs at the wall. Because the wall boundary is a function of time, it is necessary to define an average stress which is related to the instantaneous vessel and radius. A convenient and useful choice is to use a reference stress which is related to the well defined wall stress given by equation below, in terms of the vessel diameter D .

$$(A.43) \dots \tau_w = \frac{D p'}{4} + \tau_Y - (\tau_Y p' D)^{1/2}$$

Equation A.43 represents the maximum value of shear stress in the blood. From this maximum value, it decreases to zero at some radial position away from the wall. For a Newtonian fluid, this point corresponds to the center of the vessel. For a fluid having the rheological properties given by equation A.36, the point of zero shear occurs closer to the vessel wall. To utilize eq. A.38 and calculate the apparent viscosity, it is useful to use the average shear stress defined as one half the difference between the maximum and the minimum shear. Since the minimum shear is zero, the average shear defined in this fashion is simply one half of the wall shear stress. Using this relationship in eq. A.38 results in an expression for the apparent viscosity in terms of the yield stress defined by eq. A.39 and the wall shear stress which may be evaluated by eq. A.43. The general form of eq. A.38 may thus be written as eq. A.44 below.

$$(A.44) \dots \eta_a = \eta \left[1 + \frac{\left(\frac{2\tau_y}{\tau_w} \right)^{1/2}}{1 - \left(\frac{2\tau_y}{\tau_w} \right)^{1/2}} \right]^2$$

D. Instantaneous Resistance, Pressure, and Flow

The results obtained in the previous sub-sections bear on the properties and behavior of the individual components and parameters of a flow regime in which variable viscosity, non-Newtonian fluid, and rhythmic dynamics contribute. In this sub-section, these separate results will be combined so that the totality of these effects on pressure, flow, and resistance of rhythmically active vessels may be

evaluated. To accomplish this, use shall be made of the general analytical model (figure 3.1 of Chapter Three), to which will be assigned numerical values for source and load as determined from the calculations of Chapter Three. The pressure-flow relationship within the active vessel will first be formulated in a form which permits the inclusion of the non-Newtonian regime.

1. General Equation

a. Assumptions

The principal assumption to make is that the Reynolds number is small enough so that all convective acceleration terms in the equation of motion are insignificant. Order of magnitude arguments based on the dimensions and axial flow velocity show that the prevailing Reynolds number is conservatively .01 in the vessels of interest in this analysis. Thus, the assumption seems justified. It is further assumed that the flow regime is symmetric with respect to the axis, and that only the axial component of velocity is significant.

b. Form of Equation

Under these assumptions, we may write in a manner similar to Wilkinson (1960) eq. A.45, which is applicable for flow in a cylindrical vessel of a fluid having any rheological properties. In eq. A.45 Q is the flow, a is the radius, τ is the axial shear stress, and τ_w is the shear stress at the wall.

$$(A.45) \dots \frac{Q}{\pi a^3} = \frac{1}{\tau_w^3} \int_0^{\tau_w} \tau^2 f(\tau) d\tau$$

2. Specific Rheology

The functional rheologic relationship required is that defined by eq. A.36. Using this in eq. A.45 leads to:

$$(A.46) \dots \frac{Q}{\pi D^3} = \frac{\tau_w}{8\eta} \left[1 - \frac{16}{7} \left(\frac{\tau_y}{\tau_w} \right)^{1/2} + \frac{4}{3} \left(\frac{\tau_y}{\tau_w} \right) - \frac{1}{21} \left(\frac{\tau_y}{\tau_w} \right)^4 \right]$$

To express eq. A.46 in terms of the pressure gradient p' , we make use of eq. A.43 and get:

$$(A.47) \dots Q = \frac{\pi p' D^4}{128\eta} \left[1 - \frac{32}{7} \left(\frac{\tau_y/D}{p'} \right)^{1/2} + \frac{16}{3} \left(\frac{\tau_y/D}{p'} \right) - \frac{4}{21} \left(\frac{\tau_y/D}{p'} \right)^4 \right]$$

Further defining $\frac{\tau_y/D}{p'} = \theta$ we get:

$$(A.48) \dots Q = \frac{\pi p' D^4}{128\eta} \left[1 - \frac{32}{7} \theta^{1/2} + \frac{16}{3} \theta - \frac{4}{21} \theta^4 \right]$$

$$= \frac{\pi p' D^4}{128\eta} F(\theta)$$

Note that eq. A.48 is the same form as the Poiseuille eq. except that its effective viscosity is equal to $\frac{\eta}{F(\theta)}$. The ratio of the corresponding resistances are thus determined by the respective values

of yield stress gradient τ_y/D compared to the pressure gradient p' . Thus, we may write for the resistance of the rhythmically active vessel:

$$(A.49) \dots R(t, \eta, \tau_y) = K_1 \left[\frac{\eta(H)}{D^4(t) F(\theta)} \right]$$

and as the general equation for the analytical model:

$$(A.50) \dots p' \ell (Z_s + Z_d) D^4(t) F(\theta) + p' \ell K_1 \eta(H) - p_s K_1 \eta(H) = 0$$

Solution of eq. A.50 allows the pressure gradient to be evaluated and thereby produces solutions for the active vessel resistance and flow.

Appendix B...Wall Equations

I. Introduction

As was shown in Chapter Four (eq. 4.6), the dynamic behavior of the rhythmically active vessel could be approximately described by eq. B.1 below, in which $\sigma(t)$ is the circumferential wall stress, $\epsilon(t)$ is the strain, and E and K_η correspond to the lumped elastic and viscous coefficients respectively.

$$(B.1) \dots \sigma(t) = E\epsilon(t) + K_\eta \dot{\epsilon}(t).$$

To be able to utilize eq. B.1, it is necessary to include the muscle contraction effects and to take into account the fact that the small venous vessels may not be construed as being "thin walled", as, for example, the large veins are often taken to be. This requires that an appropriate radius for these non-thin walled vessels be defined so that the strain terms of eq. B.1 may be interpreted unambiguously.

To fulfill these requirements, it will first be shown that the stress corresponding to that of the geometric mean of the vessel wall is precisely equal to the equilibrium stress averaged over the entire vessel wall. It will then be shown that under conditions of equilibrium, and subject to the normal range of intravascular pressure, this same radius may be used as a reference radius corresponding to a fully relaxed vessel state, the data for which is obtained from in vivo information. The effect of the contracting muscle will then be introduced as an additional force tending to reduce the vessel radius

and thus disturb a quasi equilibrium state assigned to the relaxed vessel. The difference between the intravascular distending forces and the active contracting force then becomes the effective driving force on the wall. The subsequent change in the vessel dimensions is then determined by equation B.1 in which the relative strain is measured from the reference state.

II. Analysis

A. Mean Stress in Vessel Wall

The geometry of the vessel is assumed to be cylindrical in shape with inside radius a , and outside radius b . Due to intravascular pressure P_1 there is a force F_1 per unit longitudinal length acting radially outward. Due to perivascular pressure P_2 and possibly structural characteristics surrounding the vessel, there is a force F_2 per unit length acting radially but in a direction opposite to F_1 . Considering the circumferential direction only, these two forces result in a circumferential force per unit length F_θ . The circumferential force present in the wall tending to oppose the action of F_θ is T_θ . At equilibrium, these forces are equal. In general, however, T_θ may be expressed in terms of the circumferential stress distribution per unit length as in equation B.2.

$$(B.2) \dots T_\theta = \int_a^b \int_0^{2\pi} \sigma_\theta d\theta dr$$

In the present case, the stress in the wall is determined in part by the so called passive vessel wall constituents (σ_p) and the contraction effects of the vascular smooth muscle (σ_m). If we assume for the moment that the stress distribution due to both factors are uniformly distributed throughout the wall, then we may write for T_θ from eq. B.2.

$$(B.3) \dots T_\theta = \sigma_\theta (b - a) 2\pi$$

For equilibrium in the radial direction, we require that:

$$(B.4) \dots F_2 + 2T_\theta \sin(d\theta/2) = F_1$$

since $F_1 = P_1 (d\theta/2\pi) (2\pi a)$ and $F_2 = P_2 (d\theta/2\pi) (2\pi b)$

we write eq. B.4 as eq. B.5:

$$(B.5) \dots P_2 d\theta b = 2T_\theta \sin(d\theta/2) = P_1 d\theta a$$

Now since we may choose $d\theta$ as small as we like, the equilibrium condition may be written as:

$$(B.6) \dots T_\theta = P_1 a - P_2 b$$

Equation (B.6) is a quite general result. For the special conditions leading to equation (B.3) (i.e., uniform stress distribution), the equilibrium condition may be written in terms of circumferential stress as:

$$(B.7) \dots \sigma_\theta = (a/h)(P_1 - P_2) - P_2$$

Now the well known expression for the circumferential stress distribution in a thick walled cylinder having uniform material characteristics (Timishenko, 1958) is given by eq. (B.8) below.

$$(B.8) \dots \sigma_\theta = \frac{a^2 P_1 - b^2 P_2}{b^2 - a^2} + \frac{(P_1 - P_2) a^2 b^2}{b^2 - a^2} \cdot \frac{1}{r^2}$$

In order to evaluate the stress at the geometric mean radius, $\overline{r}_g$, we let $r = (ab)^{.5}$ in eq. (B.8). After making this substitution, we find that the stress at the geometric mean is:

$$(B.9) \dots \sigma_g = (a/h)(P_1 - P_2) - P_2$$

Comparing equations (B.7) and (B.9), the equilibrium circumferential stress at the geometric mean is precisely the same as the circumferential stress determined using the assumption that the radial distribution of circumferential stress is uniform.

B. Reference Radius

From eq. (B.9), the stress at the geometric mean will be

zero when:

$$(B.10) \dots \frac{P_2}{P_1} = \frac{a/h}{1 + a/h}$$

The range of a/h values lies well within the range $3 \leq a/h \leq 9$ for the vessels here being studied. For the extreme points, the pressure ratio yielding zero stress at $\bar{r}_g$ corresponds to $.75 \leq \frac{P_2}{P_1} \leq .9$. Under conditions for which eq. (B.10) is satisfied, then the geometric mean radius may be used as an approximation to the so called zero strain state from which subsequent strain may be measured. Let us call the inside radius and outside radius corresponding to this state a_0 and b_0 , respectively. Physically this state shall be that corresponding to the passively relaxed vessel. Thus we imagine that the muscle had previously contracted reducing the inside radius to some value, say a_c , and outside radius to b_c . The contraction force has subsided, and the muscle is refractory. The driving forces acting on the wall are the lumen pressure P_1 and the external pressure P_2 . The relaxed vessel state then corresponds to the value of the radius which would be reached in the absence of a subsequent contraction. If we can show that in this relaxed state the state of strain is not significantly different from the true zero strain case (i.e., a_0 and b_0), then this radius becomes an ideal reference, since its value may be determined by experimental observation. To do this, the unstrained quantities are written in terms of the strained quantities as in equations (B.11) and (B.12) below using $\gamma = a/h$.

$$(B.11) \dots a_0 = \frac{a}{1 + \left\{ \frac{P_1[(\gamma + 1)^2 + \gamma^2] - 2P_2(\gamma + 1)^2}{E(2\gamma + 1)} \right\}}$$

$$(B.12) \dots b_0 = \frac{b}{1 + \left\{ \frac{P_1 [2\gamma]^2 - P_2 [(\gamma + 1)^2 + \gamma^2]}{E [2\gamma + 1]} \right\}}$$

What will be demonstrated using (B.11) and (B.12) is that for the physiological range to which these vessels are exposed, the bracketed quantities in the denominators, though not insignificant, are small enough to render (a) an adequate approximation to a_0 for use as a reference.

In the dilated state, the a/h ratio is largest. Data of Baez (1969) indicates the average wall thickness of 38μ diameter venules is 5.8μ which yields an a/h ratio of 3.3. In order to make a "worst case" estimate, however, an a/h value of 9 shall be used in (B.11) and (B.12). E is of the order of 10^6 dynes cm^{-2} and the transmural pressure $P_1 - P_2$ is of the order 10×10^3 dynes cm^{-2} . It may thus be seen that even with the extremely conservative a/h value used, $a = 1.1a_0$.

These results allow the use, in the present simulation, of the relaxed vessel as a reference "unstrained" state, and the use of the mean radius as a reference value.

The inclusion of the influence of the contracting muscle is affected by expressing the left hand side of eq. (B.1) as the difference between the stress tending to dilate the vessel, and the developed stress associated with the contracting muscle. The general wall equation may finally be written as eq. (B.13).

$$(B.13) \dots \gamma (P_1 - P_2) - P_2 - \sigma_m = E \epsilon + K_m \dot{\epsilon}$$

C. Parameters

1. Wall Coefficients

The wall volume may be expressed as in equation (B.14) below.

$$(B.14) \dots V_w = \pi h(2a + h)l$$

For convenience, a wall constant K_w may be defined as $V_w/\pi l$; thus:

$$(B.15) \dots K_w = h(2a + h)$$

By calculating from the data of Baez (1969), the value of K_w for vessels corresponding to those of interest here (venules and small veins) is determined to be $2.5 \times 10^{-6} \text{ cm}^3/\text{cm}$. This value corresponds to an a/h ratio of 3.3. The volume per unit vessel length is πK_w .

The nominal value for the coefficient of viscosity is estimated from the data of Wiederhelm (1965) to be 5×10^5 in cgs units, and the nominal elastic modulus to be 1×10^6 dynes/cm².

2. Active Stress (σ_m)

The active stress is an independent variable in the model. As is discussed in Chapter Four, Section V-C, the time course of the active stress is simulated by a trapezoidal function with rise, fall, and contraction durations which may be adjusted to approximate the normal (or abnormal) time course of contracting muscle. In order to have a reasonable estimate of the maximum developed stress applicable to the small vessel contraction mode we are simulating the in vivo data of Wiederhelm is used to calculate it. In a sequence of experiments in which a variety of microvessels were subjected to topical norepinephrine the peak pressure developed by the contracting

