

THE MICROCIRCULATION: THEORY AND EXPERIMENT

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PART 2 chapters 3-4

CHAPTER THREE... HEMODYNAMICS OF RHYTHMICALLY ACTIVE VESSELS

I. Introduction

In the development of Chapter Two the post capillary vasculature was treated as a passive vessel system. As has been described in Chapter One a rhythmical and often pronounced fluctuation in the diameter of the post capillary vessels is present. The physiological significance of these dynamics is unknown. It is the objective of this chapter to analytically investigate the hemodynamics associated with these rhythmically varying vessels, collectively referred to as venomotion, for the purpose of gaining some insight into their possible physiological significance.

The basic approach to be followed is to develop expressions for the flow, pressure and volume variations associated with venomotion. These results or quantities derived from them such as resistance and transit time are then compared with corresponding results obtained from non-rhythmic vessels having comparable dimensions. In this way the basic hemodynamic properties of the rhythmic vessels are elucidated, and, by appropriate comparisons with non-rhythmic vessels, insight may be gained relating to their potential physiologic significance.

The initial part of the analysis focuses on the vessel dynamics per se. Thus, rheological complications associated with non-constant viscosity and non-Newtonian behavior are not included. After obtaining the basic equations characteristic of the rhythmic dynamics, these factors are then incorporated in an attempt to

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evaluate their significance within the dynamic flow regime.

II. Characterization of Rhythmically Active Vessel Dynamics

A. Assumptions

1. Each vessel is cylindrical and exhibits sinusoidal type diameter variation without change in cross sectional shape.
2. There is no change in the length of the vessel associated with these active diameter changes.
3. The blood behaves in a Newtonian fashion.
4. The viscosity is constant.

B. Analytical Model

Figure 3.1 depicts the general model to which the initial analysis is directed. It embodies the basic features of the dynamic process in which we are presently interested. That is, vessels with rhythmically varying diameter $D(t)$, bounded by impedances (Z_s and Z_d) which represent the up- and downstream impedances seen by the active vessel and an equivalent upstream pressure source P_s , which represents the arterial driving pressure as seen by the rhythmically active vessel.

C. Mathematical Formulation

1. Mode of Diameter Variation

The author's observations of venomotion in the bat wing (see for example Chapter Six) have revealed that the contraction amplitude (i.e., difference between maximum and minimum diameter) is not constant. Further, a change in contraction amplitude may occur without substantial change in the vessel's maximum diameter. On the other hand, different contraction amplitudes on occasion appear to

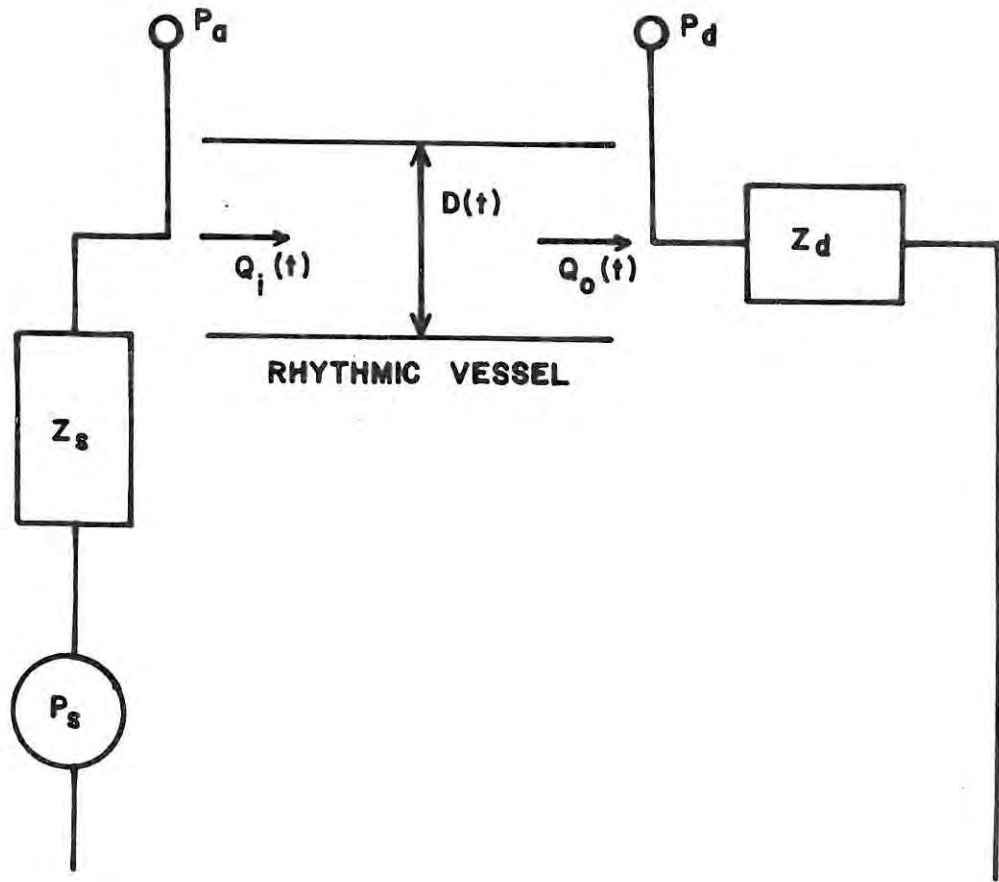


Fig. 3.1. General active vessel model for analyzing hemodynamics associated with rhythmical dynamics. $D(t)$ is vessel instantaneous inside diameter, $Q_i(t)$ is instantaneous inflow, $Q_o(t)$ is outflow, Z_s , Z_d , and P_s are equivalent source, drain and pressure as "seen" by active vessel. P_a and P_d are the pressures that would be measured at the upstream and downstream sites as shown.

have essentially the same average diameter. Since we are interested in the hemodynamics associated with the in vivo diameter variations as a function of contraction amplitude it is necessary to consider both of these cases. Thus we shall distinguish between a mode I (fig. 3.2a) in which the mean diameter of the active vessel (D_o) remains constant with changing contraction amplitude ($\hat{D}$), and a mode II (fig. 3.2b) in which the maximum vessel diameter (D_m) remains constant with changing contraction amplitude. Defining the relative contraction amplitude β as $\hat{D}/D_o$ for mode I and as $\hat{D}/D_m$ for mode II the instantaneous diameters for the two cases may be written as in equations 3.1 and 3.2 below.

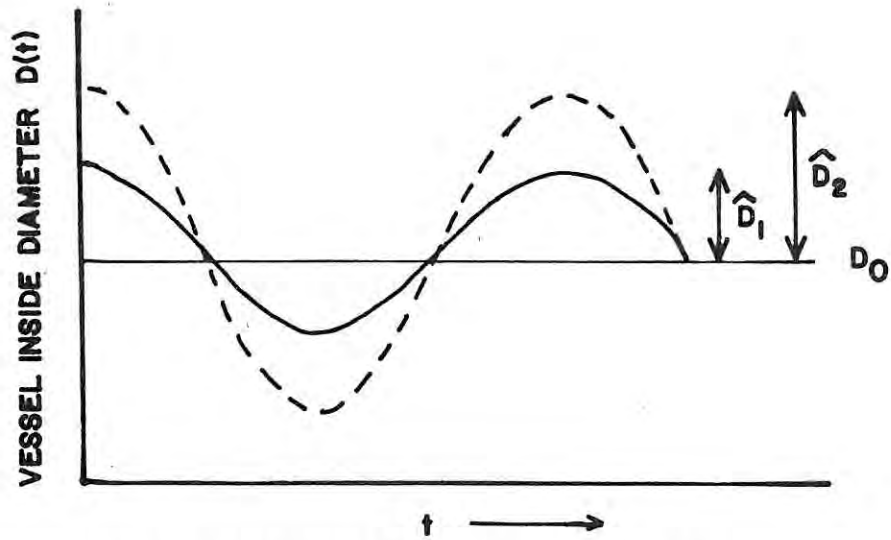
$$(3.1) \dots D(t)_I = D_o + \hat{D} \cos \omega t = D_o (1 + \beta \cos \omega t) \quad \text{For mode I}$$

$$\begin{aligned} (3.2) \dots D(t)_{II} &= \bar{D} + \hat{D} \cos \omega t & \bar{D} &\equiv \text{average diameter} \\ &= D_m - \hat{D} + \hat{D} \cos \omega t \\ &= D_m (1 - \beta + \beta \cos \omega t) \\ &= D_m [1 - \beta (1 - \cos \omega t)] & \text{For mode II} \end{aligned}$$

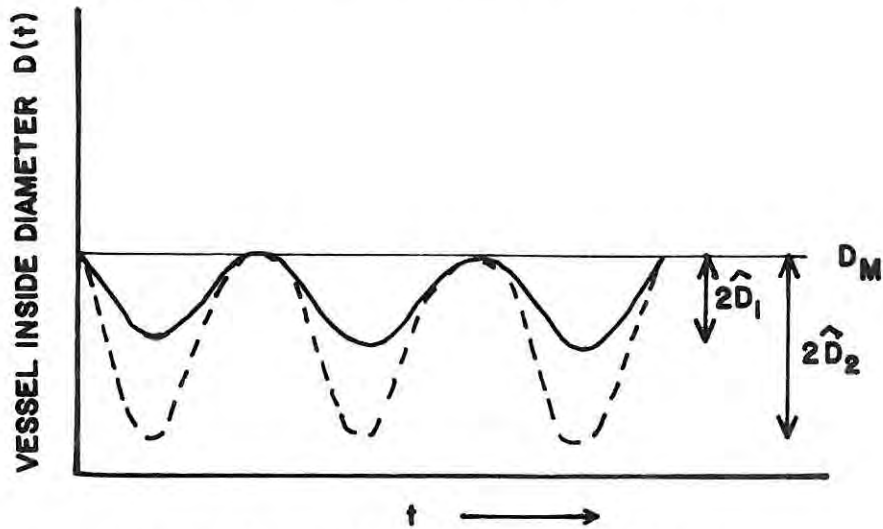
For convenience of notation the sinusoidal argument (ωt) will be replaced by x in equations which utilize 3.1 or 3.2.

2. Hemodynamic Quantities Derived from the General Analytical Model

The hydraulic resistance to flow of the active vessel is defined as $R(t)$ and according to the assumptions stated above is given by equation 3.3 below in which η is the blood viscosity and l is the vessel length.



(a) MODE I DIAMETER VARIATION



(b) MODE II DIAMETER VARIATION

Fig. 3.2. Modes of rhythmic vessel diameter variation. In (a) the vessel average diameter D_0 is constant and independent of changes in the contraction amplitude D . In (b) the maximum diameter of the vessel D_m is constant whereas the average vessel diameter is a function of the contraction amplitude. In the illustrations the frequency difference between (a) and (b) has no significance.

$$(3.3) \dots R(t) = \frac{128\eta\ell}{\pi D^4(t)}$$

Defining the instantaneous volume of the active vessel as $V(t) = \frac{\pi\ell}{4} D^2(t)$, the instantaneous volumes of the active vessel for mode I and mode II are then given by equations 3.4 and 3.5 respectively.

$$(3.4) \dots V(t)_I = \frac{\pi D_o^2 \ell}{4} [1 + 2\beta \cos x + \beta^2 \cos^2 x]$$

$$(3.5) \dots V(t)_{II} = \frac{\pi D_m^2 \ell}{4} [1 - 2\beta + \beta^2 + \beta[(2 - \beta)\cos x + \beta \cos^2 x]]$$

Taking into account the boundary conditions and driving pressure the active vessel inflow, $Q_i(t)$, is given by equation 3.6.

$$(3.6) \dots Q_i(t) = \frac{P_s}{Z_s + Z_d + R(t)}$$

From the continuity equation as applied to figure 3.1 one obtains an equation for the outflow, $Q_o(t)$, as in equation 3.7.

$$(3.7) \dots Q_o(t) = Q_i(t) - \dot{V}(t)$$

Using this equation together with equations 3.4, 3.5 and 3.6 leads to equations 3.8 and 3.9 which express the active vessel outflow in terms of the relative contraction amplitude and other pertinent parameters for mode I and mode II diameter variation respectively.

$$(3.8) \dots Q_o(t)_I = \frac{P_s \pi D_o^4 [1 + \beta \cos x]^4}{\pi D_o^4 (Z_s + Z_d) [1 + \beta \cos x]^4 + 128 \eta \ell} +$$

$$\frac{\pi D_o^2 \ell \omega \beta}{4} [2 \sin x + \beta \sin 2x]$$

$$(3.9) \dots Q_o(t)_{II} = \frac{P_s \pi D_m^4 [1 - \beta(1 - \cos x)]^4}{\pi D_m^4 (Z_s + Z_d) [1 - \beta(1 - \cos x)]^4 + 128 \eta \ell} +$$

$$\frac{\pi D_m^2 \ell \omega \beta}{4} [(2 - \beta) \sin x + \sin 2x]$$

For the purpose of later comparison with hemodynamic quantities associated with non-rhythmic vessels it is convenient to determine the time average of the active vessel quantities. The time averages of equations 3.4, 3.5, 3.8 and 3.9 are given by equations 3.10, 3.11, 3.12 and 3.13. Average quantities are denoted by bars. In the case of equations 3.8 and 3.9 it should be noted that the time average of change in volume associated with the dynamics (the right hand member) is zero. This means that the average inflow is equal to the average outflow. Thus it is no longer necessary to distinguish input and output quantities when average values are used. Thus the subscript notation is dropped in equations 3.12 and 3.13.

$$(3.10) \dots \overline{V(\tau)}_I = \frac{\pi D_o^2 \ell}{4} \left[1 + \frac{\beta^2}{2} \right]$$

$$(3.11) \dots \overline{V(\tau)}_{II} = \frac{\pi D_m^2 \ell}{4} \left[1 - 2\beta + \frac{3}{2} \beta^2 \right]$$

$$(3.12) \dots \overline{Q(\tau)}_I = \frac{P_s D_o^4}{2} \int_0^{2\pi} \frac{(1 + \beta \cos x)^4 dx}{\pi D_o^4 (Z_s + Z_d) (1 + \beta \cos x)^4 + 128 \eta \ell}$$

$$(3.13) \dots \overline{Q(t)}_{II} = \frac{P_s D_m^4}{2} \int_0^{2\pi} \frac{[1 - \beta(1 - \cos x)]^4 dx}{\pi D_m^4 (Z_s + Z_d) [1 - \beta(1 - \cos x)]^4 + 128\eta l}$$

Equations 3.8 and 3.9 as well as their time averages given by equations 3.12 and 3.13 are written in terms of the equivalent driving source P_s as described in section II-B. Thus the axial pressure difference appearing across the ends of the active vessel does not explicitly appear. Because this quantity is a hemodynamic variable that is of considerable interest for present and later comparison purposes it is useful to express the flow as an explicit function of the pressure difference $P_a - P_v$. For convenience we define this pressure difference as $\Delta p(t)$ and use equations 3.6 and 3.7 to find the corresponding equations for instantaneous and average flow as given by equations 3.14 and 3.15 below.

$$(3.14) \dots Q_o(t) = \frac{\Delta p(t) - \dot{V}(t)[R(t) + Z_d]}{R(t)}$$

$$(3.15) \dots \overline{Q(t)} = \left[\frac{\overline{\Delta p(t)}}{\overline{R(t)}} \right] - \overline{\dot{V}(t)} - \left[\frac{\overline{V(t)}}{\overline{R(t)}} \right] Z_d$$

3. Hemodynamic Quantities Derived from Constant Pressure and Constant Flow Analytical Models

The flow equations 3.8, 3.9 and 3.12 through 3.15 apply quite generally to the analytical model of fig. 3.1. In order to separate and analyze the significance of the up- and downstream conditions on the active vessel hemodynamics two special cases of interest will be considered.

a. P Model

The first case corresponds to an analytical

model in which the pressure difference axially across the rhythmic vessels remains constant. This implies that the source as seen by the active vessel is one of constant pressure and the drain impedance is small compared to that of the active vessel. Physiologically this upstream condition would simulate a situation in which the large blood volume contained in the very small venules together with their frequent and extensive anastomosing serves to maintain a relatively constant upstream pressure. The downstream condition simulates the situation in which the relatively small diameter rhythmic vessel discharges into a relaxed and much larger diameter venous segment. The analytical model for this case is illustrated in fig. 3.3a and is referred to as P Model.

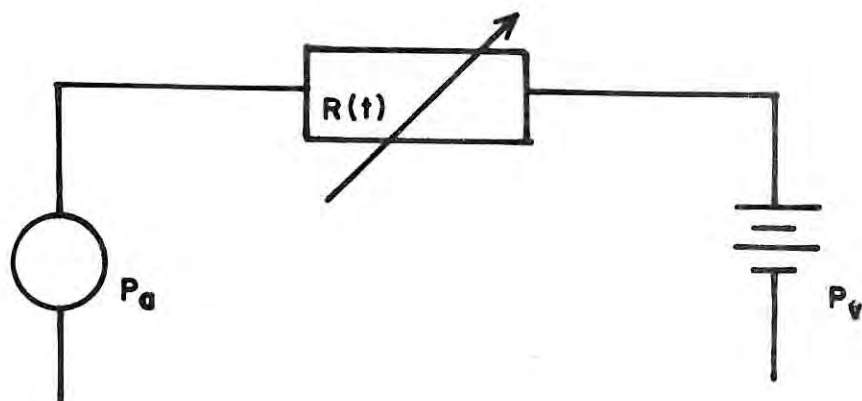
The equations for this model are obtained by defining the reciprocal of the instantaneous resistance as $G(t) = 1/R(t)$, $\Delta p(t) = \Delta p_0$, and by making use of equation 3.15. The general result is given by equation 3.16 which expresses the average active flow for P Model.

$$(3.16) \dots \overline{Q(t)} = \Delta p_0 \overline{G(t)}$$

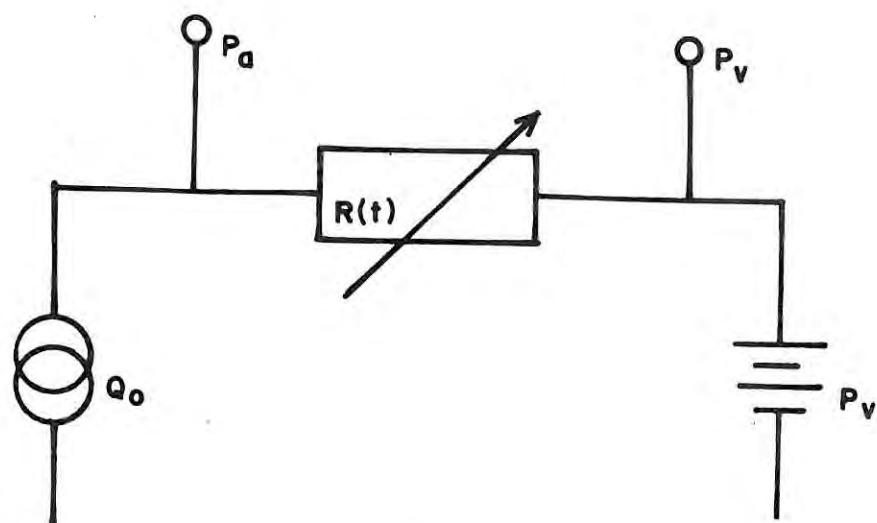
Using equations 3.1 and 3.2 together with the definition, $K = \frac{128\eta l}{\pi}$, the average flows corresponding to modes I and II are given by equations 3.17 and 3.18 respectively.

$$(3.17) \dots \overline{Q(t)}_I = \frac{\Delta p_0 D_o^4}{2\pi K} \int_0^{2\pi} (1 + \beta \cos x)^4 dx = \frac{\Delta p_0}{K D_o^4} (1 + 3\beta^2 + \frac{3}{8} \beta^4)$$

$$(3.18) \dots \overline{Q(t)}_{II} = \frac{\Delta p_0 D_m^4}{K} (1 - 4\beta + 9\beta^2 - 10\beta^3 + \frac{35}{8} \beta^4)$$

MODEL P

(a)

MODEL Q

(b)

Fig. 3.3. Analytical models for two limiting cases. In (a) the source and drain impedances are taken as small compared with the active vessel. In (b) the source is taken as large compared to the sum of active vessel and drain.

b. Q Model

The second special case of interest corresponds to an analytical model in which the flow through the active vessels is essentially constant. This implies that the source impedance is large with respect to the sum of drain and active vessel impedance. Physiologically this would simulate an upstream condition in which the large capillary and precapillary resistances dominate the mean flow properties of the post capillary vessels. The analytical model for this case is shown in figure 3.3b and is referred to as Q Model. Defining Q_0 to be the constant flow and using equation 3.14 rearranged leads to equations 3.19 and 3.20 for the instantaneous and average axial pressure differences respectively.

$$(3.19) \dots \Delta p(t) = Q_0 R(t) + \dot{V}(t) R(t) + \dot{V}(t) Z_d$$

$$(3.20) \dots \overline{\Delta p(t)} = Q_0 \overline{R(t)} + \overline{\dot{V}(t) R(t)}$$

Using equations 3.1, 3.2, 3.4 and 3.5 the instantaneous pressures corresponding to mode I and mode II are given by equations 3.21 and 3.22 respectively.

$$(3.21) \dots \Delta p(t)_I = \frac{KQ_0}{D_o^4 (1 + \beta \cos x)^4} - \frac{32\eta l^2}{D_o^2} \beta \omega \frac{2 \sin x + \beta \sin 2x}{(1 + \beta \cos x)^4}$$

$$(3.22) \dots \Delta p(t)_{II} = \frac{KQ_0}{D_m^4 [1 - \beta(1 - \cos x)]^4} - \frac{32\eta l^2}{D_m^2} \beta \omega \frac{[(2 - \beta) \sin x + \sin 2x]}{[1 - \beta(1 - \cos x)]^4}$$

To obtain the average active vessel axial pressure differences corresponding to modes I and II requires integration of equations 3.21 and

3.22 respectively. The second term on the right hand side of each equation may be handled by substituting $\cos x = 0$ and $d0 = \sin x dx$. After quite a lengthy procedure the integral of the right hand side of equation 3.21 may be shown to be

$$(3.23) \dots \frac{32\eta\ell^2}{D_o^2\beta\omega} \int_0^{2\pi} \frac{2 \sin x + \beta \sin 2x}{(1 + \beta \cos x)^4} dx =$$

$$\frac{32\eta\ell^2}{D_o^2} \left[\frac{\omega}{(1 + \beta \cos x)^2} \right]_0^{2\pi} = 0$$

Thus the average contribution of this term is identically zero. Similarly the right hand term of equation 3.22 averaged over one veno-motion cycle is also zero. Retrospectively it appears that these results may have more simply been obtained by taking the limit as the angular frequency approaches zero. However since in the case of time varying parameters this method may sometimes lead to erroneous results the longer method was the safer and more formal course.

Proceeding to carry out the integration of the first term of each equation yields results for mode I and mode II which are respectively given by equations 3.24 and 3.25.

$$(3.24) \dots \overline{\Delta p(t)}_I = KQ_o D_o^{-4} \frac{(1 + \frac{3}{2} \beta^2)}{(1 - \beta^2)^{7/2}}$$

$$(3.25) \dots \overline{\Delta p(t)}_{II} = KQ_o D_m^{-4} \frac{1 + \frac{3}{2} \left(\frac{\beta}{1 - \beta}\right)^2}{\left[(1 - \beta)^4 \left\{1 - \left(\frac{\beta}{1 - \beta}\right)^2\right\}\right]^{7/2}}$$

III. Analysis

A. Method of Comparison with Non-rhythmic Vessels

In order to gain insight into the possible physiological significance of the rhythmically varying vessels it is useful to compare the hemodynamics associated with these with hemodynamics which would be present in non-rhythmic vessels. In making such comparisons a choice must be made with respect to the characteristics of the non-rhythmic vessel used as a reference. For example in figure 3.4 two possible choices of reference vessels are illustrated. In figure 3.4 the pattern of rhythmic diameter variation corresponding to mode I is shown on the left for different values of relative contraction amplitude β . For this mode the mean vessel diameter D_0 is independent of β . An appropriate and useful comparison or reference vessel would be one having the same mean diameter. Such a vessel is represented in figure 3.4(a) on the right hand side. Alternately it is of interest to use as a reference vessel one which has a constant diameter equal to the maximum diameter of the rhythmic vessel. Such a reference vessel is represented in the right hand side of figure 3.4(b).

A similar set of comparisons may be made for mode II diameter variation. These are illustrated in figure 3.5. An additional comparison is useful for mode II diameter variation. This is illustrated in figure 3.6, where it may be seen that the rhythmic vessel is compared with a reference vessel having the same minimum diameter. In figure 3.6 the maximum diameter represents the fully relaxed vessel diameter (muscle completely inactive). Activation

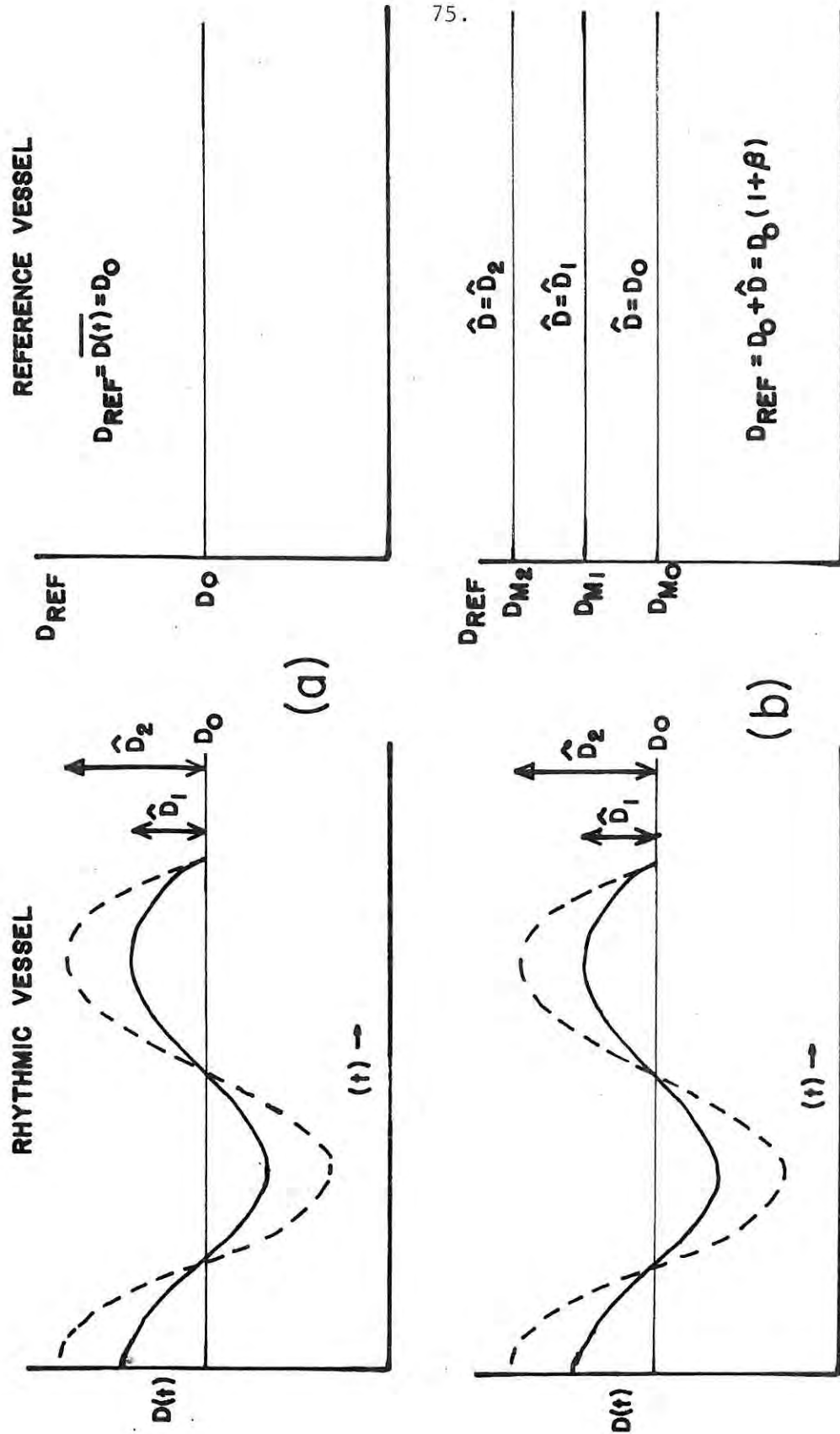


Fig. 3.4. Mode I diameter variation, $D(t)$, and reference vessel dimensions used for comparison purposes. In (a) the rhythmic vessel is compared with reference vessel having the same average diameter, D_0 , whereas in (b) it is compared with a vessel having the same maximum diameter D_m .

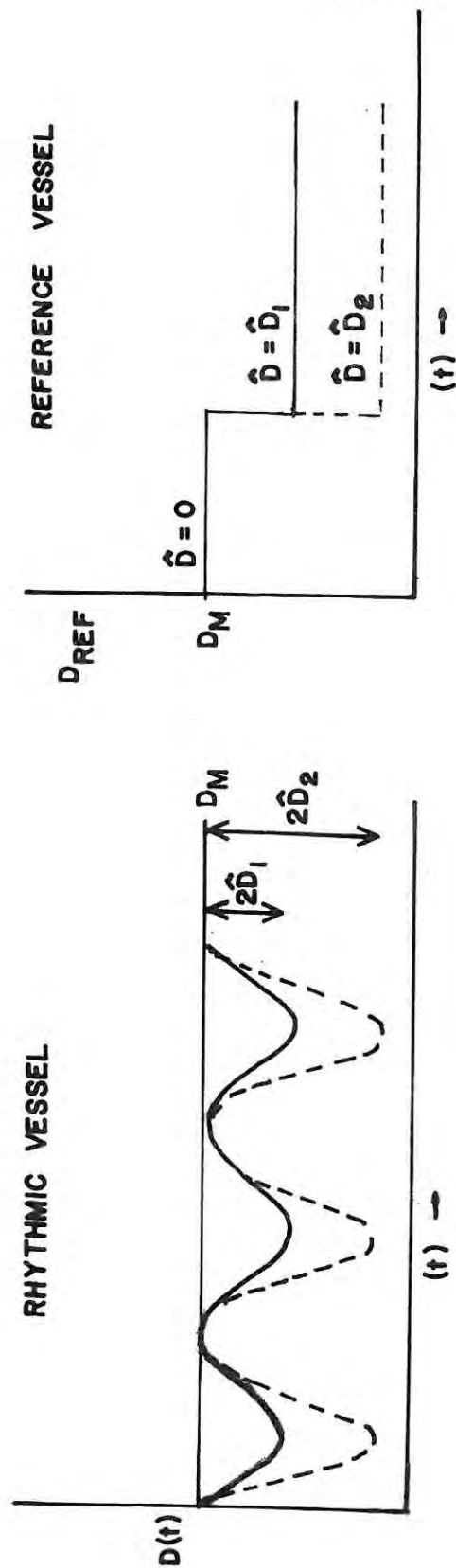


Fig. 3.6. Mode II diameter variations and Type 3 reference vessel used for comparison purposes. See text for description of physiological significance.

of the muscle occurs rhythmically for the vessel represented on the left. The total relative excursion of the diameter from the maximum value is twice β . This then represents the normal mode II diameter variation. For the vessel on the right, muscle activation is assumed to be constant at any one level with transient effects due to step-wise change being neglected. The resultant total change in diameter is equal to twice β . A comparison of the hemodynamics associated with these types of vessel diameter variation thus produces information on the effectiveness of rhythmic versus steady tonic control of vessel diameter.

Hemodynamic comparisons made in vessels having the same average diameter as the rhythmic vessel are defined as type 1 comparisons [figs. 3.4(a) and 3.5(b)]. Hemodynamic comparisons made in vessels having a diameter equal to the maximum diameter of the rhythmic vessel are defined as type 2 comparisons [figs. 3.4(b) and 3.4(a)]. Hemodynamic comparisons made in vessels having a diameter equal to the minimum diameter of the rhythmic vessel are defined as type 3 comparisons (fig. 3.6).

B. P Model and Q Model Equations

To carry out the above comparisons the pertinent equations describing the hemodynamics associated with the rhythmic vessels and non-rhythmic reference vessels are graphed separately and as ratios. For P Model the pertinent hemodynamic quantities are the average flow and blood volume. For Q Model the pertinent quantities are the average axial pressure difference and average blood volume. Another quantity which we will have occasion to utilize for

comparison purposes is the mean transit time, defined as the ratio of average blood volume to average flow.

In the equations to follow hemodynamic quantities for the non-rhythmic reference vessels are written without time dependence but with a subscript notation indicating the type of comparison and mode. For example, $Q(t)_I$ would represent the average flow associated with mode I dynamics, whereas $(Q_1)_I$ and $(Q_2)_I$ would represent respectively the flow in a reference vessel having the same mean diameter as the rhythmic vessel, i.e., type 1 comparison and the flow in a reference vessel having the same maximum diameter as the rhythmic vessel, i.e., type 2 comparison. Thus the Arabic numerals indicate the type of comparison, while the Roman numerals indicate the dynamic mode being compared.

1. P Model

a. Mode I

Defining $K_v = \pi \ell / 4$, The reference vessel equations are:

$$(3.26) \dots (V_1)_I = K_v D_o^2$$

$$(3.27) \dots (V_2)_I = K_v D_o^2 (1 + \beta)^2$$

$$(3.28) \dots (Q_1)_I = \frac{\Delta P_o}{K} D_o^4$$

$$(3.29) \dots (Q_2)_I = \frac{\Delta P_o}{K} D_o^4 (1 + \beta)^4$$

Forming the ratios of equations 3.10 to 3.26, 3.10 to 3.27, 3.17 to 3.28, and 3.14 to 3.29 yields respectively equations 3.30, 3.31,

3.32 and 3.33 which are the pertinent comparison ratios.

$$(3.30) \dots \frac{\overline{V(t)}_I}{(V_1)_I} = 1 + \frac{\beta^2}{2}$$

$$(3.31) \dots \frac{\overline{V(t)}_I}{(V_2)_I} = \frac{1 + \frac{\beta^2}{2}}{(1 + \beta)^2}$$

$$(3.32) \dots \frac{\overline{Q(t)}_I}{(Q_1)_I} = \frac{\overline{G(t)}_I}{(G_1)_I} = 1 + 3\beta^2 + \frac{3}{8} \beta^4$$

$$(3.33) \dots \frac{\overline{Q(t)}_I}{(Q_2)_I} = \frac{\overline{G(t)}_I}{(G_2)_I} = \frac{1 + 3\beta^2 + \frac{3}{8} \beta^4}{(1 + \beta)^4}$$

It may be noted that in equations 3.32 and 3.33 the flow ratios are identical to the conductance ratios.

b. Mode II

$$(3.34) \dots (V_1)_{II} = K_v D_m^2 (1 - \beta)^2$$

$$(3.35) \dots (V_2)_{II} = K_v D_m^2$$

$$(3.36) \dots (V_3)_{II} = K_v D_m^2 (1 - 2\beta)^2$$

$$(3.37) \dots (Q_1)_{II} = K \Delta p_o D_m^4 (1 - \beta)^4$$

$$(3.38) \dots (Q_2)_{II} = K \Delta p_o D_m^4$$

$$(3.39) \dots (Q_3)_{II} = K \Delta p_o D_m^4 (1 - 2\beta)^4$$

Forming the ratios of equations 3.11 to 3.34, 3.11 to 3.35, 3.11 to 3.36, 3.18 to 3.37, and 3.18 to 3.39 yields respectively equations 3.40 through 3.45.

$$(3.40) \dots \frac{\overline{V(t)}_{II}}{(V_1)_{II}} = \frac{(1 - 2\beta + \frac{3}{2} \beta^2)}{(1 - \beta)^2}$$

$$(3.41) \dots \frac{\overline{V(t)}_{II}}{(V_2)_{II}} = 1 - 2\beta + \frac{3}{2} \beta^2$$

$$(3.42) \dots \frac{\overline{V(t)}_{II}}{(V_3)_{II}} = \frac{1 - 2\beta + \frac{3}{2} \beta^2}{(1 - 2\beta)^2}$$

$$(3.43) \dots \frac{\overline{Q(t)}_{II}}{(Q_1)_{II}} = \frac{1 - 4\beta + 9\beta^2 - 10\beta^3 + \frac{35}{8} \beta^4}{(1 - \beta)^4} \quad \beta < 1$$

$$(3.44) \dots \frac{\overline{Q(t)}_{II}}{(Q_2)_{II}} = 1 - 4\beta + 9\beta^2 - 10\beta^3 + \frac{35}{8} \beta^4$$

$$(3.45) \dots \frac{\overline{Q(t)}_{II}}{(Q_3)_{II}} = \frac{1 - 4\beta + 9\beta^2 - 10\beta^3 + \frac{35}{8} \beta^4}{(1 - 2\beta)^4} \quad \beta < .5$$

Equations 3.30 through 3.33 and 3.40 through 3.45 represent the comparison ratios of volume and flow for modes I and II dynamics respectively. One additional quantity of interest is the average transit time defined as the average volume to average flow. For mode II dynamics this is given by equation 3.46 below.

$$(3.46) \dots \tau(t)_{II} = \frac{\overline{V(t)}_{II}}{\overline{Q(t)}_{II}} \frac{32\eta\ell^2}{\Delta p_o D_m^2} \frac{(1 - 2\beta + \frac{3}{2} \beta^2)}{(1 - 4\beta + 9\beta^2 - 10\beta^3 + \frac{35}{8} \beta^4)}$$

The transit time corresponding to, say type 3 reference vessel, would be given simply by equation 3.47.

$$(3.47) \dots (\tau_3)_{II} = \frac{32\eta\ell^2}{\Delta p_o D_m^2} \frac{1}{(1 - 2\beta)^2}$$

2. Q Model

Corresponding comparison equations for Q Model are obtained in a fashion similar to that for P Model presented above. The volume expressions are identical, but instead of average flow the principal other hemodynamic quantity of interest is the average axial pressure difference or resistance of the rhythmic vessel. The pertinent comparison equations are summarized below.

$$(3.48) \dots \frac{\overline{\Delta p(t)}_I}{(\Delta p_1)_I} = \frac{1 + \frac{3}{2} \beta^2}{(1 - \beta^2)^{7/2}}$$

$$(3.49) \dots \frac{\overline{\Delta p(t)}_I}{(\Delta p_2)_I} = \frac{(1 + \beta)^4 (1 + \frac{3}{2} \beta^2)}{(1 - \beta^2)^{7/2}}$$

$$(3.50) \dots \frac{\overline{\Delta p(t)}_{II}}{(\Delta p_1)_{II}} = \frac{1 + \frac{3}{2} \left(\frac{\beta}{1 - \beta} \right)^2}{\left[1 - \left(\frac{\beta}{1 - \beta} \right)^2 \right]^{7/2}}$$

$$(3.51) \dots \frac{\overline{\Delta p(t)}_{II}}{(\Delta p_2)_{II}} = \frac{1 + \frac{3}{2} \left(\frac{\beta}{1 - \beta} \right)^2}{(1 - \beta)^4 \left[1 - \left(\frac{\beta}{1 - \beta} \right)^2 \right]^{7/2}}$$

C. Inclusion of Variable Viscosity and Non-Newtonian Properties

In the above equations 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 downstream vessel depends on the ratio of the downstream vessel diameter to the source (upstream) 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 (Merril, 1967) 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 concerned with here, the imposed pressure gradient must exceed a certain positive value. Analyses have been carried out in order to investigate the possible effect and hemodynamic significance of each of these factors. The details of these may be found in Appendix A.

Briefly the procedure used in analyzing the significance of variable viscosity consists of four parts. 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. This is done by comparing the resistance obtained (when variable viscosity effects are included) with the resistance associated with pure time dependence and the reference vessels described in section III-A.

The procedure for evaluating the effect and significance of the non-Newtonian behavior on rhythmic vessels 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 is 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 of figure 3.1. The extent to which resistance, pressure and flow in the rhythmic vessel are affected is then evaluated.

Using the following definitions the pertinent resulting equations from these analyses are summarized in equations

3.52 through 3.61 (for details see Appendix A).

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.

τ_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_i) is the resistance of the reference vessels with no time variation ($i = 1, 2$).

D_o is the average vessel diameter.

D_m is the maximum vessel diameter.

S_Q is given by $(1 + \frac{\beta}{1 - \beta} \cos x)$.

p' is the rhythmic vessel pressure gradient.

K_1 is a constant given by $128\ell/\pi$.

K_y is an empirical quantity from Merrill (1967).

H_0 is an empirical quantity from Merrill (1967).

θ is given by $\frac{\tau_y/D(t)}{p'}$.

$F(\theta)$ is given by $1 - \frac{32}{7} \theta^{1/2} + \frac{16}{3} \theta - \frac{4}{21} \theta^4$.

$$(3.52) \dots \eta = \eta_p \left(1 + 2.5 \frac{H}{1-H} \right)$$

$$(3.53) \dots H_I = \frac{H_s}{1+\beta} \{ [D_o(1+\beta)\alpha + 1](1+\beta \cos x) - \alpha D_o(1+\beta \cos x)^2 \}$$

$$(3.54) \dots H_{II} = H_s \{ (1 + \alpha D_m)(1 - \beta) S_Q - \alpha D_m (1 - \beta)^2 S_Q^2 \}$$

$$(3.55) \dots R(t, \eta)_I = K_1 \left[\frac{\eta(H_I)}{D_I^4(t)} \right]$$

$$(3.56) \dots R(t, \eta)_{II} = K_1 \left[\frac{\eta(H_{II})}{D_{II}^4(t)} \right]$$

$$(3.57) \dots \eta_a = \eta \left[1 + \frac{(2\tau_y/\tau_w)^{1/2}}{1 - \left(\frac{2\tau_y}{\tau_w} \right)^{1/2}} \right]^2$$

$$(3.58) \dots \tau_y = K_y (H - H_0)^3$$

$$(3.59) \dots \tau_w = \frac{D(t)p'}{4} + \tau_y - [2\tau_y p' D(t)]^{1/2}$$

$$(3.60) \dots p' \ell (Z_s + Z_d) D^4(t) F(\theta) + p' \ell K_1 \eta(H) - p_s K_1 \eta(H) = 0$$

$$(3.61) \dots R(t, \eta, \tau_y) = K_1 \left[\frac{\eta(H)}{D^4(t) F(\theta)} \right]$$

IV. Results and Discussion

Results which illustrate the hemodynamic characteristics of the rhythmically active vessels are shown in figures 3.7 through 3.11 for the P Model and figures 3.12 through 3.22 for the Q Model. The effects of non-Newtonian rheology are illustrated by results obtained from the Q Model as shown in figures 3.13 through 3.22.

Figure 3.7 shows the rhythmic to non-rhythmic vessel flow ratio as a function of the relative contraction amplitude β . Curves A, B, C, and D correspond to equations 3.43, 3.32, 3.33 and 3.44 respectively. Curves A and B correspond to type 1 comparison, and curves C and D correspond to type 2 comparison. In figure 3.8 are similar graphs for volume ratios. Curves A, B, C, and D correspond to equations 3.40, 3.30, 3.31 and 3.41 respectively.

Examination of figures 3.7 and 3.8 shows the following:

- (1) The flow (or conductance) and volume associated with the rhythmic vessels are larger than the corresponding quantities in non-rhythmic vessels having the same mean diameter (curves A and B), but are smaller than in vessels with the same maximum diameter (curves C and D).
- (2) For the same relative contraction amplitude, β , the flow (or conductance) and volume ratios are either larger for mode II diameter variation (of A to B) or smaller (of C to D), again depending on whether the comparison is made on the basis of the same mean diameter or maximum diameter.

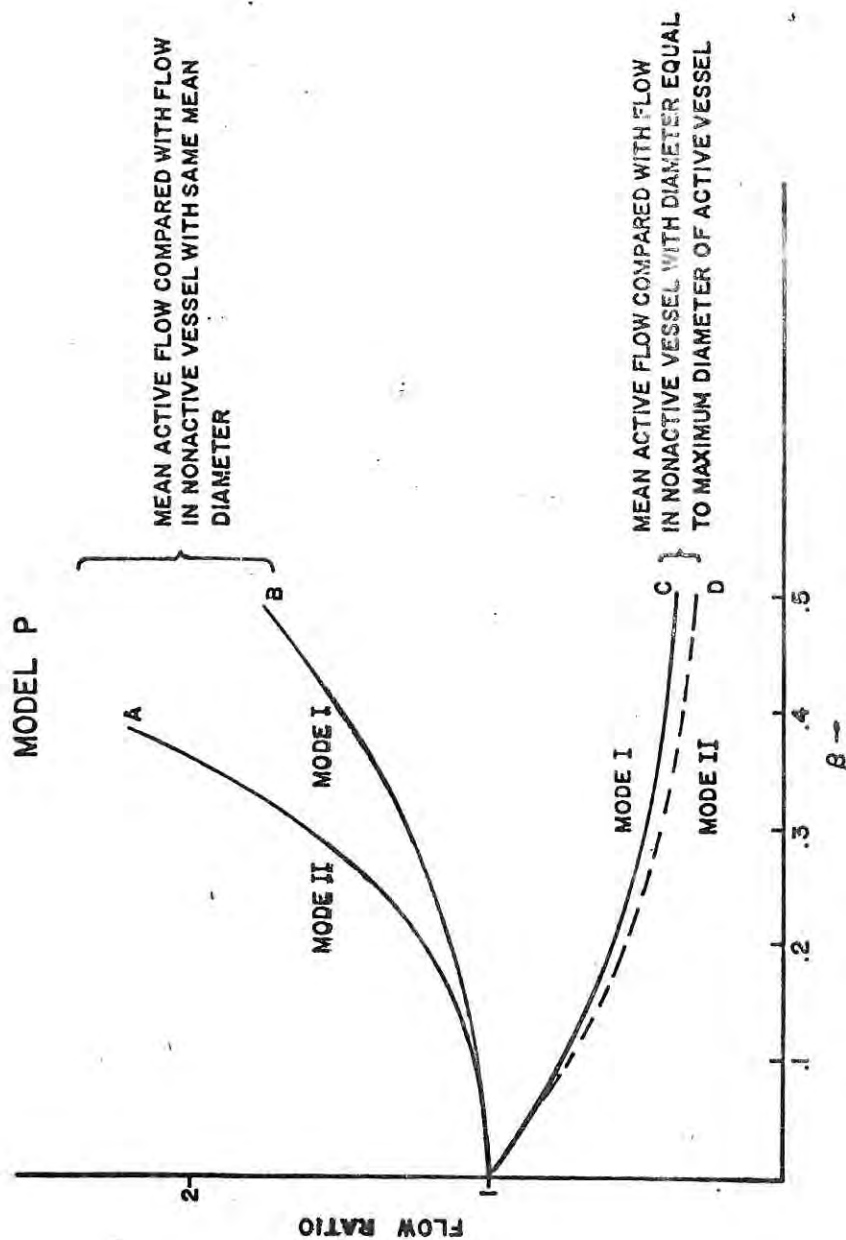


Fig. 3.7 Rhythmic to nonrhythmic flow ratio as a function of relative contraction amplitude. A, B, C, and D are used for reference purposes in text. A and B correspond to type 1 comparison and C and D to type 2 comparison as defined on the figure adjacent to the brackets.

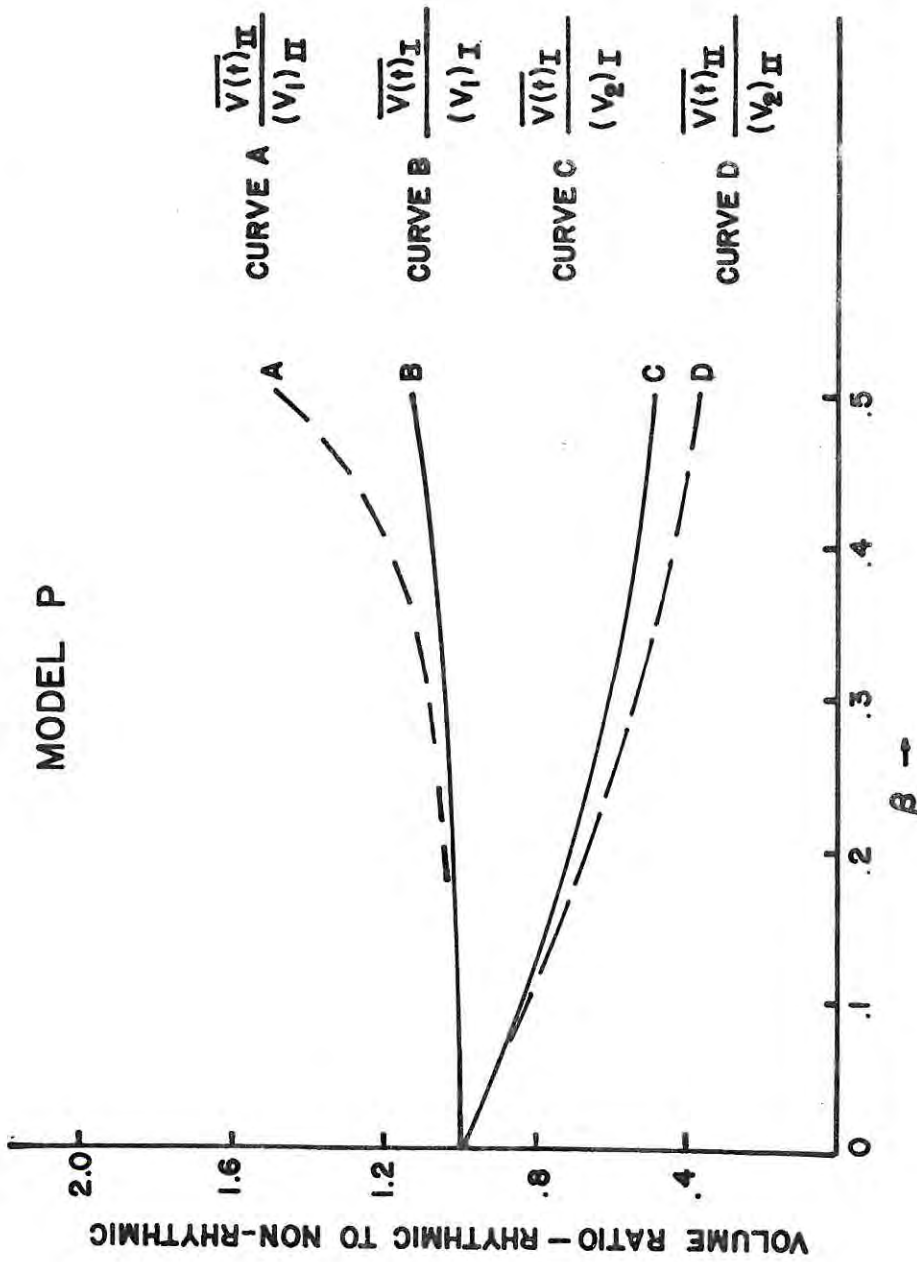


Fig. 3.8. Rhythmic to non-rhythmic vessel volume ratio as a function of relative contraction amplitude.

The results 1 and 2 are ambiguous. Depending on the choice of the reference vessel, the conductance and volume may be larger or smaller in the rhythmic vessels. In vivo observations by the author of the spontaneously active vessels favor mode II dynamics and a type 2 comparison as physiologically more appropriate. That is, amplitude changes occurring naturally or promoted by perturbation usually produce greater changes in contraction amplitude than in the maximum diameter. Moreover, cessation of venomotion as witnessed by the author in near death states of the animal, and in severe hemorrhage (Harris, 1969), are accompanied by only small changes in maximum vessel diameter. However because the pressure within these vessels was not monitored at these times the selection of type 1 versus type 2 as a more appropriate reference vessel is still speculative. Assuming that it is correct, then the rhythmicity gives rise to a reduced conductance and volume, and according to result 2 the effect of increasing the contraction amplitude is to further reduce both of these quantities.

In figures 3.9, 3.10 and 3.11 the normalized average conductance, volume and average transit time for mode II and type 3 reference vessel are graphed separately as a function of β . Examination of these figures shows the following:

- (3) For the same blood volume the average conductance of the rhythmic vessels is less than the corresponding non-rhythmic vessels.
- (4) For the same average conductance the average blood volume in the rhythmic vessels is less than the non-rhythmic vessels.

MODEL P

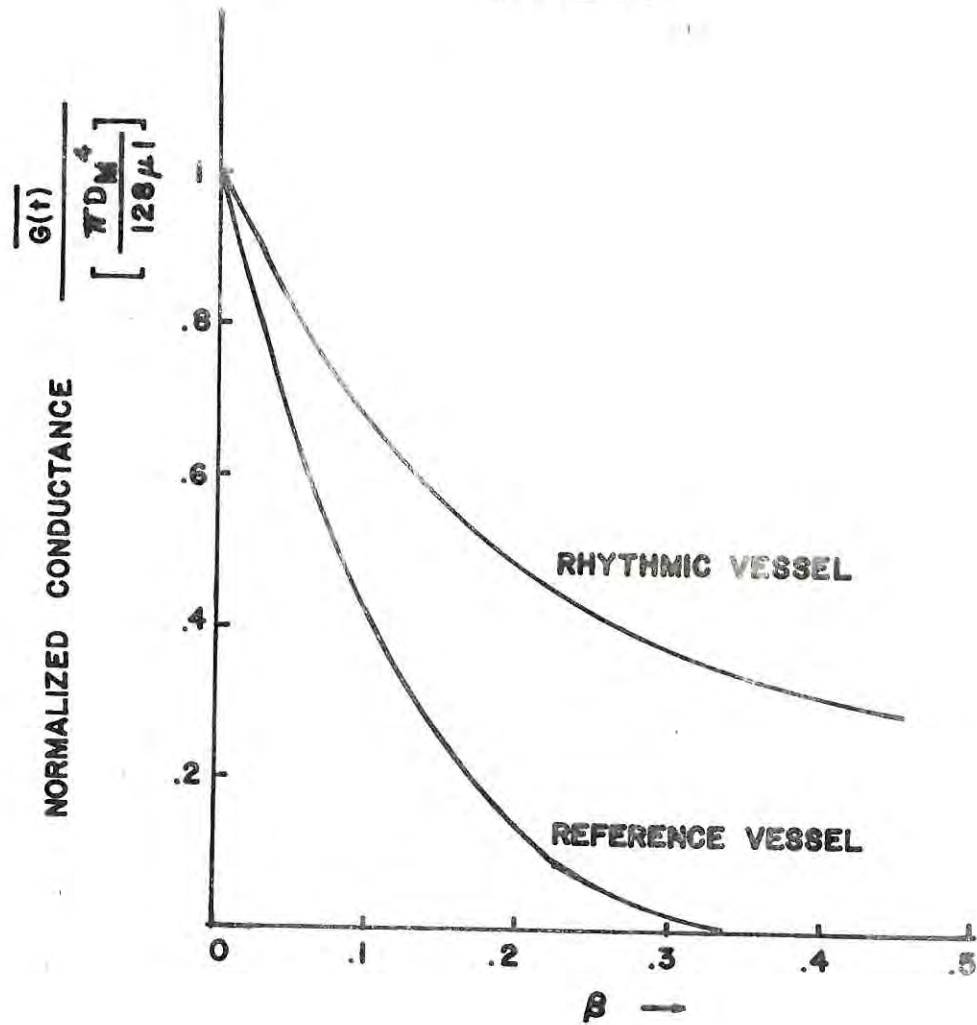


Fig.3.9. Average conductance of rhythmic vessel as a function of relative contraction amplitude compared with Type 3 reference vessel. Rhythmic vessel undergoing Mode II diameter variation. Conductances are normalized to values associated with maximum vessel diameters D_m .

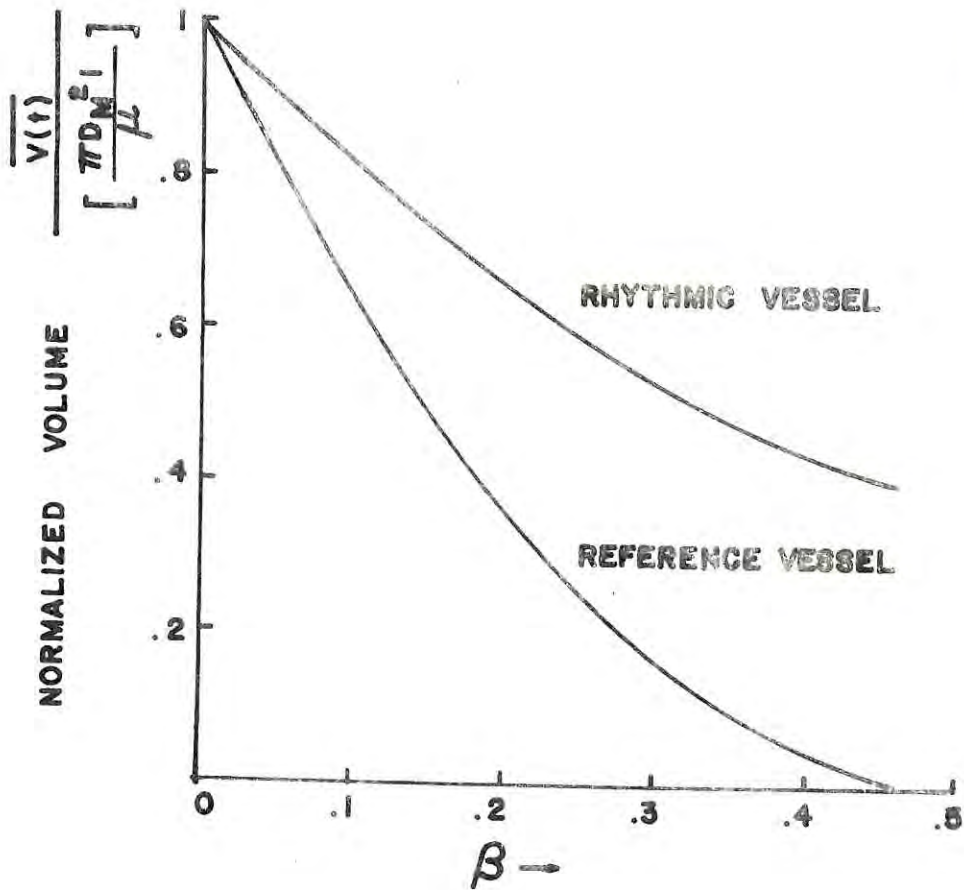


Fig.3.10 Average blood volume in rhythmic vessel as a function of relative contraction amplitude compared with Type 3 reference vessel. Rhythmic vessel undergoing Mode II diameter variation. Volume normalized to volume associated with maximum diameter (D_m).

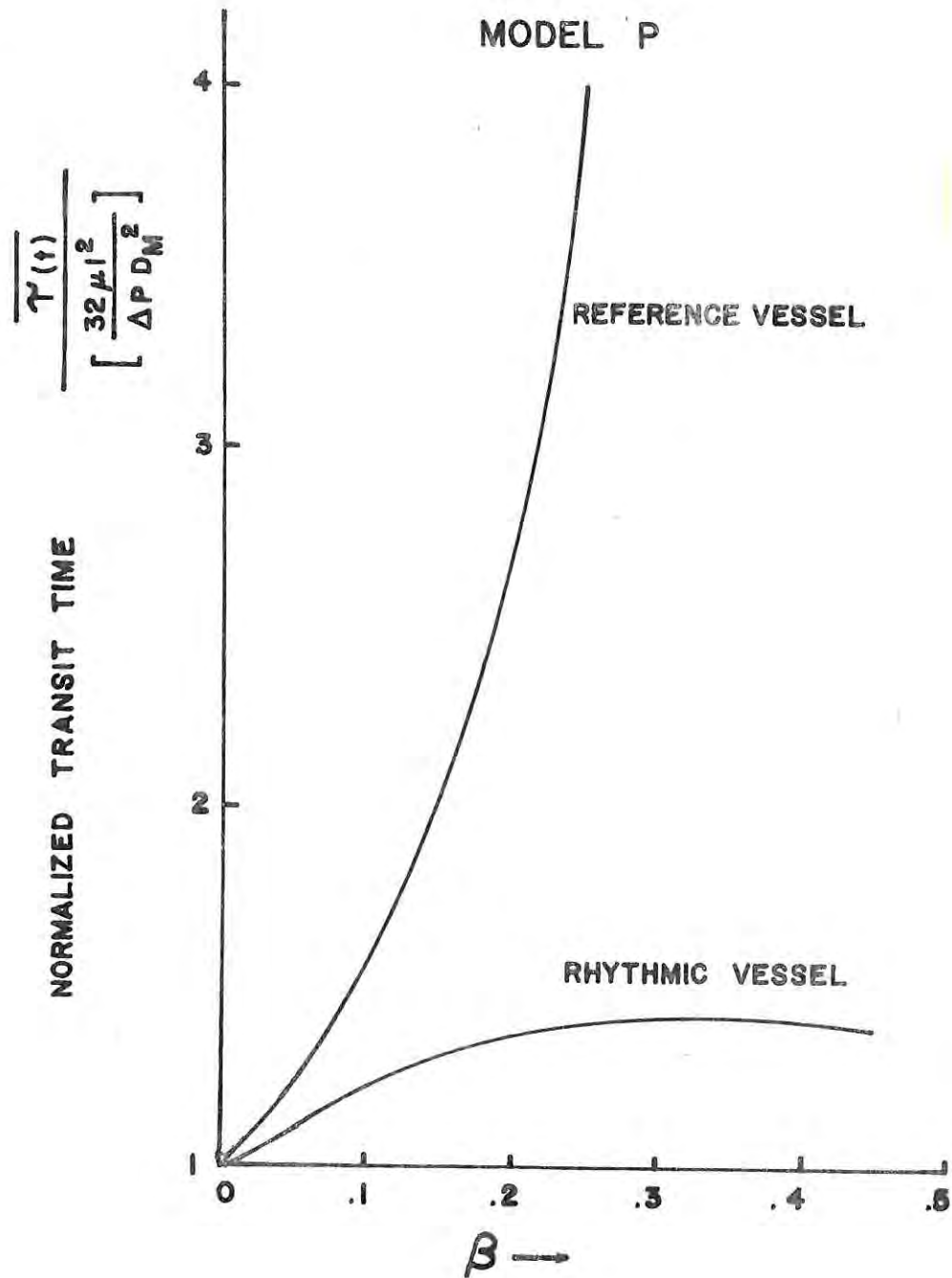


Fig.3.11. Average transit time of rhythmic vessel as a function of relative contraction amplitude compared with Type 3 reference vessel. Rhythmic vessel undergoing Mode II diameter variation. Transit times are normalized to those associated with vessel maximum diameter D_m .

(5) In all cases the average transit times associated with the rhythmic vessels are less than the non-rhythmic ones.

(6) For the rhythmic vessels the rate of change of average transit time with respect to a change in contraction amplitude is small.

The results 3 through 6 permit an assessment of the hemodynamic differences to be expected when vessel diameter is controlled by rhythmic excitation of vascular smooth muscle as compared with continuous excitation which produces the same total diameter change. These results show that the rhythmic vessel has a larger volume and conductance but a significantly smaller and relatively constant average transit time. Thus changes in contraction amplitude of the rhythmic vessel induced by changes in local environment may be more effective in producing appropriate hemodynamic changes with smaller changes in transit time than would be possible with maintained contractions. The significance of the relative constancy of the average transit time is at this time speculative but may relate to heat transfer properties of the wing vasculature.

In figure 3.12 the rhythmic to non-rhythmic resistance ratio for Q Model is shown as a function of relative contraction amplitude. The results shown are for mode I dynamics, but similar results are obtained for mode II. It is seen that the average resistance associated with the rhythmic vessels is always larger than the corresponding non-rhythmic reference vessels. Thus increases in the amplitude of contraction are associated with increases in rhythmic vessel average resistance. The ratio of rhythmic to non-rhythmic resistance increases non-linearly with increasing contraction

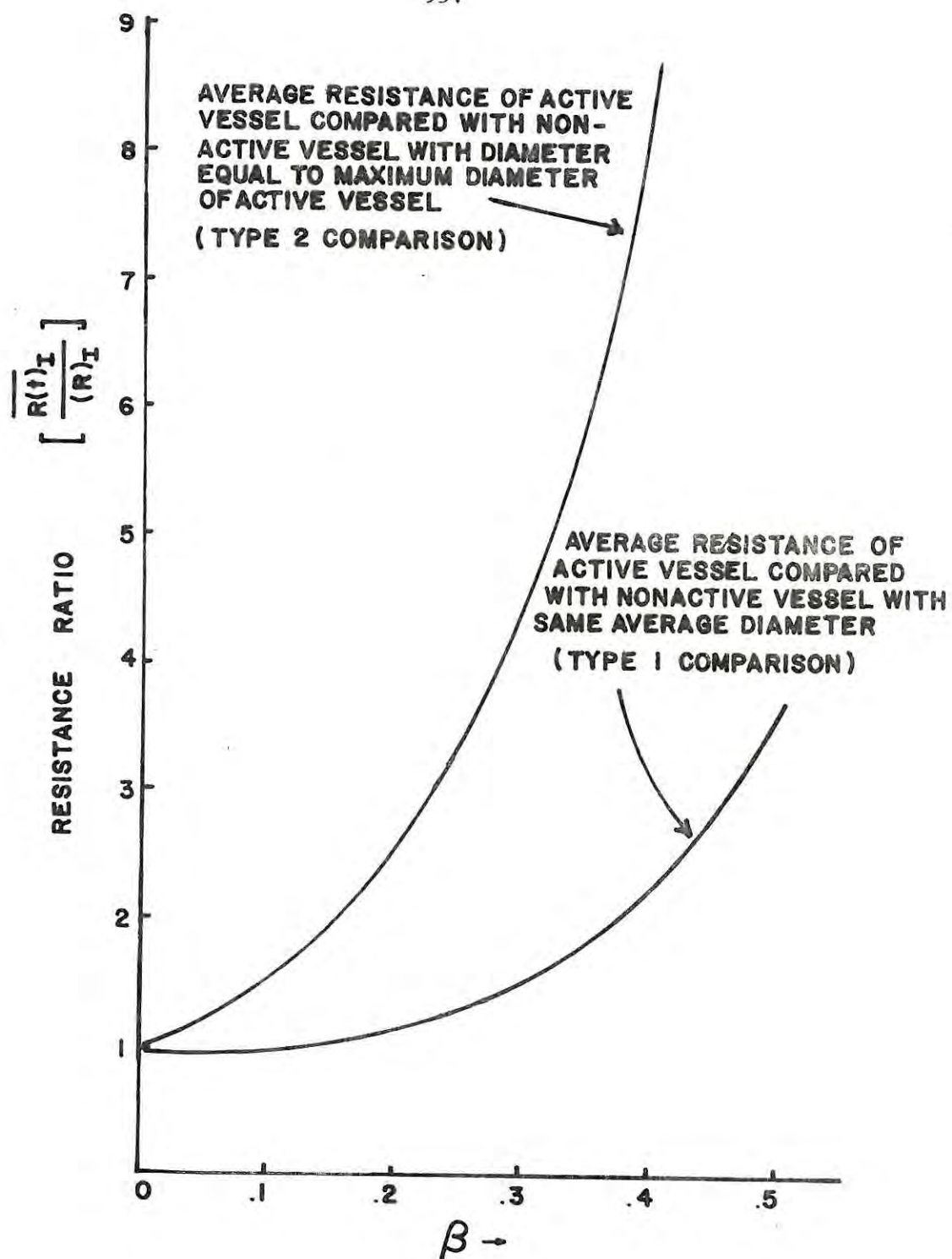


Figure 3.12. Ratio of rhythmic vessel resistance to reference vessel resistance for mode I diameter variation. β is relative contraction amplitude.

amplitude, and this trend is independent of the type of vessel used for comparison purposes. This property implies that the average small venule and capillary pressures may be changed with smaller changes in relative contraction amplitude. Thus capillary pressure may be controlled by a higher "gain" system due to the rhythmicity.

Characteristic results elucidating the significance of variable viscosity on rhythmic vessel resistance are graphed in figures 3.13 through 3.18. In figure 3.13 the ratio $\frac{\overline{R(t,\eta)}_I}{(R_2)_I}$ is graphed as a function of relative contraction amplitude for source hematocrits of zero and .4. For $H_S = 0$ the graphed ratio corresponds to that of figure 3.12. That is, since $H_S = 0$ there can be no change in viscosity due to the diameter change. Thus for this value the increase in the ratio with increasing contraction amplitude is due solely to the rhythmic diameter change. Further, as can be seen in figure 3.13, the effect of including the variable viscosity component is quite small with respect to this ratio. However it does have the effect of reducing the active vessel resistance with respect to the uniform vessel of the same average diameter.

In figure 3.14 the ratio $\frac{\overline{R(t,\eta)}_I}{\overline{R(t)}_I}$ is graphed as a function of source hematocrit for two values of contraction amplitude. For $H_S = 0$ the variable viscosity effect is zero, and hence the ratio is unity independent of β . Increasing the source hematocrit has the effect of decreasing the active vessel resistance relative to that which would be calculated without including the viscosity effect. The significance increases with increasing contraction amplitude, but

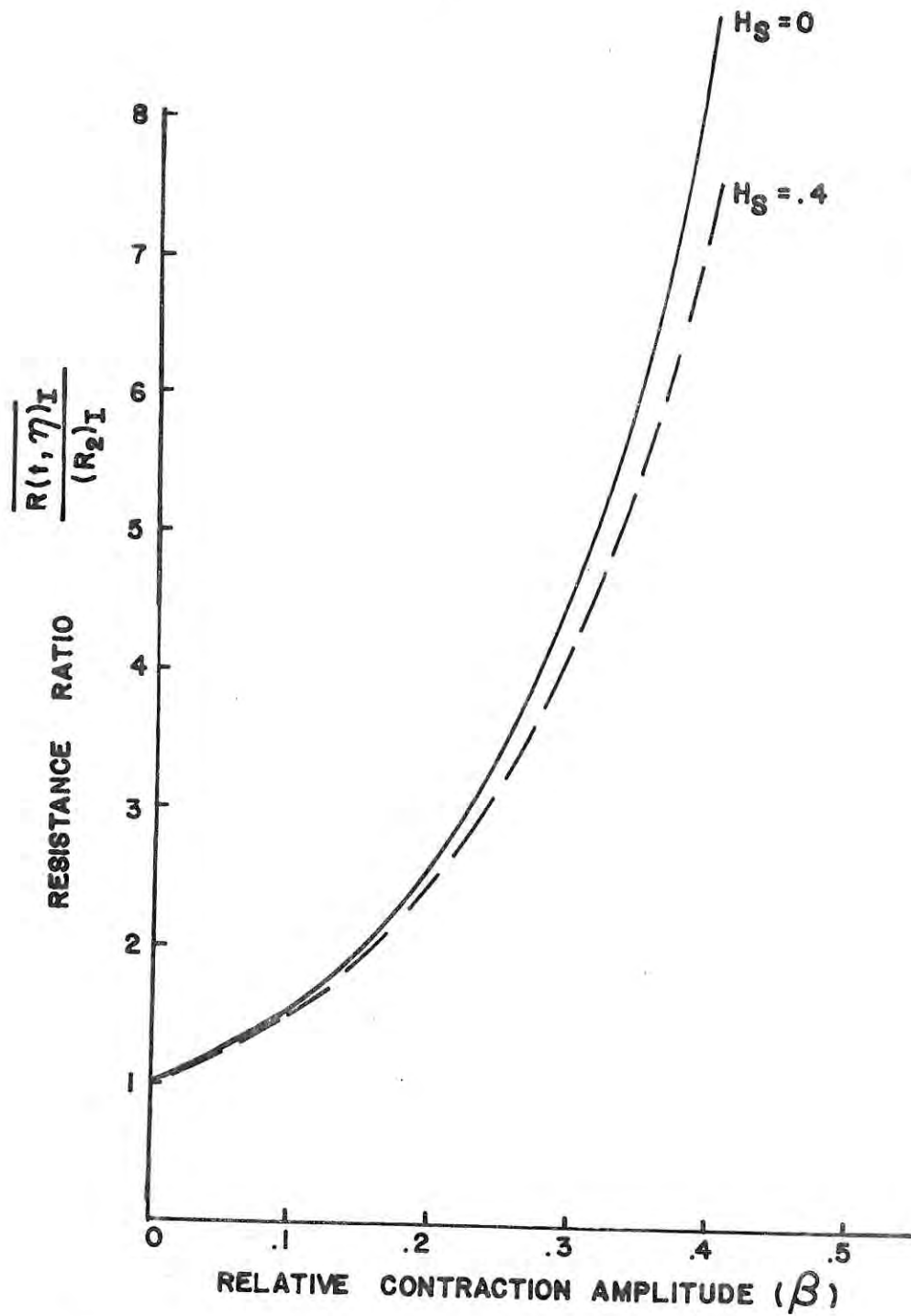


Figure 3.13. Ratio of rhythmic vessel resistance to reference vessel resistance when variation in vessel hematocrit is taken into account (Mode I). H_s is the source hematocrit.

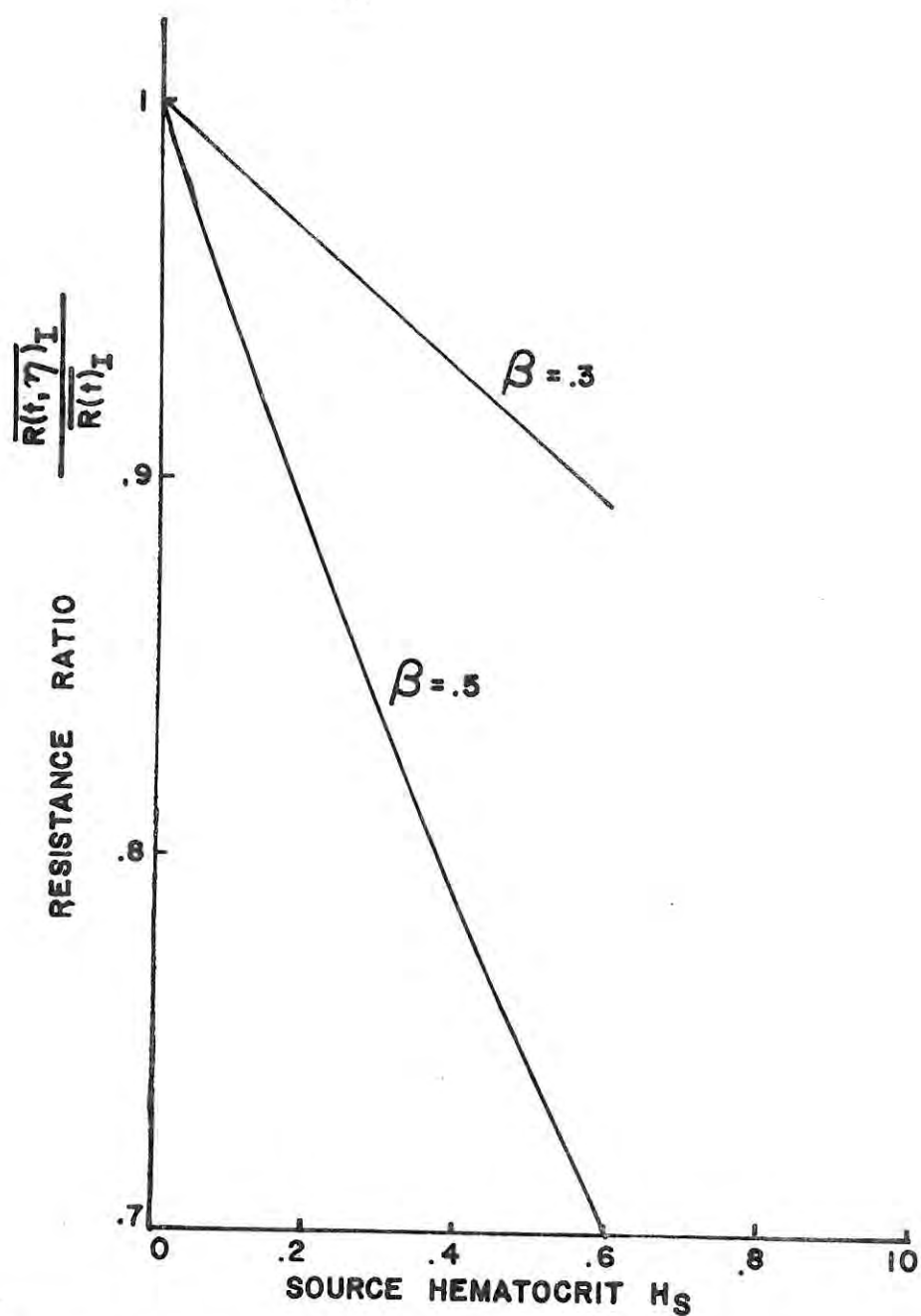


Figure 3.14. Ratio of rhythmic vessel resistance with and without inclusion of time variation in vessel viscosity (Mode I). Viscosity effect is seen to decrease ratio with increasing H_S and relative contraction amplitude β .

for the normal contraction and hematocrit ranges the correction is only about 10%.

In figure 3.15 the ratio $\frac{R(t,\eta)_{II}}{R(t)_I}$ is graphed as a function of β for several different source hematocrit levels. Again for $H_S = 0$ (pure plasma) the ratio is independent of β . For non-zero H_S the ratio decreases with increasing contraction amplitude and source hematocrit.

In figure 3.16 the ratio $\frac{R(t,\eta)_{II}}{(R_2)_{II}}$ is graphed as a function of source hematocrit for different values of contraction amplitude. The intercept of the ordinate corresponds to the resistance ratio as determined solely by the diameter variation. Consistent with the results for constant viscosity, this value increases with increasing β . As the viscosity of the source is increased, however, the amount of this increase relative to the constant diameter reference vessel diminishes.

The results illustrated by figures 3.13 through 3.15 show that results obtained assuming constant viscosity hold with only small corrections required to account for hematocrit variations and their subsequent viscosity effects. The implication of this is that much simpler equations may adequately be used to approximately describe the associated hemodynamics. In addition by examining the variable viscosity effects another property of the rhythmic vessels system has been elucidated. Specifically, the rhythmic type diameter variation appears to be less sensitive to increases in hematocrit than are constant diameter reference vessels. Thus increases

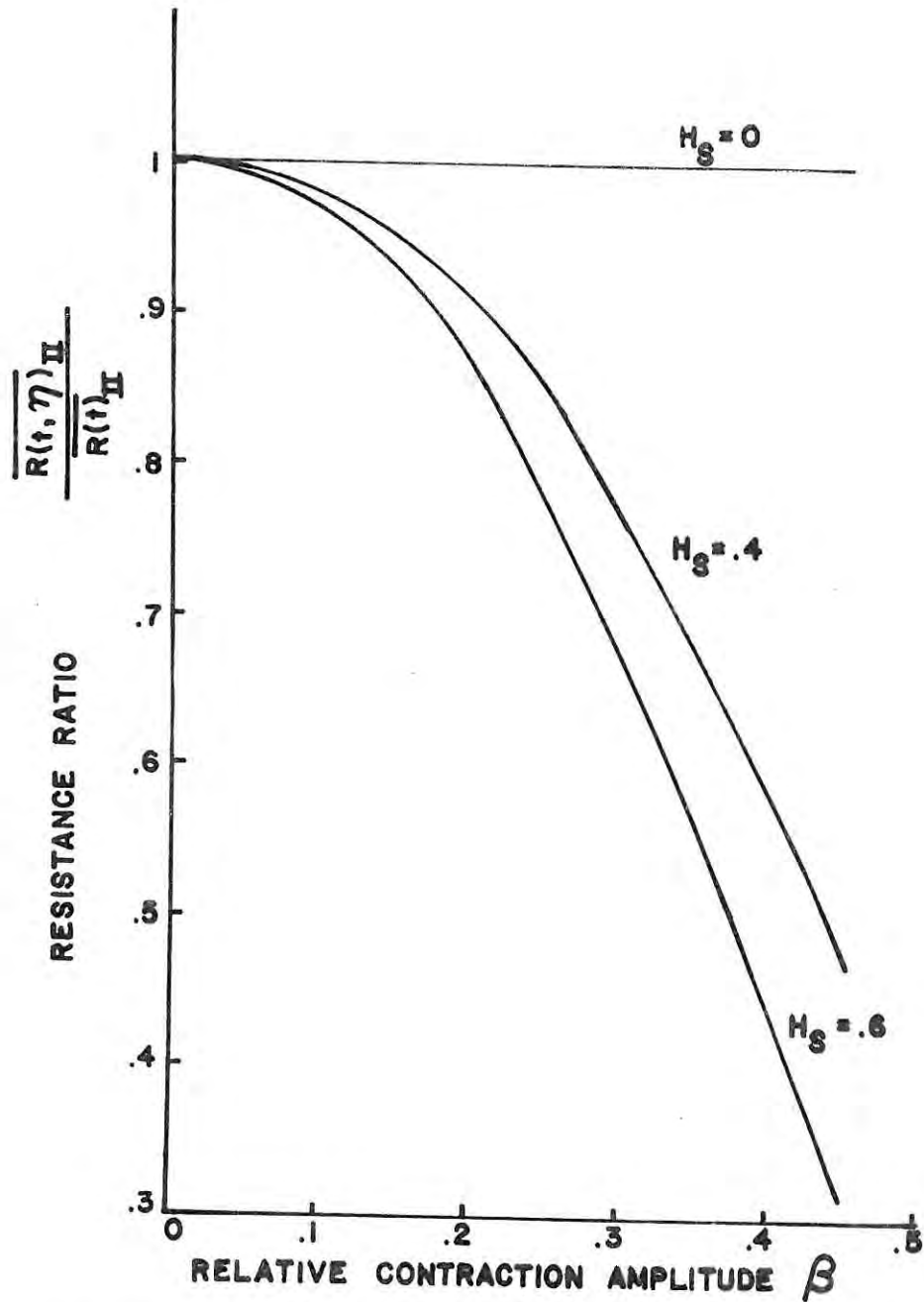


Figure 3.15. Ratio of rhythmic vessel resistances with and without inclusion of time variation in vessel viscosity (Mode II). Ratio is seen to decrease with increasing source hematocrit (H_s) and contraction amplitude (β).

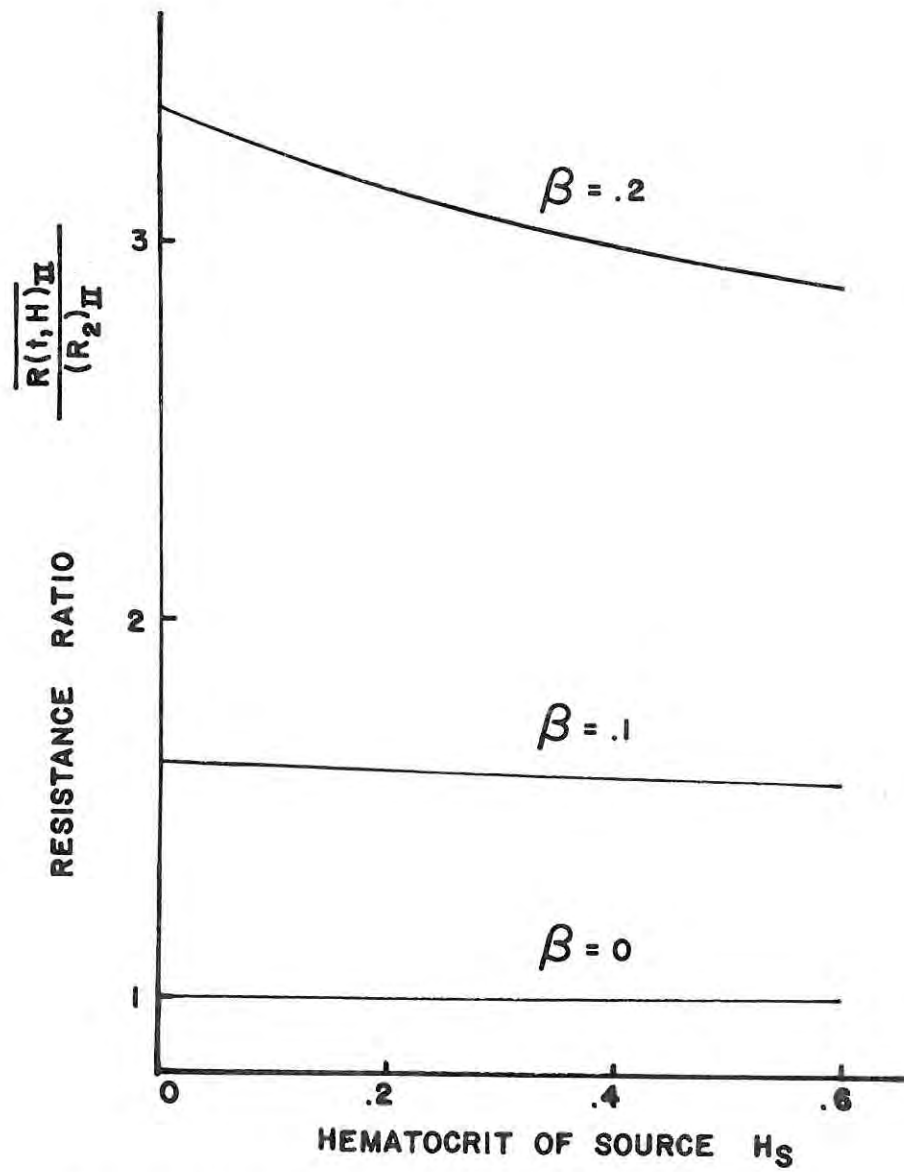


Figure 3.16. Ratio of rhythmic vessel resistance to reference vessel resistance when variation in vessel hematocrit is taken into account (Mode II).

in hematocrit or viscosity in these vessels are accompanied by a smaller relative increase in resistance.

In figures 3.17 through 3.22 the effect of including a non-zero value for yield stress in the defining hemodynamic equations is illustrated. As shown by equation 3.57 the apparent viscosity depends on the value of the yield stress and the wall shear stress. Since the wall shear stress depends on the axial pressure gradient which is varying over the venomotion cycle, it is expected that all the quantities shall be subject to considerable variation over one cycle. The form of the pressure variation is shown in figure 3.17 over one contraction cycle with relative contraction amplitudes of 0, .1, and .3. In this and the remaining figures parameter values used in the general analytical model of figure 3.1 are as follows: Source hematocrit = .4; Flow = $4 \times 10^{-7} \text{ cm}^3 \text{ sec}^{-1}$; Plasma viscosity = .013 Poise; and Vessel average diameter = .004cm.

It is seen from figure 3.17 that for $\beta = 0$ the pressure gradient is constant, which of course corresponds to a vessel with constant diameter. As β is increased to a value of .1 the pressure gradient varies, decreasing with vessel dilation and increasing with vessel contraction. The time average gradient is slightly larger than the constant value corresponding to $\beta = 0$. The increase in β to a value of .3 is associated with a considerable rise in the peak gradient in the contraction phase. Thus the amount by which the pressure rise exceeds the baseline level is about 4 times as

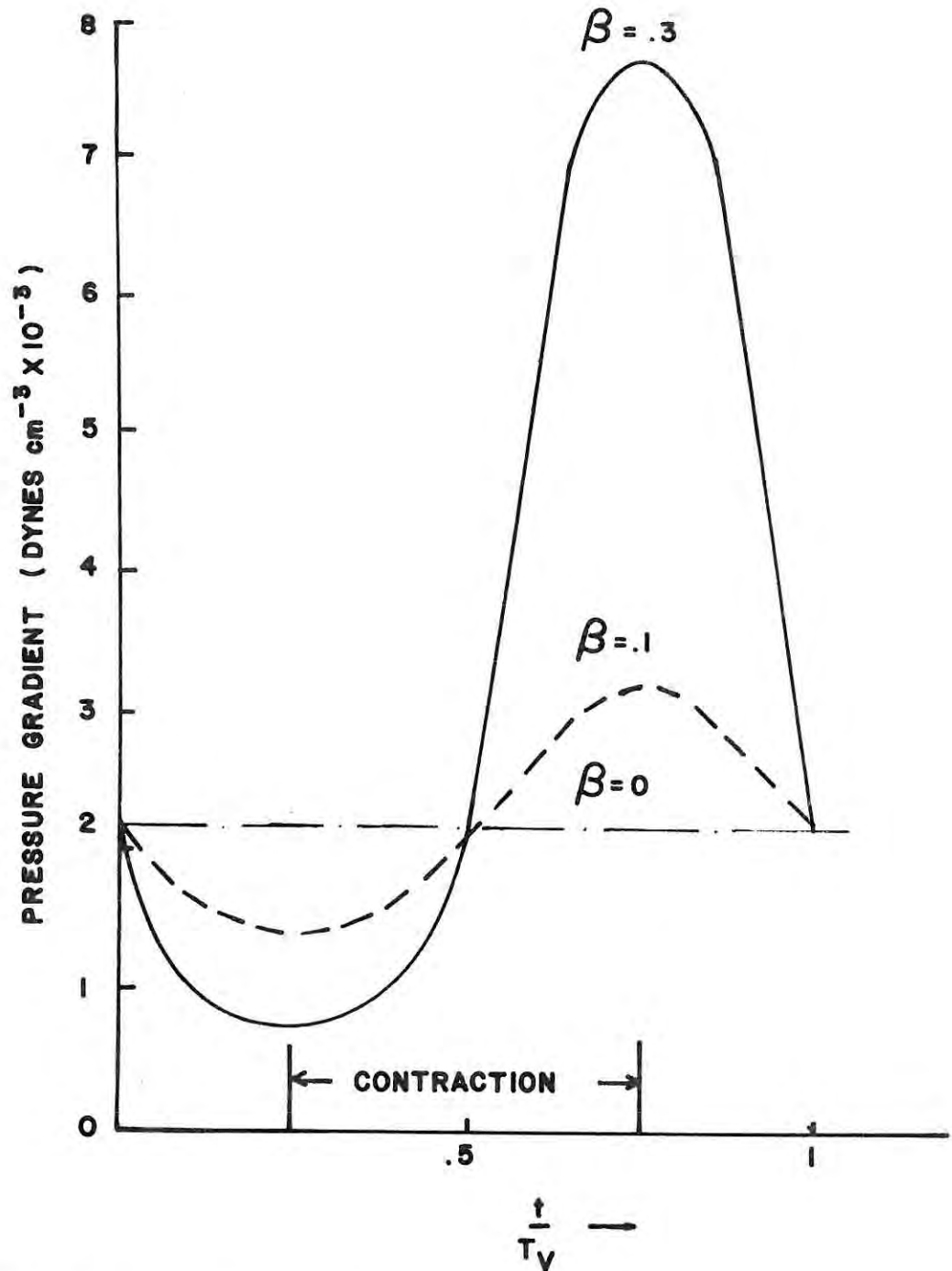


Fig. 3.17. Instantaneous pressure gradient associated with rhythmic vessel parameter values used for Model Q are $Q_0 = 4 \times 10^{-7} \text{ cm}^3 \text{ sec}^{-1}$, $H_S = .4$, vessel average diameter = 40 microns. Pressure gradient is plotted for one venomotion cycle. T_V is venomotion period.

great as the dilation phase is below it.

Using these values of $p'(t)$ the instantaneous shear stress at the wall and yield stress are determined using equations 3.54, 3.58 and 3.59. These quantities are graphed in figure 3.18. The shear stress is the broken line, and the yield stress is the solid line. Each is graphed over one contraction cycle for contraction amplitudes of 0 and .3.

In figure 3.18 we note that the shear stress is decreasing during the dilation phase while increasing during the contraction phase with a peak to peak ratio of about 5. Such behavior is consistent with that for flow in which the spatial mean shearing stress $\bar{\tau}$ is, for a given flow, proportional to (η/D^3) . In the present case, even though there are diameter dependent changes in viscosity (increase during dilation), the change in diameter per se dominates the behavior of the instantaneous shear stress.

The yield stress is observed to experience an initial small increase at the onset of dilation and at the beginning of contraction followed by a considerable decrease throughout the contraction phase. The variations in yield stress represent the effect of the time dependent active vessel hematocrit.

In figure 3.19 the ratio of shear stress to yield stress (dotted) and the ratio of an apparent viscosity to Newtonian viscosity (solid) are plotted. We observe that the maximum stress ratio and consequently the minimum viscosity occur at the peak of the contraction phase. We further note that even though the stress ratio is quite asymmetric with respect to its value for a non-active

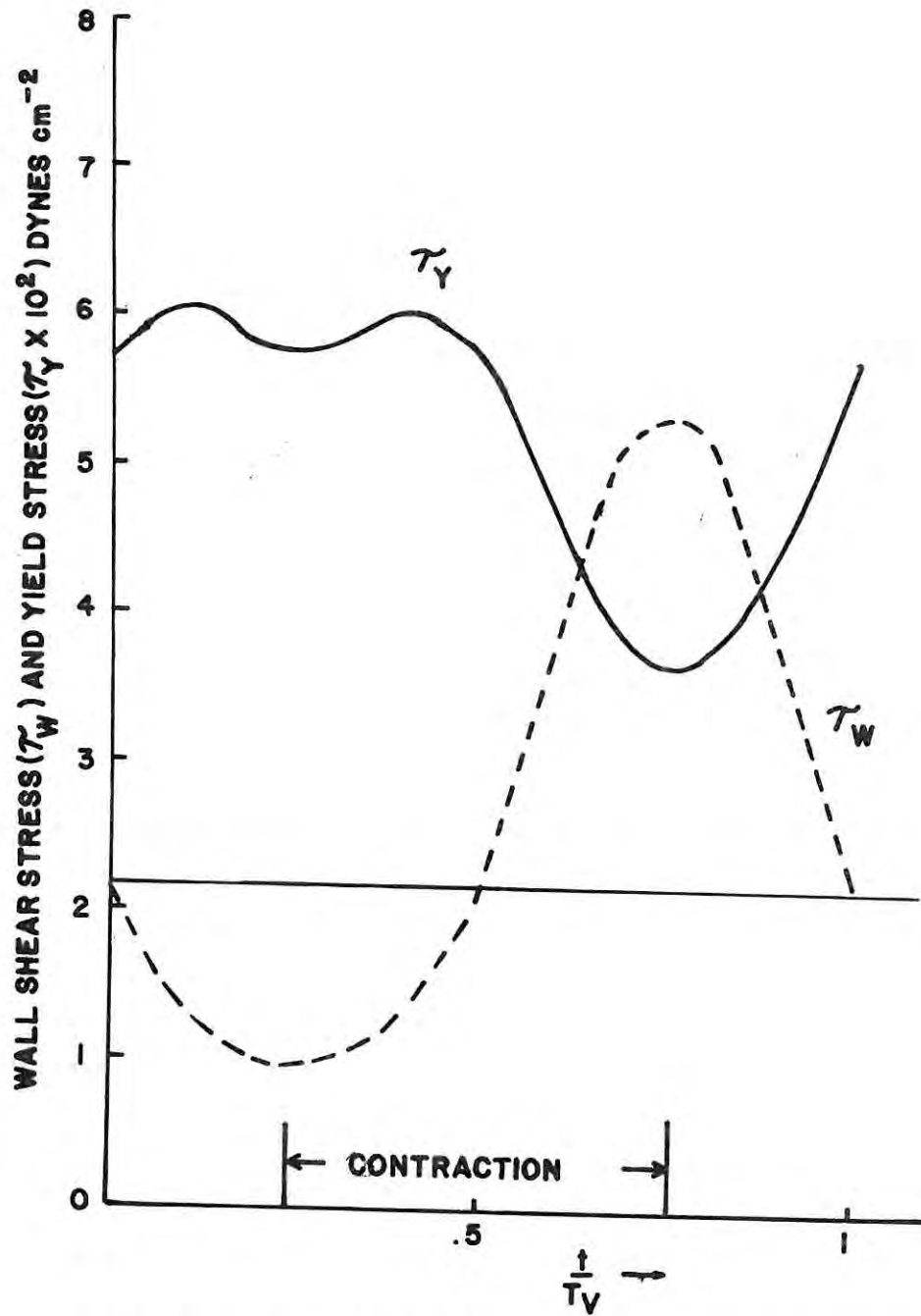


Figure 3.18. Instantaneous wall shear stress and yield stress. Parameter values used are $Q_0 = 4 \times 10^{-7} \text{ cm}^3 \text{ sec}^{-1}$, $H_s = .4$, $\beta = .3$, $\eta_p = .013$ Poise. T_v is venomotion period.

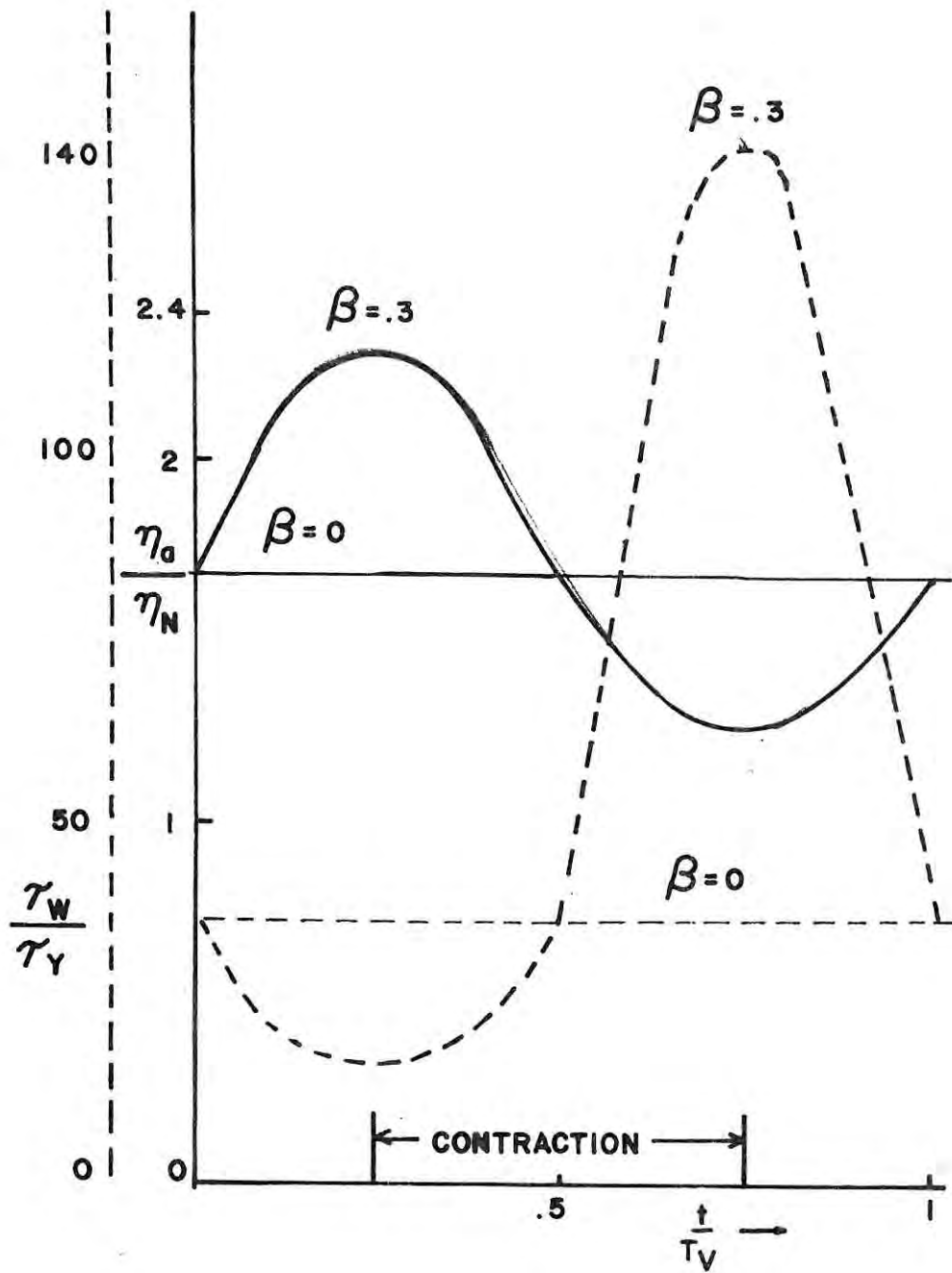


Fig. 3.19. Instantaneous ratios of wall shear stress τ_w to yield stress τ_y (broken lines) and apparent viscosity, η_a , to Newtonian viscosity, η_N (solid lines). Ratios are plotted over one venomotion cycle for $\beta = 0$ and $\beta = .3$. Parameter values the same as previous figure.

vessel, i.e., $\beta = 0$, the viscosity ratio is much less asymmetric.

The results illustrated by figures 3.17 through 3.19 characterize the properties and behavior of the individual components and parameters of a flow regime to which variable viscosity, non-Newtonian fluid, and rhythmic dynamics contribute. In figures 3.20 through 3.22 these separate results are combined so that the totality of these effects on pressure, flow and resistance of rhythmically active vessels may be evaluated.

The result for p' (figure 3.20) is obtained by the simultaneous solution of equation 3.60, which contains p' as an implicit function, together with equation 3.58, which relates yield stress to active vessel hematocrit, and equation 3.52, which relates vessel hematocrit to vessel instantaneous diameter. The result of the numerical solution is shown in figure 3.20, in which the instantaneous pressure gradient is shown and compared with the pressure gradient which would be present if the yield stress were taken as zero (solid line).

Using the calculated values of p' for each instant of time, the active vessel resistance and flow are calculated. Instantaneous flow is shown in figure 3.21 and resistance in figure 3.22, and in each case compared with corresponding quantities for zero yield stress.

In the case of the flow variation, we note that the amount by which the dynamics alter flow is extremely small, owing to the large value of effective upstream resistance. In addition, we note that the effect of inclusion of a non-zero yield stress is

to admit a slightly smaller flow with the maximum difference between the zero yield stress case occurring at the peak of contraction. The resistance variation shown in figure 3.22 reflects the instantaneous pressure gradient variation in form.

From these results and the preceding discussion it may properly be concluded that the predominant factor controlling the form of the hemodynamics associated with rhythmically varying vessels is the diameter change itself. This issue will be taken up in detail in the following chapters. Variable viscosity effects and the existence of a non-zero yield stress modify slightly the average resistance of these vessels in addition to altering the instantaneous values of pressure and flow. Thus, though these factors slightly alter the quantitative aspects of the hemodynamics, they play no significant role in the pressure and flow distribution.

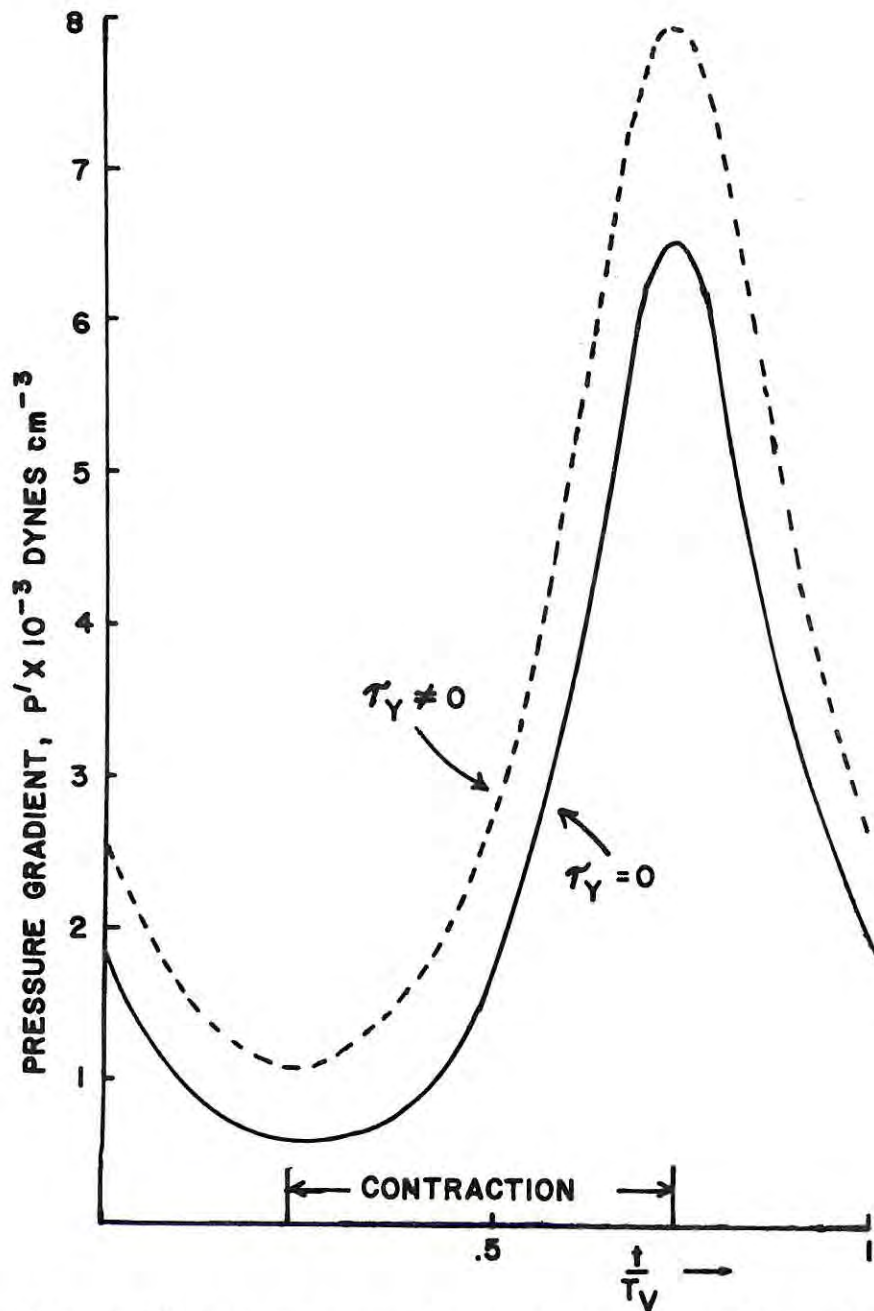


Fig. 3.20. Instantaneous pressure gradient with and without yield stress effects. Parameter values $Z_s = 1.5 \times 10^{11}$ dynes cm^{-5}sec . $Z_d = 1 \times 10^8$ dynes cm^{-5}sec , $\beta = .3$, $H_s = .4$. T_V is venomotion period.

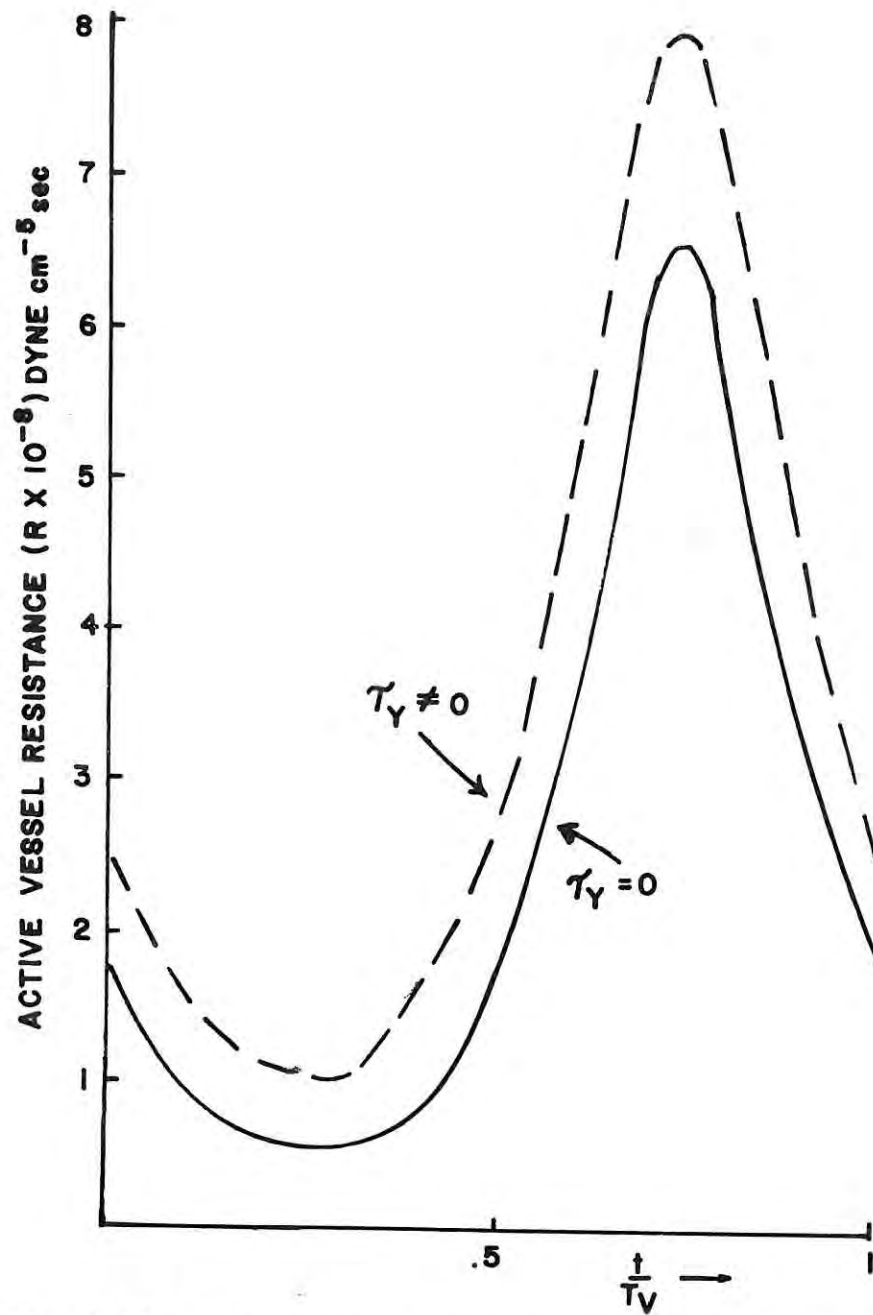


Fig. 3.22. Instantaneous vessel resistance with and without yield stress effects. Parameter values $Z_s = 1.5 \times 10^{11}$ dynes cm^{-5}sec . $Z_d = 1 \times 10^8$ dynes cm^{-5}sec , $\beta = .3$, $H_s = .4$. T_v is venomotion period.

CHAPTER FOUR... MICROVASCULAR MODEL AND COMPUTER SIMULATION

I. Introduction

It will be recalled that in Chapter Two an idealized version of the wing vascular topology was used to calculate the vascular bed resistance. In this representation termed the Topological Model (shown in figure 2.5) the arterioles give rise to five branches, each of which includes the hydraulic resistive characteristics of the terminal arterioles, precapillary sphincters, true capillaries and post capillary venules. Each of the vascular segments terminates in a muscular venule which in turn becomes one of the inflowing branches to the small vein.

This characterization was perfectly adequate for study of the macroscopic variable-vascular bed input resistance and resistance distribution. It is now the objective to examine in more detail hemodynamic and functional aspects of the small pre-capillary, capillary, and postcapillary vessels.

To help accomplish this a Microvascular Model will be utilized and in this chapter the development of this model will be presented. There are two basic criteria which have served as guidelines in this development process. The first concerns the amount of detail with which the microvascular aspects are represented and the second concerns the overall form or structure of the model.

The amount of detail which is required to adequately represent the different microvascular aspects depends on a number

factors, but principally should be determined from considerations of the specific purpose and intended use of the Microvascular Model. As was described in Chapter One, one of the main objectives is to study the way in which vascular dynamics including venous venomotion and arteriolar vasomotion separately and together influence hemodynamics and function within the microvasculature. Thus it is appropriate that characterization of these aspects should include an amount of pertinent detail at least as great as the other aspects to be included in the model.

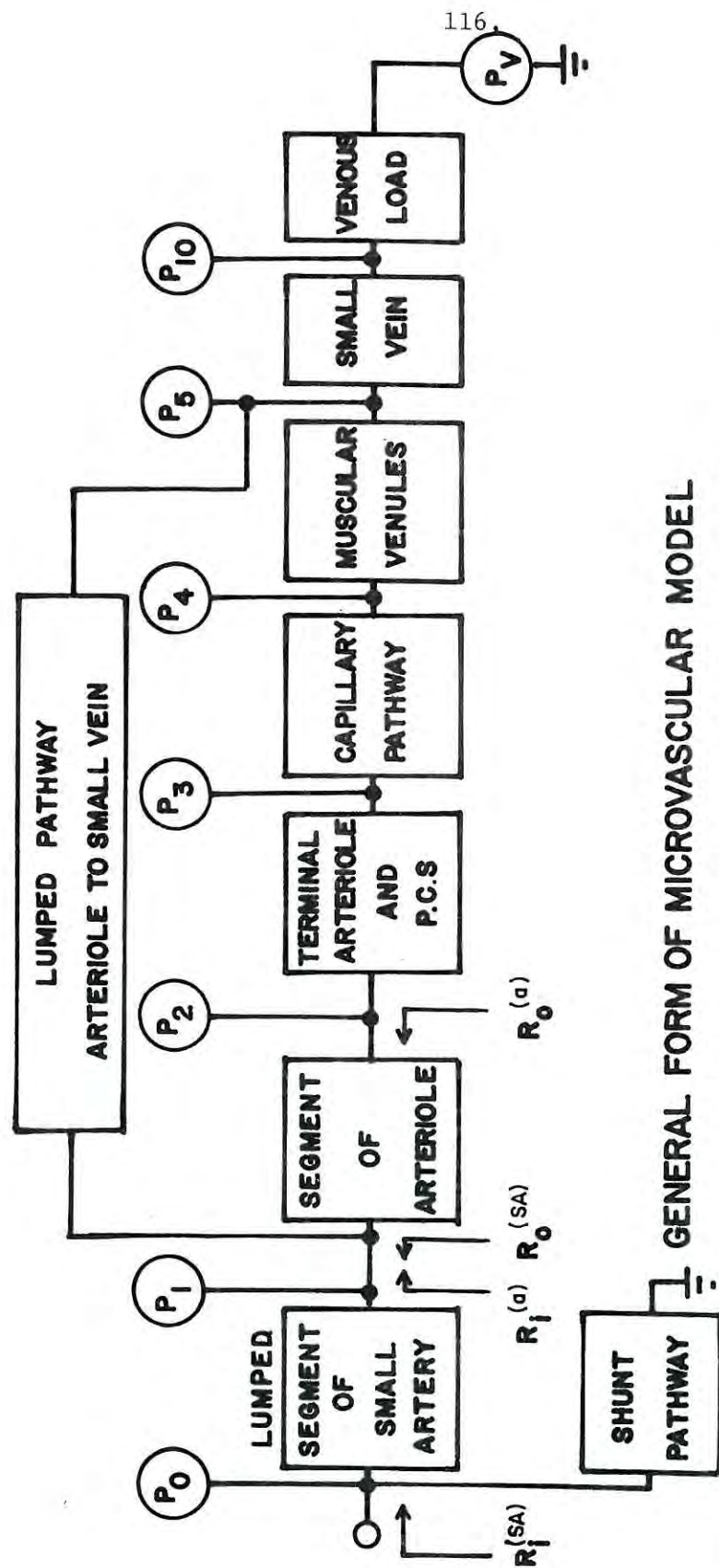
Secondly since each part of a microvascular region is to some degree effected by local conditions both upstream and downstream, and since these local conditions are effected by the macrocirculation, it is necessary to represent the microvascular region being studied in a way which includes its pertinent intrinsic characteristics as well as maintaining the appropriate macroscopic properties of the total vascular bed. For example, the representation must adequately simulate the actual order of magnitude of pressure and flow in the small veins as well as the individual feeding vessels both pre and post capillary. The small vein flow is due to a composite of flows from a system of progressively branching vessels. For the wing vasculature the small vein flow is on the average due to the flow emerging from 14 muscular venules. Each of these is on the average fed by five capillary segments. On the average then (assuming all precapillary sphincters are open) the ratio

of small vein flow to capillary flow is about 70. The general requirement then is to be able to simultaneously simulate physiologic conditions in each of these microvascular regions.

II. General Form of Model

The general form of a microvascular model which satisfies the structural requirement is shown in figure 4.1. The relative amount of detail associated with the identified microvascular regions is not indicated but will be discussed in depth in subsequent sections. The purpose of figure 4.1 is to show the basic structure of the model and to serve as a guide for the description of the synthesis of the parts. The meaning and reasoning behind the inclusion of each part of the model is as follows.

The region bounded by the pressures P_0 and P_{10} (excluding the parts called shunt pathway and venous load) represents a vascular unit from small artery through small vein. The part labeled shunt pathway is to account for the fact that there are in fact multiple such pathways, as shown in figure 2.3. Thus, the box marked shunt pathway in figure 4.1 incorporates the effect of the multiple branches of the small artery symbolized by the straight arrows in figure 2.3. The resistance $[R_i^{(SA)}]$, seen looking into the point labeled P_0 , corresponds to that computed in Chapter Two from the topological model. The input and output resistance distributions, as represented by the quantities $R_i^{(a)}$, $R_o^{(SA)}$, and $R_o^{(a)}$, also correspond to these previously determined quantities. The parts called "lumped segment of small artery" and "segment of arteriole" thus must and do have values which when combined with the remainder of the model satisfy this requirement. The part called "terminal arteriole and precapillary sphincter" (P.C.S.) represents the dynamic properties



$R_i^{(SA)}$	$R_i^{(a)}$	$R_o^{(SA)}$	$R_o^{(a)}$	= EQUIVALENT INPUT RESISTANCE "SEEN"	
"	"	"	"	"	LOOKING INTO SMALL ARTERY FROM ARTERY
"	"	"	"	"	LOOKING INTO ARTERIOLE FROM SMALL ARTERY
"	"	"	"	"	LOOKING BACK INTO SMALL ARTERY FROM ARTERIOLE
"	"	"	"	"	LOOKING BACK INTO ARTERIOLE SUPPLYING CAPILLARY PATHWAY

Figure 4.1.

of vasomotion and the hydraulic characteristics. The part labeled "capillary pathway" includes the filtration characteristics of the true capillaries and the hydraulic properties of the capillary and post capillary venule. The part labeled "muscular venules" represents a lumped characterization of the distributed muscular venules. The part labeled "lumped pathway arteriole to small vein" represents the remainder of the arteriole-small vein pathways associated with the vascular unit and will be discussed in detail in section IV of this chapter. The part labeled "small vein" represents the dynamic and hydraulic characteristics of the rhythmically active post capillary vessels. "Venous load" and " P_v " represent the impedance seen by the small veins and the central venous pressure.

The region P_1 - P_2 - P_3 - P_4 - P_5 represents the properties and behavior of a most basic subdivision of the microvascular field. Thus, capillary behavior is simulated in a setting in which physiologic pressures, flows and impedances are obtained as a natural consequence of the interaction between pre and post capillary regions. In addition, in the pre and post capillary regions physiological conditions are also obtained, thus permitting the study of both local microvascular aspects and macrocirculatory interactions.

The remainder of this chapter is devoted to the development of a detailed representation of the component parts of the model and their mathematical description. For this purpose the use of electrical analogs has shown itself to provide a convenient method of visualizing the details of the microvascular aspects and their

interrelationships as well as providing a concise way of representing the defining mathematical equations. Such analogs are thus employed freely, but it should be emphasized that there is no intention to physically construct them. Rather the equations which are embodied in the analogs are to be solved by computer simulation.

III. Model of Rhythmically Active Post Capillary Vessels

In this section the region bounded by P_5 and P_{10} as shown in figure 4.1 will be modeled. The vessels of this region show as their most dominant characteristic rhythmic changes in their diameter. Thus we seek to represent this active characteristic as well as the passive characteristics of these vessels.

A. Vessel Segment Representation

In developing the model of these spontaneously active vessels the lead of Noordergraaf (1960) of using an electrical analog representation is followed. The four element passive electrical network representation of a segment of vessel having finite length Δz is shown in figure 4.2 below.

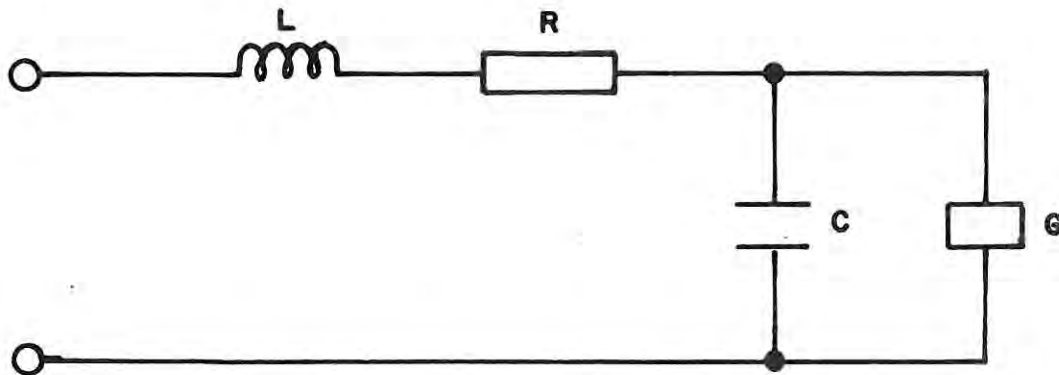


Figure 4.2. Four element network representation of vessel segment. Symbols are defined in Table 4.1.

The correspondence between electrical and mechanical quantities in this representation is as shown in Table 4.1.

Table 4.1. Correspondence between electrical and mechanical quantities for analog representation.

<u>MECHANICAL</u>	<u>ELECTRICAL</u>
Pressure (P)	Voltage (V)
Flow (Q)	Current (I)
Resistance (R)	Resistance (R)
Compliance (C)	Capacitance (C)
Inertance (I)	Inductance (L)
Leakage (L)	Conductance (G)

In some ways the characterization shown in figure 4.2 is more complex than is necessary to adequately represent the essential hemodynamic properties of the small vessels of the post capillary vasculature with which we are presently concerned. On the other hand, there are some additional aspects which need to be included to account for some of the unique properties of these vessels. Our first task then is to suitably modify figure 4.2. A reduction of this representation is dealt with first, followed by a refinement to include pertinent aspects associated with the muscular venule and small vein.

1. Reduction

The inductance in figure 4.2 represents the fluid inertia. In the region of the vasculature toward which the present modeling effort is directed, the fluid inertia is quite small as compared with the viscous factors which are represented by the series resistance in figure 4.2. This conclusion is based on an examination of the prevailing Reynolds number (N_R) which expresses the ratio of inertial to viscous forces existing in the small post capillary vessels. On this basis the inductance in figure 4.2 may be neglected. There are further implications of this dominance of viscous forces which will be discussed in Chapter Six.

The conductance (G) in figure 4.2 represents the leakage flow which leaves the vessel segment via branches. In the post capillary vasculature flow for the most part enters the vessel at a branch point so that the conductance representation of leakage serves no useful purpose and may be eliminated.

2. Refinement

As described in Chapter One, the muscular venules and small veins exhibit rhythmic variation in vessel diameter. Peak to peak diameter variations over the range of 5 to 40% and fundamental frequencies from about .1 to .5 Hz have been recorded, as shall be described in detail in Chapter Six. The existence of this time varying process requires that the element values of the reduced vessel segment representation by time varying quantities. Figure 4.3 is the basic analog representation which serves as the reduced and refined version of the classical one given by figure 4.2.

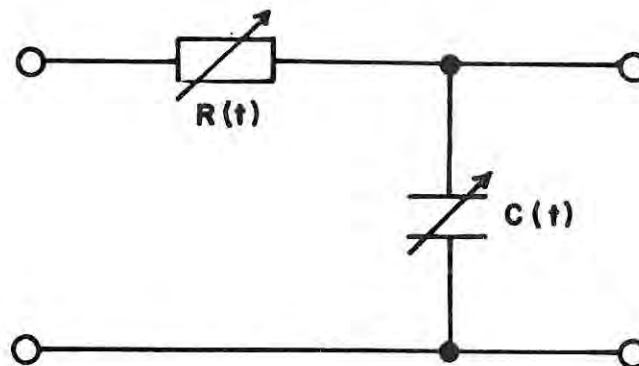


Figure 4.3. Representation of vessel segment of rhythmically active vessel. $R(t)$ and $C(t)$ denote the time varying behavior of the vessel resistance and compliance respectively.

B. Total Vessel Representation

In section A the representation of a vessel segment was developed. In this section the characterization of a vessel of length and properties corresponding to those in the post capillary vasculature will be presented.

1. Resistance and Compliance

The vessel is taken to be straight and cylindrical in shape. Denoting the inside radius as a , wall thickness as h , and total length as l_t , the resistance (r) and compliance (c) per unit length are given by equations 4.1 and 4.2 respectively, in which η is the blood viscosity and E is the elastic modulus of the vessel wall. When r and c are multiplied by the segment length Δz , the analog model parameters R and C are obtained.

$$(4.1) \dots r = \frac{8\eta}{\pi a^4}$$

$$(4.2) \dots c = \frac{3\pi a^2}{E} \left\{ \frac{\left(\frac{a}{h} + 1\right)^2}{\left(2\frac{a}{h} + 1\right)} \right\}$$

The pertinent topological and dimensional data required to calculate the values of r and c are presented in table 2.1 and Chapter Two. In table 4.2 below the calculated values are listed for various diameters. The values for c are calculated using a representative value of 1×10^6 dynes cm^{-2} for E and an a/h ratio of 3.3 extrapolated from the data of Baez (1969) (except for the 80 micron radius vessel in which the calculation is based on a value of a/h of 10). The value of r is calculated on the basis of a viscosity of .035 Poise.

Table 4.2. Calculated per unit length values of resistance (r), compliance (c), time constant (rc) and area factor ($3a^2$) for different values of vessel radius (a). Units: a in 10^{-4} cm, r in 10^8 dynes sec cm^{-6} , c in 10^{-12} dynes $^{-1}$ cm^4 , rc in sec cm^{-2} , $3a^2$ in 10^{-6} cm^2 .

<u>a</u>	<u>r</u>	<u>c</u>	<u>rc</u>	<u>3a²</u>
10	890	23.5	2.1	9.4
20	56	94	.53	37.6
30	11	210	.24	84.5
40	3.5	375	.013	150
80	.014	3400	.0048	600

2. Characterization of Vessel Wall Dynamics

So far the form of the segmental variation in the resistance and compliance has been left unspecified. As can be seen from equations 4.1 and 4.2, both of these parameters depend on the vessel radius and, in the case of the compliance, on the radius to wall thickness ratio, γ , and the wall elastic modulus. Thus, in order to characterize the time varying nature of these parameters, this mutual dependence on vessel radius must be taken into account. Further, since changes in vessel radius are associated with changes in the radius to wall thickness ratio, the radius variation may not be arbitrarily chosen as a parameter forcing function. Thus, for the model to be reasonably realistic it is necessary to describe the vessel radius and wall thickness variation in terms of the physical processes producing this variation.

To accomplish this we take as a starting point the general characterization of the viscoelastic vessel wall properties developed

by Westerhof and Noordergraaf (1971). Defining E_c to be the complex elastic modulus and E to be its low frequency limit value they showed that a general form, valid over a broad frequency band, is that given by eq. 4.3 below.

$$(4.3) \dots E_c(s) = E \frac{\prod_{n=1}^M b_n \prod_{n=1}^N (s+a_n)}{\prod_{n=1}^N a_n \prod_{n=1}^M (s+b_n)}$$

in which M, N, a_n , and b_n are constants and s is the Laplace operator. Since $E_c(s)$ may be expressed as the ratio of wall stress $\sigma(s)$ to wall strain $\epsilon(s)$ equation 4.3 may be alternatively expressed as eq. 4.4.

$$(4.4) \dots \sigma(s) = \epsilon(s) E \frac{\prod_{n=1}^M b_n \prod_{n=1}^N (s+a_n)}{\prod_{n=1}^N a_n \prod_{n=1}^M (s+b_n)}$$

The values for a_n and b_n are unknown for the small venous vessels. However, if for practical purposes we limit ourselves to the special case in which $M=N=1$ then for the low frequency and narrow frequency band case with which we are presently interested we may write approximately:

$$(4.5) \dots \sigma_s \doteq \epsilon(s) E \frac{(s + a_1)}{a_1}$$

Transforming eq. 4.5 back to the time domain and defining $K_\eta = E/a_1$ we obtain:

$$(4.6) \dots \sigma(t) = E\varepsilon(t) + K_{\eta} \dot{\varepsilon}(t)$$

Written in this form it may be seen that eq. 4.6 is the defining equation for the Voigt model of the vessel wall in which E and K_{η} correspond to the lumped elastic and viscous coefficients.

To be able to utilize eq. 4.6 it is necessary to include the muscle contraction effects and to take into account the fact (as shown by the data of Table 4.2) 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. 4.6 may be interpreted unambiguously.

In Appendix B it is shown that under conditions of equilibrium and subject to the normal range of intravascular pressure the radius corresponding to a fully relaxed vessel state is ideally suited as such a reference radius. Further it is shown that the effect of the contracting muscle may be taken into account by associating with the contraction process an additional force tending to reduce the vessel radius and thus disturb a quasiequilibrium 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 4.6 in which the relative strain is measured from the reference state.

Thus the inclusion of the influence of the contracting muscle is affected by expressing the left hand side of eq. 4.6 as the

difference between the stress tending to dilate the vessel and the developed stress σ_m associated with the contracting muscle. Defining the radius to wall thickness ratio as γ and the inside and outside pressures as P_i and P_o respectively, the equation whose solution describes the wall dynamics is given by eq. 4.7 below.

$$(4.7) \dots \gamma(P_i - P_o) - P_o - \sigma_m = E\varepsilon + K_\eta \dot{\varepsilon}$$

3. Determination of the Number of Sections to be Used

a. Approach

The number of sections required to adequately represent the vessel depends on the physical length represented by each segment in relation to the smallest wavelength disturbance present in the vessel. As mentioned previously the predominant frequencies present (and those which represent the main source of periodic disturbance) lie in the frequency band from .1 to .5 Hz.

In order to determine the minimum wavelength, the wave velocity or its equivalent must be determined in connection with the relationship given by equation 4.8 below. In eq. 4.8 λ is wavelength, f is frequency and v is the wave velocity.

$$(4.8) \dots \lambda = \frac{v}{f}$$

To determine the smallest wavelength present the largest frequency is used together with the smallest calculated wave velocity.

b. Wave Velocity Determination

Using standard transmission line theory the general form of the propagation function (Γ) is given by eq. 4.9 below in which r , c , l , and g correspond to per unit length values of R , C , L , and G respectively.

$$(4.9) \dots \Gamma = \sqrt{(r + j\omega l)(g + j\omega c)}$$

In the present representation for reasons already described $r \gg \omega l$ and $g \ll \omega c$, therefore eq. 4.9 may be written as eq. 4.10 below, in which Γ_R and Γ_I represent the real and imaginary parts of Γ .

$$(4.10) \dots \Gamma = \Gamma_R + j\Gamma_I = \sqrt{j\omega rc} = \sqrt{\omega rc/2} (1 + j)$$

From eq. 4.10 it may be seen that the real and imaginary parts of the propagation function are equal to each other and are given by equation 4.11 below.

$$(4.11) \dots \Gamma_R = \Gamma_I = \sqrt{\omega rc/2}$$

Recognizing that $\lambda = \frac{2\pi}{\Gamma_I}$, the phase velocity given by equation 4.8

may be written as:

$$(4.12) \dots v = \frac{\omega}{\Gamma_I} = \sqrt{2\omega/rc}$$

Using equations 4.1 and 4.2 in equation 4.12 yields the wave velocity in terms of fundamental quantities, which is given by equation 4.13.

$$(4.13) \dots v = \frac{a \sqrt{2\omega}}{\left(\frac{a}{h} + 1\right)} \sqrt{\frac{E \left(2 \frac{a}{h} + 1\right)}{24\eta}}$$

Before proceeding further it is instructive to compare equation 4.13 with similar expressions which have been developed for the calculation of wave speed without reference to the transmission line analogy. One such equation, due to Morgan and Kiely (1954), may be written in the form of equation 4.14 below (ρ = density, ν = kinematic viscosity). In equation 4.14 the assumption that $a\sqrt{\frac{\omega}{\nu}} \ll 1$ (which has been previously shown to be valid for the present case) has been made.

$$(4.14) \dots v = a \left(\frac{\omega}{3\nu}\right)^{1/2} \left(\frac{Eh}{2\rho a}\right)^{1/2}$$

In order to compare this formula with that obtained from the transmission line analogy, equation 4.13 is simply rewritten as equation 4.15 below.

$$(4.15) \dots v = a \left(\frac{\omega}{3\nu}\right)^{1/2} \left(\frac{E}{2\rho}\right)^{1/2} \left(\frac{2 \frac{a}{h} + 1}{\left(\frac{a}{h} + 1\right)^2}\right)^{1/2}$$

Comparison of eqs. 4.14 and 4.15 shows that these solutions converge for large a/h ratios and that equation 4.15 is in reality a more general relationship.

Using numerical values in eq. 4.15 corresponding to those for the small vein ($a=20u$, $a/h=3.3$, $\eta=.035$ Poise, $E=1 \times 10^6$ dynes cm^{-2} and $f=.5$ Hz) yields a calculated velocity of 4.9 cm/sec. Using eq. 4.8 this corresponds to a wavelength of 9.8 cm.

The above calculation estimates the approximate wavespeed and wavelength of the fundamental frequency based on the mean diameter of the vessel. In order to obtain a "worst case" estimate (i.e., the smallest possible wavelength), a calculation based on a larger a/h and concomitantly smaller radius corresponding to a 50% contracted state may be performed. Thus, taking $a/h=10$ the velocity is reduced to a 3.2 cm/sec. Using this ratio in conjunction with a $10u$ radius further reduces the velocity to 1.6 cm/sec. This corresponds to a wavelength of 3.2cm.

C. Number of Sections Used

Recalling that the mean length of the small vein is .34 cm and the muscular venule even smaller it appears that the total vessel length itself is small compared to the smallest wavelength at the highest fundamental frequency. However as will be shown in Chapter Six the diameter variation and associated pressure variations are not purely sinusoidal and thus contain some higher frequency energy.

In order to include the effect of the higher harmonics,

five segments are used to represent the vessel. Thus when the model is used to represent a vessel that has a total length L_t each segment corresponds to a physical length of L_t/n where n is the number of sections. For the small vein $n=5$ and the physical length is 680u, and for the venule the physical length represented by one segment is 200u. The vessel model at this point in its development is shown in figure 4.4 below.

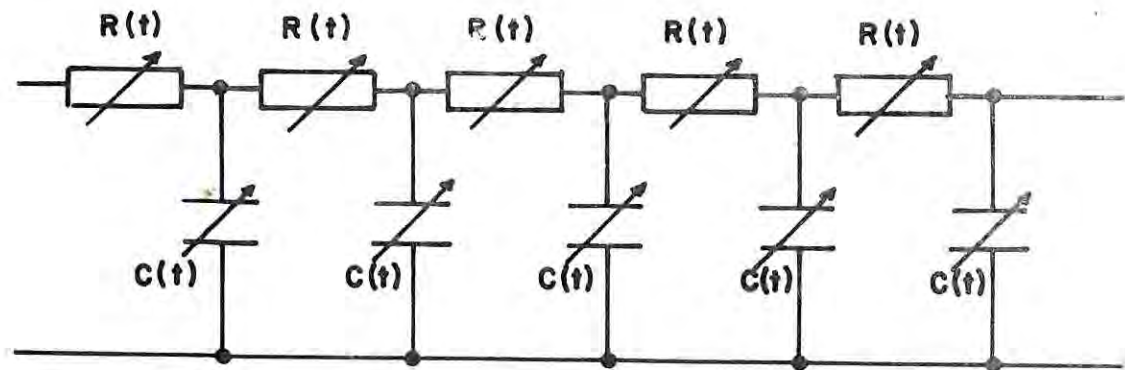


Figure 4.4 Representation of rhythmically active vessel as five consecutive segments of time varying resistance and compliance.

4. Branch Flow and Non-uniform Contraction

There are two additional features which have been included in the model to increase its generality. These are the potential for branch flow and non-uniform contraction of the rhythmically active vessel. As was discussed in Section A, the use of a simple resistor was not an adequate representation for the venous vasculature with respect to branch flow. Experimental observations clearly indicate

that following a contraction of the active vessel and subsequent reduction in intravascular volume, there is a "filling" phase during the time that the vessel relaxes. The inflow during this period is not generally emanating from a single source point but is more often affected by a summation of inflows from individual branches. A detailed representation of this inflow process is indeed complex. However, in order to include the essence of its effect, it may be simulated by associating with each segment a flow source, $Q_b(t)$, as illustrated in figure 4.5 below.

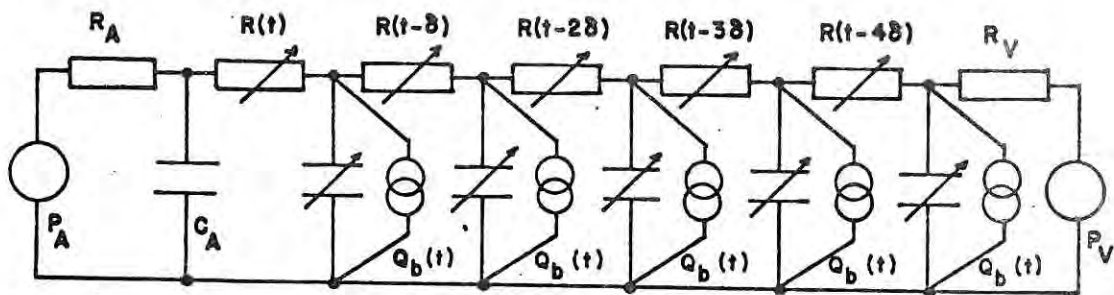


Figure 4.5 Representation of rhythmically varying vessel which includes branch flow, $Q_b(t)$, and provision for temporal phase differences between contraction of spatially separated vessel regions. δ is the time delay between adjacent sections. See text for details.

The use of this representation and the manner in which it is included in the simulation (Section V) gives a great deal of

flexibility with the types of problems which may be studied. For example, the effect of valves guarding the entrance of the branches to the small vein may be studied by allowing the branch flow to be zero over part of the venomotion cycle, or to exclude it entirely by making it identically zero. Thus for example to model the situation in which the change in segmental volume accompanying venomotion is due to a modulation of the feeding branch's flows we have:

$$(4.16) \dots\dots Q_b(t) = 2\pi a \dot{a} \Delta z$$

in which Δz is the segment length. Then to model the effect of the presence of the valves at the entrance regions we would require that:

$$(4.17) \dots\dots Q_b(t) = \begin{cases} 2\pi a \dot{a} \Delta z & \dot{a} \geq 0 \\ = 0 & \dot{a} < 0 \end{cases}$$

Thus these relationships establish the branch flow pattern such that during the relaxation phase of venomotion flow enters from the branches and during the contraction phase the inflow is stopped. To exclude the branch flow entirely $Q_b(t)$ is made zero.

The other feature incorporated into the model shown in fig. 4.5 is the provision for temporal phase differences between contraction

of spatially separated vessel regions. This feature is represented by associating with each segment's resistance and compliance a time delay δ (note that in the figure only the resistance is so labeled for clarity of presentation). The inclusion of this non-uniform characteristic in the model permits evaluation of the significance of so-called peristaltic character sometimes associated with rhythmic diameter variations of the type seen in the post capillary vessels. Since by making the time delay zero uniform vessel contraction is obtained, the model shown in figure 4.5 is a most general representation, and subsequent references to the rhythmic vessel model shall refer to figure 4.5.

IV. Model of Pre Capillary and Capillary Region

It is possible to study the characteristics of the vessel model indicated in figure 4.5 by using quite simple and arbitrarily chosen boundary conditions at its input (source) and at its output (load), for example a constant pressure or flow source at the input terminals. However, with a few exceptions, such simplifications tend to reduce the utility of the model and deviate from reality. A more appropriate characterization is one which includes those functional aspects of the source and load which approximate reality and are sufficient and necessary for the particular process being studied. Thus to be able to study effectively the hemodynamics within the active vessel or the effects of these hemodynamics on the hemodynamic pattern upstream and downstream, or the effect of upstream hemodynamics on active vessel dynamics, it is necessary to adequately represent the capillary and pre capillary vasculatures. In this section then, the region bounded by P_1 and P_5 as shown in figure 4.1 will be modelled. In section V the model developed here will be coupled to the model of section III, and the resultant model will be the Microvascular Model.

A. Model Structure

In figure 4.6 is shown a more detailed version of the vascular region from arteriole to muscular venule originally included as part of the Topological Model shown in figure 2.3 (Chapter Two). In figure 4.6 the parts labeled R_a correspond to segments of the arteriole, R_{ta} represents the terminal arteriole and pre capillary sphincter, and R_c represents the capillary region. The segmented

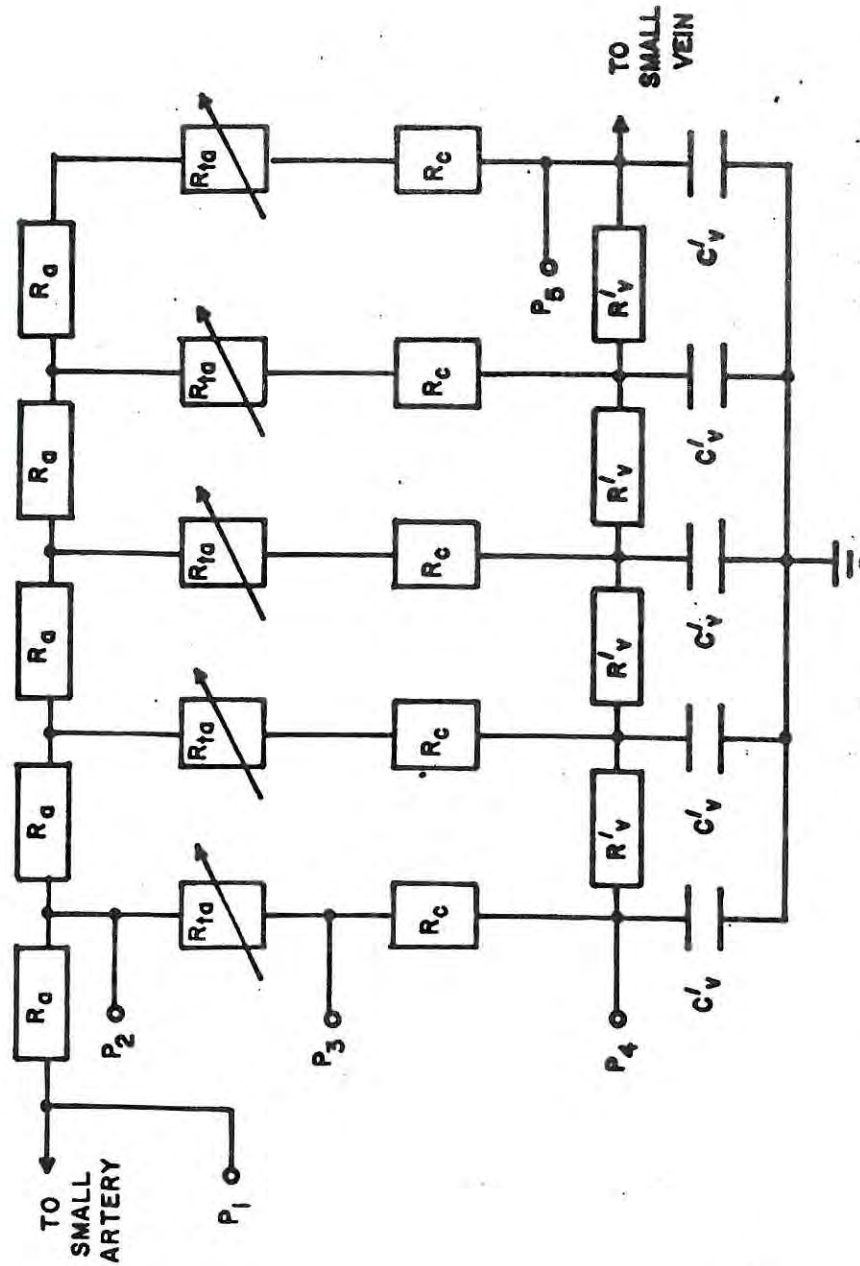


Figure 4.6 Vascular Region from Arteriole to Muscular Venule. R_a , R_{ta} , R_c , and R'_v represent segments of arteriole, terminal arteriole, capillary, and muscular venule respectively. C'_v represents muscular venule compliance. P_1 through P_5 correspond to pressures shown in figure 4.1.

RC network identified by R'_v and C'_v and into which the capillaries terminate represents the muscular venule. The equations which characterize the hemodynamics in these vessels will be presented in section C. It is our present purpose to utilize figure 4.6 as a reference to describe the synthesis of a reduced representation which will be coupled to the model of the rhythmically active vessel developed in section II. Our objective is to obtain a reduced version which contains the basic features of the more detailed version of figure 4.6.

B. Synthesis of Reduced Model

The first step is to lump the distributed venule which serves as the load for the capillary pathways and as the source for the small vein. Next because we are interested in isolating a single capillary pathway from the remainder of the network for detailed study, we permit one of the pathways shown in figure 4.6 to enter the lumped venule at its origin and the remainder of the pathways to enter at the junction of the venule and small vein. The model at this stage of its development is shown in figure 4.7.

Next to account for the fact that the flow entering the small vein is due to the composite flow of the remaining arteriole pathways which feed that small vein we represent these other pathways together with the four common pathways of figure 4.7 as a lumped pathway identified by R_{eff} in figure 4.8. The quantity R_{eff} thus represents the effective flow resistance of these combined pathways.

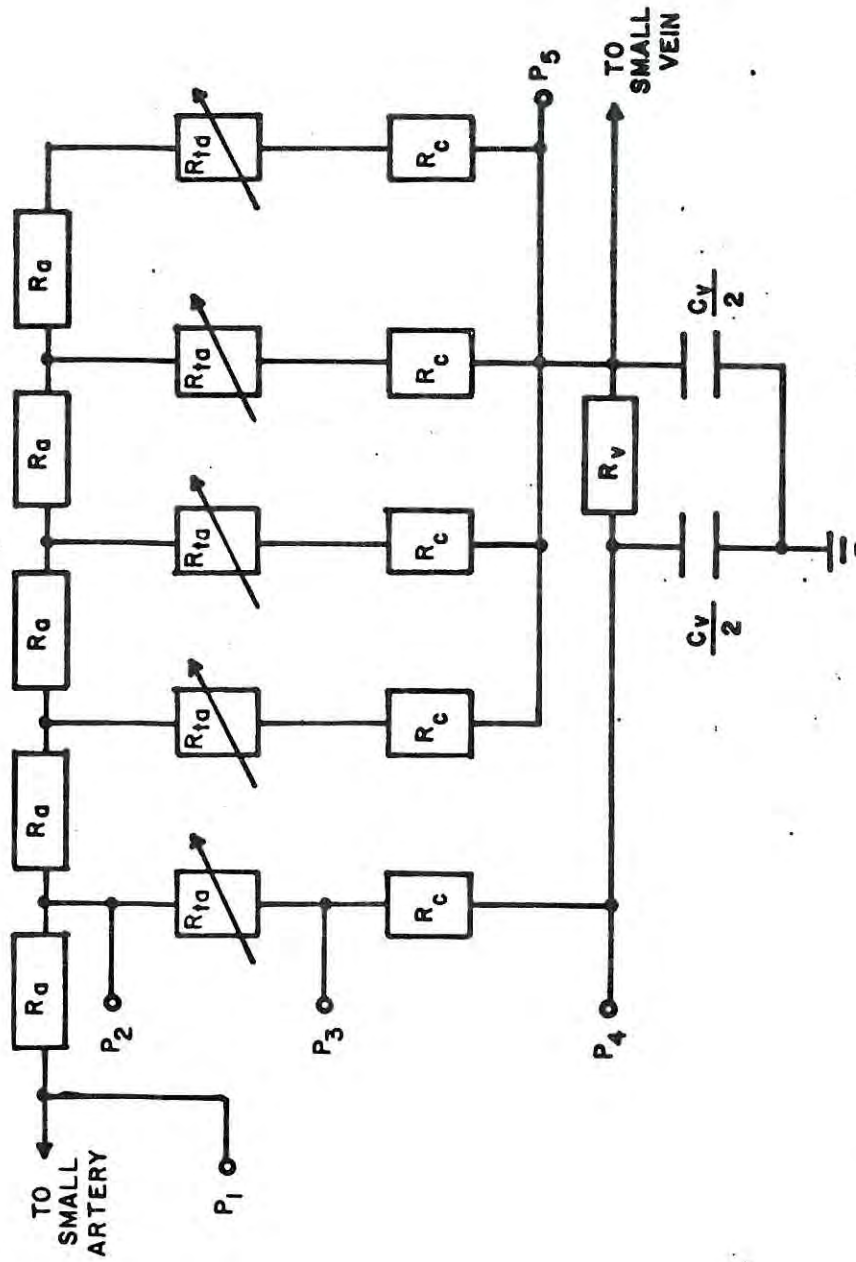


Figure 4.7 Intermediate Stage in Developing Reduced Model. R_v and C_v are respectively the lumped resistance and compliance of the muscular venule.

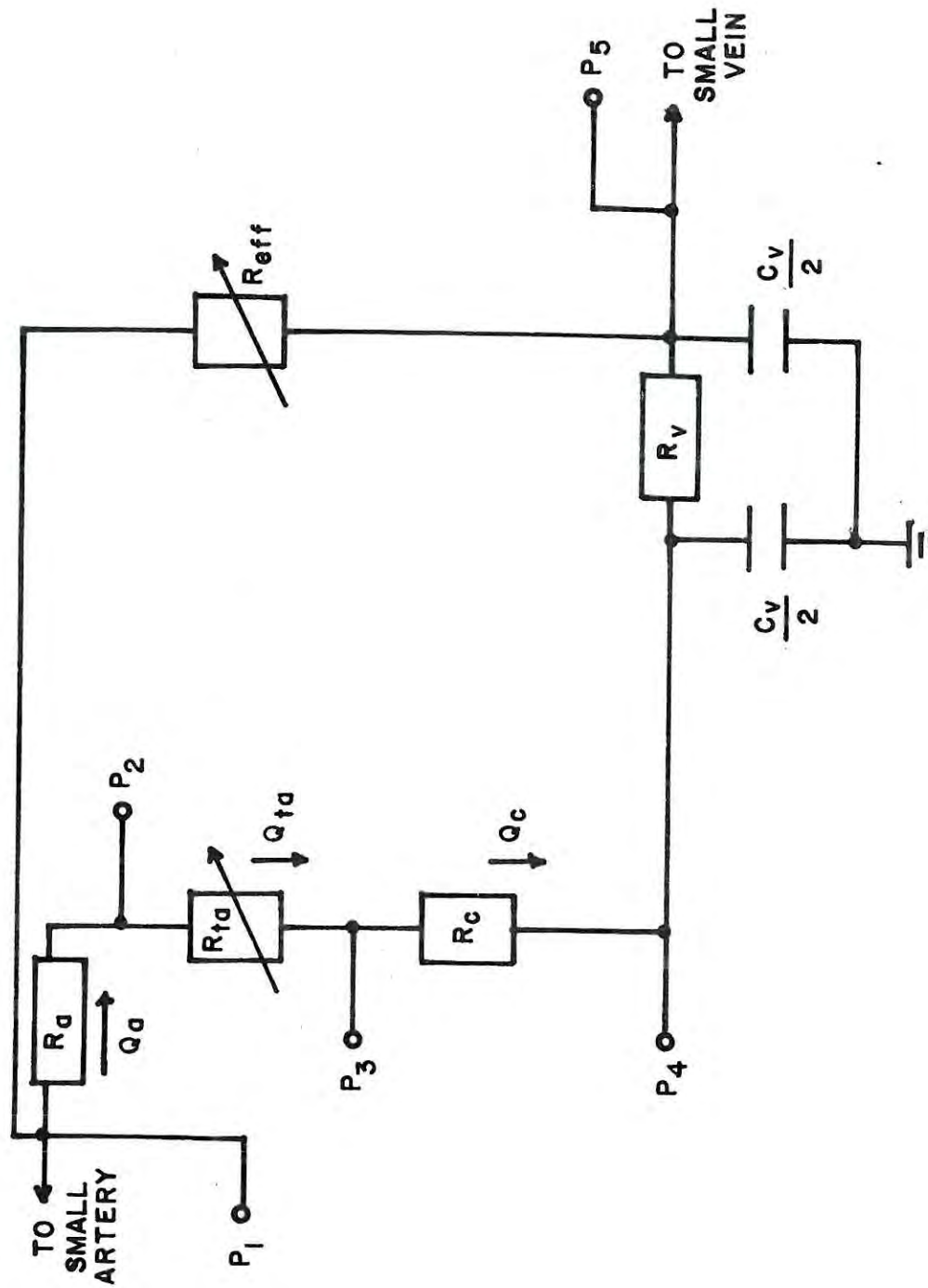


Figure 4.8. Reduced model of vascular region from arteriole to muscular venule.

C. Pressure-Flow Equations

The flow regime in the arteriole segments is taken as obeying the Casson equation developed in Chapter Three. This equation is repeated below in a form specifically applicable to the model shown in figure 4.8. In this equation D_a is the arteriole diameter, and all other quantities have been previously defined.

$$(4.18) \dots Q_a = \frac{\pi(P_1 - P_2)D_a^4}{128\eta} \left[1 - \frac{32}{7} \theta^{1/2} + \frac{16}{3} \theta - \frac{4}{21} \theta^4 \right]$$

Similar to the approach taken in Chapter Two, the Poiseuille resistance is defined as R_p such that:

$$(4.19) \dots R_p = \frac{128\eta}{\pi} D_a^4$$

so that equation 4.18 may be written as:

$$(4.20) \dots Q_a = \frac{P_1 - P_2}{R_p} F(\theta)$$

The flow regime in the terminal arteriole, capillary and venule is described by equation 2.9 of Chapter Two. Taking the diameter of the terminal arteriole as D_{ta} and for the capillary D_c and assuming equal plasma and cell lengths, we obtain for the terminal arteriole:

$$(4.21) \dots P_2 - P_3 = Q_{ta} R_{ta}$$

in which:

$$(4.22) \dots R_{ta} = \frac{128\eta}{\pi} \left\{ \frac{(2 - e^{-k/v_{ta}}) \left[1 + \frac{v_{ta}}{4} + \left(\frac{v_{ta}}{4} \right)^4 \right] (1 + 0.6e^{-\beta s}) l_{ta}}{D_{ta}^4} \right\}$$

for the capillary:

$$(4.23) \dots P_3 - P_4 = Q_c R_c$$

in which:

$$(4.24) \dots R_c = \frac{128\eta}{\pi} \left\{ \frac{(2-e^{-k/v_c}) \left[1 + \frac{v_c}{4} + \left(\frac{v_c}{4} \right)^4 \right] (1+.6e^{-\beta_s}) l_v}{D_c^4} \right\}$$

and for the muscular venule:

$$(4.25) \dots R_v = \frac{128\eta}{\pi} \left\{ \frac{(2-e^{-k/v_v}) \left[1 + \frac{v_v}{4} + \left(\frac{v_v}{4} \right)^4 \right] (1+.1e^{-\beta_s}) l_v}{D_v^4} \right\}$$

D. Inclusion of Pre Capillary Sphincter Activity

In figures 4.6 through 4.8 the quantity R_{ta} is shown with an arrow through it. This representation is to call attention to the fact that because of the vasomotion associated with this microvascular region, the resistance is a dynamic function. This aspect is included in the model implicitly via equation 4.22 by simulating vasomotion as a controlled variation D_{ta} and v_{ta} . Thus all one needs to do is represent these quantities as appropriate time functions. However, the physiological question of which microvascular factor or factors is the dominant controller of sphincter activity has yet to be resolved. Theories concerning sphincter control may be grouped into two rather broad categories: direct mechanical effects controlling sphincter activity and metabolic control. Under mechanical effects would be the myogenic theory which maintains that contraction is simulated by elevation in intravascular pressure and the tissue pressure theory which maintains that sphincter activity can be

explained on the basis of diameter induced changes due to direct coupling of the tissue pressure to the vessel. In the second category are included the array of chemicals and other vasoactive substances whose concentrations in the tissue vary as a function of the local tissue metabolic state.

In the present model the pre capillary sphincter activity is controlled in such a fashion so as to maintain (within physiological limits) the tissue pressure in the dependent micro-vascular regions. There are several reasons for this type of characterization. First from the limited amount of experimental data available the normal tissue pressure appears to be maintained within narrow limits. This, of course, does not necessarily mean such maintenance is because of sphincter activity but does offer that possibility. Secondly, use of an extravascular quantity (tissue pressure) rather than an intravascular one (capillary pressure) permits the controlled quantity to reflect more closely the local tissue environment which, in the final analysis, must be the ultimate controlled variable. Thirdly, by using tissue pressure we in effect include the myogenic theory as a special case. Thus, for example, if osmotic quantities are held constant in the model (see section E) the resultant sphincter activity should be similar to those associated with the maintenance of the capillary pressure. And finally, by using such a control representation and then comparing the resulting hemodynamics and filtration predictions with available experimental data it is hoped to gain insight into the

relationship between mechanical and metabolic factors. It should be emphasized that at this point no postulation or speculation is made concerning the mechanism of sphincter control, only that its activity is such as to maintain the tissue pressure within specified limits.

To accomplish this mathematically, the terminal arteriole is taken to have a maximum and minimum inside diameter corresponding to those observed in vivo and denoted as D_r and D_c , respectively. Denoting the upper and lower tissue pressure limits as P_{tu} and P_{tl} , the terminal arteriole diameter D_{ta} and lumen to red cell ratio v_{ta} in equation 4.22 are then parametrically controlled by the tissue pressure according to equation 4.26 below, in which m is the rate of change of vessel diameter.

$$\begin{aligned}
 (4.26) \dots D_{ta} &= D_c & P_t &\geq P_{tu} \\
 D_{ta} &= D_r & P_t &\leq P_{tl} \\
 D_{ta} &= D_c + m_1 t & P_{tl} < P_t < P_{tu} & \quad (\text{dilation phase}) \\
 D_{ta} &= D_r - m_2 t & P_{tl} < P_t < P_{tu} & \quad (\text{contraction phase})
 \end{aligned}$$

E. Inclusion of Capillary Filtration

Classically, considerations of capillary filtration have been approached by describing filtration and reabsorption by using steady state fluid balance equations. Using the following definitions, these equations take the form of equations 4.27 and 4.28.

$$P_c = \text{capillary pressure;}$$

P_T = tissue pressure;

π_{PL} = osmotic pressure of plasma (intravascular);

π_T = osmotic pressure of tissue (extravascular);

$\Delta\pi = \pi_{PL} - \pi_T$;

K_F = filtration coefficient;

K_R = reabsorption coefficient;

Q_F = filtration flow rate;

Q_R = reabsorption flow rate.

$$(4.27) \dots Q_F = K_F(P_C - P_T - \Delta\pi)$$

$$(4.28) \dots Q_R = K_R(P_T - P_C + \Delta\pi)$$

In figure 4.9 is shown a representation of the filtration-reabsorption process, which includes the steady state relationships described by equations 4.27 and 4.28. In addition, the representation shown in figure 4.9 takes into account the effects of lymph flow and, as represented by C_t , the compliance of the perivascular space. These aspects are important, especially the compliance, when the dynamic character of the fluid exchange process is to be taken into account. The model equations for this region are listed in sect. V.B.

In figure 4.9, R_{ta} and venous compliance and resistance which are not part of the filtration model per se are shown in order to call attention to the fact that capillary hemodynamics and hence the fluid exchange process are by no means of a steady nature. In view of this unsteady aspect, it should be expected that the protein concentration in the extravascular space will vary with

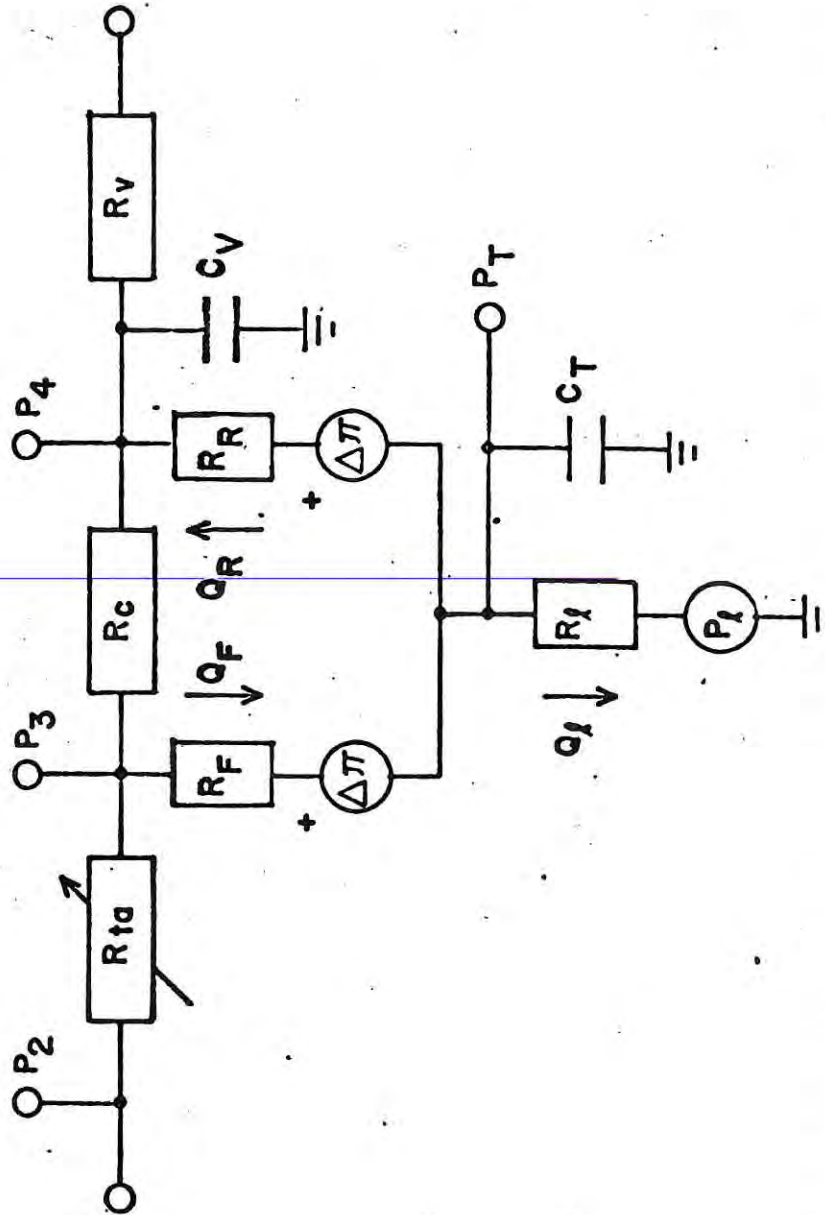


Figure 4. 9. Inclusion of Capillary Filtration. Flows Q_f , Q_r , and Q_i represent filtration, reabsorption and lymph flow respectively. P_i is a pressure source representing the pressure in the lymph vessels and $\Delta\pi$ is a pressure source representing the effective intravascular-extravascular osmotic pressure difference. P_3 and P_4 are the pressures that would be measured at the arterial and venous side of the capillary respectively. R_f and R_r represent the effective resistance to filtration and reabsorption and are related to the filtration and reabsorption coefficients.

intravascular dynamics. Since the osmotic pressure difference depends on this concentration, it may be concluded that the parameter $\Delta\pi$ in the model of figure 4.9 is subject to parametric variation. The precise form of this parametric variation is unknown. Most experiments which have attempted to examine the dynamic character have done so under conditions where the lymph flow was zero. We take this condition as the starting point in an attempt to characterize the time dependence of this process.

We take the quantity $\Delta\pi_0$ to represent an equilibrium value defined for the condition $Q_F = Q_R$ and lymph flow, $Q_1 = 0$. Under these conditions there is a corresponding equilibrium tissue volume V_0 and pressure P_{T_0} . A perturbation in intravascular pressures must then be accompanied by a change in $\Delta\pi$, i.e., away from its equilibrium value. This change may be taken as being proportional to the change in tissue fluid volume. Mathematically

$$d(\Delta\pi_0) \propto dV_0;$$

$$d(\Delta\pi_0) \propto C_T dP_T;$$

$$d(\Delta\pi_0) = K_\pi C_T dP_T.$$

$$(4.29) \dots \Delta\pi = \Delta\pi_0 + K_\pi C_T (P_T - P_{T_0})$$

Equation 4.29 thus relates the osmotic pressure difference to the reference osmotic value $\Delta\pi_0$ and the deviation of the tissue pressure from a corresponding reference. It is used as an approximation to describe the parametric variation in osmotic pressure difference associated with intravascularly induced alterations in tissue pressure.

V. Composite Microvascular Model and Computer Simulation

A. Model Structure

In figure 4.10 is shown the detailed microvascular model which is obtained when the model of the rhythmically active vessel (figure 4.5) is coupled to the pre capillary and capillary model of figure 4.9. Figure 4.10 thus has the same form as the general model shown in figure 4.1, but now includes a detailed representation of the individual parts. For the reader's convenience, the parameters used in the model with their definitions are listed in table 4.3.

Table 4.3. Symbols and definitions used in microvascular model of figure 4.10.

<u>Symbol</u>	<u>Definition</u>
$C'(t)$	Compliance of a segment of the rhythmically active vessel.
$R'(t)$	Resistance of a segment of the rhythmically active vessel.
δ	A time delay associated with the variation in $R'(t)$ and $C'(t)$ between axially separated segments.
R_V	The equivalent resistance seen by the rhythmically active vessel looking toward the large veins.
P_V	The central venous pressure.
C_V	The lumped compliance of the distributed muscular venules.
R_V	The lumped resistance of the muscular venule.
R_R	The effective resistance associated with fluid reabsorption from the interstitial space. It is the reciprocal of the reabsorption coefficient.

<u>Symbol</u>	<u>Definition</u>
R_F	The effective resistance associated with fluid filtration from the capillary into the interstitial space. It is the reciprocal of the filtration coefficient.
R_C	The flow resistance of the true capillary and the post capillary venule.
$\Delta\pi$	The difference between the osmotic pressure in the capillary and the interstitial space.
R_l	The flow resistance to lymph from the interstitial space to the lymph capillaries.
C_T	The effective compliance of the tissue space.
R_{EFF}	The lumped pathway for the remainder of the arteriole to small vein pathways.
R_{ta}	The flow resistance associated with the terminal arteriole and pre capillary sphincter.
C_a	The compliance (lumped) associated with the arterial vessels.
R_a	The effective resistance of the arteriole vessels.
R_A	The effective resistance associated with the small artery.
Z_{SH}	The impedance associated with the remaining branches of the small artery.
P_l	The pressure in the lymph vessels.
P_T	Tissue pressure.
$P_i \text{ } i=0 \text{ to } 10$	The pressures within the vasculature.
$Q_b(t)$	The branch inflow to the rhythmically active vessel.

In figure 4.10 the section between P_1 and P_2 represents the arteriole resistance, between P_2 and P_3 the terminal arteriole and pre capillary sphincter, between P_3 and P_4 the capillary region,

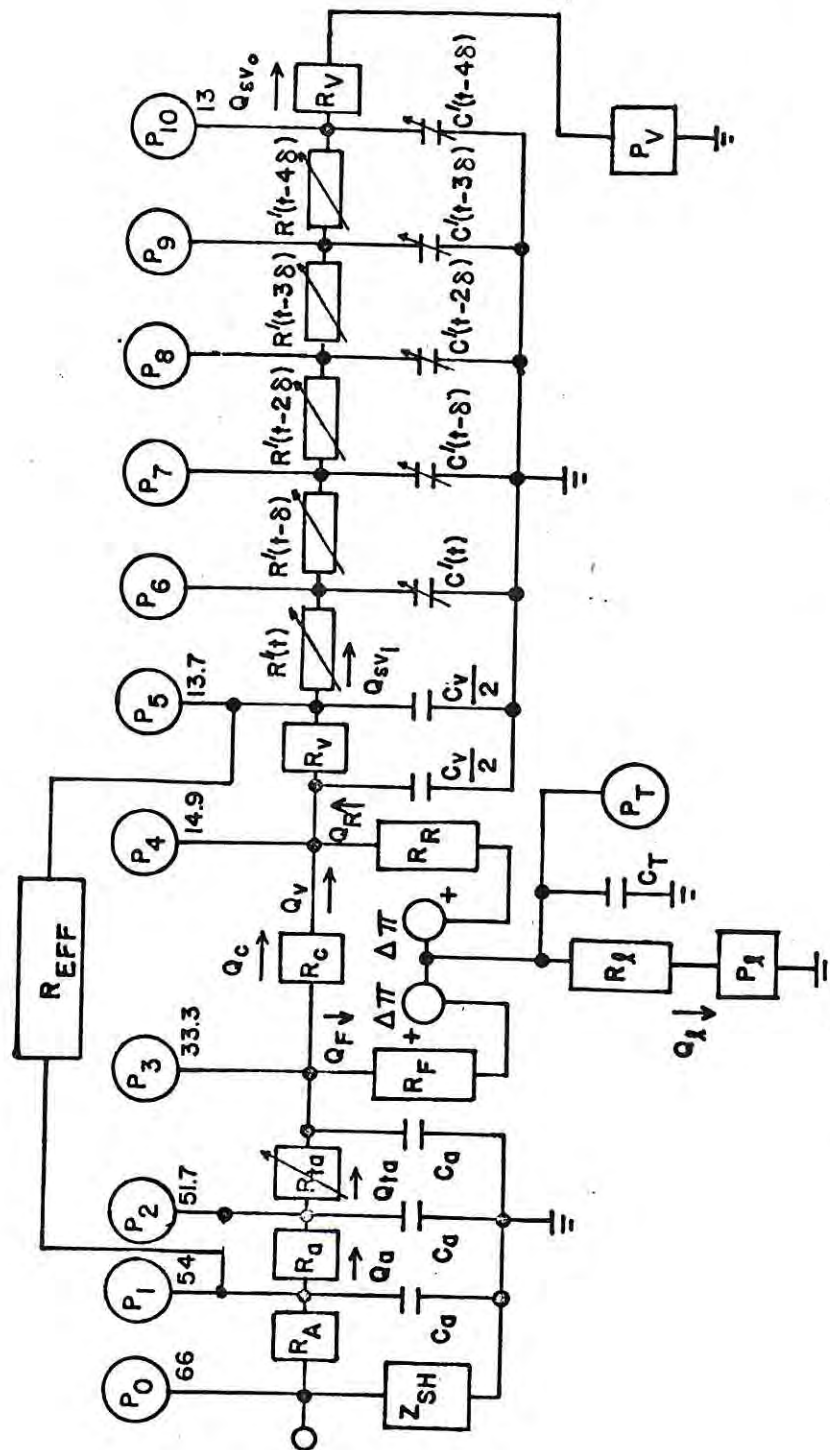


Figure 4.10. DETAILED MICROVASCULAR MODEL
Parameters defined in Table 4.3. Numbers adjacent to pressure symbols (circles) are the measured pressures at these points in mmHg.

between P_4 and P_5 the lumped muscular venule, and between P_5 and P_{10} the active vessel part of the post capillary vasculature. The pathway 1-2-3-4-5 is equivalent to a single pathway of figure 4.6, and the pathway 1-5, which is termed R_{EFF} , represents the net effect of the remaining pathways. The lumped venule is passive in this model.

The flow in the small vein is primarily determined by R_{EFF} , since the impedance of this pathway as "seen" looking back from the small vein to the arterial side is small compared to the impedance due to the single "capillary" pathway. However, in the physiological case it is also true that the flow and pressure relationships within the single, specific capillary pathway are less important for the aggregate flow than are the composite effects of a large number of them. From the point of view of the single capillary pathway, that is, with regard to the study of the effects of small vein dynamics, tissue pressure, osmotic pressure, pre capillary sphincter variation and so on, these details are necessary.

The composite representation depicted in figure 4.10 then allows for the study of both local microvascular events and macrovascular interactions within a consistent framework.

B. Model Equations

The set of equations which mathematically describe the Microvascular Model shown in figure 4.10 are as follows.

$$(4.30) \dots \dot{P}_1 = \frac{P_0 - P_1}{C_a R_A} - \frac{P_1 - P_2}{C_a R_a}$$

$$(4.31) \dots \dot{P}_2 = \frac{P_1 - P_2}{C_a R_a} - \frac{P_2 - P_3}{C_a R_{ta}} - \frac{P_2 - P_5}{C_a R_{EFF}}$$

$$(4.32) \dots \dot{P}_3 = \frac{P_2 - P_3}{C_a R_{ta}} - \frac{P_3 - P_4}{C_a R_C} - \frac{P_3 - P_T - \Delta\pi}{C_a R_F}$$

$$(4.33) \dots \dot{P}_T = \frac{P_3 - P_T - \Delta\pi}{C_v R_F} - \frac{P_T - R_L}{C_T R_L} - \frac{P_T + \Delta\pi - P_4}{C_T R_R}$$

$$(4.34) \dots \dot{P}_4 = \frac{2(P_3 - P_4)}{C_v R_C} + \frac{2(P_T + \Delta\pi - P_4)}{C_v R_R} - \frac{2(P_4 - P_5)}{C_v R_v}$$

$$(4.35) \dots \dot{P}_5 = \frac{2(P_4 - P_5)}{C_v R_v} + \frac{2(P_2 - P_5)}{C_v R_{EFF}} - \frac{2(P_5 - P_6)}{C_v R'(t)}$$

$$(4.36) \dots \dot{P}_6 = \frac{P_5 - P_6}{C'(t)R'(t)} - \frac{P_6 - P_7}{C'(t)R'(t - \delta)} + \frac{Q_b(t)}{C'(t)} - \frac{P_6 \dot{C}'(t)}{C'(t)}$$

$$(4.37) \dots P_7 = \frac{P_6 - P_7}{C'(t - \delta)R'(t - \delta)} - \frac{P_7 - P_8}{C'(t - \delta)R'(t - 2\delta)} + \frac{Q_b(t - \delta)}{C'(t - \delta)} - \frac{P_7 \dot{C}'(t - \delta)}{C'(t - \delta)}$$

$$(4.38) \dots \dot{P}_8 = \frac{P_7 - P_8}{C'(t - 2\delta)R'(t - 2\delta)} - \frac{P_8 - P_9}{C'(t - 2\delta)R'(t - 3\delta)} + \frac{Q_b(t - 2\delta)}{C'(t - 2\delta)} - \frac{P_8 \dot{C}'(t - 2\delta)}{C'(t - 2\delta)}$$

$$(4.39) \dots \dot{P}_9 = \frac{P_8 - P_9}{C'(t - 3\delta)R'(t - 3\delta)} - \frac{P_9 - P_{10}}{C'(t - 3\delta)R'(t - 4\delta)} + \frac{Q_b(t - 3\delta)}{C'(t - 3\delta)} - \frac{P_9 \dot{C}'(t - 3\delta)}{C'(t - 3\delta)}$$

$$(4.40) \dots \dot{P}_{10} = \frac{P_9 - P_{10}}{C'(t - 4\delta)R'(t - 4\delta)} - \frac{P_{10} - P_v}{C'(t - 4\delta)R_v} + \frac{Q_b(t - 4\delta)}{C'(t - 4\delta)} - \frac{P_{10} \dot{C}'(t - 4\delta)}{C'(t - 4\delta)}$$

The equations for the resistance $R'(t)$ and compliance $C'(t)$ associated with the rhythmically active vessel are given by equations 4.1 and 4.2 respectively after multiplying by the segment length. The radius and radius to wall thickness variation which determine the time properties of these parameters are given as the solutions of equation 4.7. The branch flow, $Q_b(t)$, is given by equation 4.17.

The functions which mathematically characterize the resistances R_C of the capillary region and R_V of the muscular venule region are given by equations 4.24 and 4.25 respectively. The function that characterizes the resistance R_{ta} associated with the terminal arteriole and pre capillary sphincter is given by equation 4.22, subject to the parametric variation defined by equation 4.26. The remaining resistance and compliance functions are of the form given by equations 4.1 and 4.2 using the appropriate dimensional quantities. Finally, the parametric variation in the osmotic pressure difference is determined by equation 4.29.

C. Solution of Equations and Computer Simulation

1. Approach

The pressures and flows in the Microvascular Model of figure 4.10 are variables which are dependent on the parameter values of the model. On the other hand, some of these parameters are dependent on the values of the pressures and flows. Thus, the system is inherently a nonlinear one. In order to adequately simulate the dynamic activity, for example of the rhythmically active vessel, the pre capillary sphincter activity, the parametric control, and the mutual interaction of these with the hemodynamic variables, it is necessary to have a solution method which accounts for such interaction. For example, the venomotion process depends on the contraction and subsequent relaxation of vascular smooth muscle. The contraction process will alter a number of vessel parameters and in so doing will alter the hemodynamics which depend

on these now altered parameters. The model parameters which affect the hemodynamics are $R'(t)$ and $C'(t)$. These in turn depend principally on the vessel radius, wall thickness and the material properties of the vessel. Each of these may change as a result of the altered contractile state. The amount by which these quantities change depends, however, not just on the contraction per se. Indeed, the pressure gradient across the vessel wall may be an important factor. This pressure being a hemodynamic variable will change as the contractile state is changed. Thus, the actual parameter values associated with the contraction process at any instant are, in fact, those which simultaneously satisfy the model hemodynamic equations (equations 4.20 through 4.30) and the parametric equations which characterize the rhythmically active vessel wall dynamics (equation 4.7), the parametric relation between tissue pressure and osmotic factors (equation 4.29), and the local control of pre capillary sphincter activity (equation 4.26).

In figure 4.11 is shown in diagrammatic form the analytical method utilized to solve this system of equations which we shall refer to as the simulation. This diagram will be explained below in section 2. A combination of analog and digital computing methods was utilized. The simulation was thus run on a hybrid computer consisting of an IBM 1800 digital computer coupled to an Applied Dynamics Four analog computer. The choice of a hybrid simulation rather than a pure digital or a pure analog simulation allowed the advantageous features of each to be utilized. Thus,

the efficiency with which the analog computer handles multiple differential equations could be combined with the logic and control features of the digital computer. Computer running time is thus minimized, and operator-machine interplay is optimized. It should be emphasized, however, that a pure digital simulation with presently available systems is entirely feasible, and in view of the relative scarcity of hybrid computer installations may be the approach for future simulations.

2. Technical Details of Simulation

Referring to figure 4.11, the block marked I represents the uncontrolled Microvascular Model depicted in figure 4.10 and characterized by equations 4.30 through 4.40. These equations are programmed on the analog computer. The value of each parameter in block I is controlled by inputs from the digital computer. As shown in the figure, there are two kinds of parameters: those which are variable (which do depend on instantaneous variable values) and those which are constant (in the sense that they do not depend on other variables or parameters). The manner in which these parameters are obtained and used in the simulation processes is as follows. The output variables of block I are the set of flows (Q_j) and pressures (P_j) obtained by solution of equations 4.30 through 4.40. The pressures P_j , together with wall elastic modulus E , viscous coefficient K_η , perivascular pressure P_0 , and the active muscle stress σ_m , serve as input quantities for the solution of equation 4.7 (block II), which results in output values for the instantaneous vessel radius a and vessel wall thickness ratio γ . These quantities

then serve as the input variables to block V from which the instantaneous values of active vessel resistance and compliance are calculated via equations 4.1 and 4.2. In addition, the rate of change of compliance is calculated. One of the P_j 's is the tissue pressure P_T , which serves as an input variable to both blocks III and IV. In block III the value of the osmotic pressure difference as it depends on tissue pressure via equation 4.29 is determined. In block IV the tissue pressure together with the lower (P_{tl}) and upper (P_{th}) tissue pressure thresholds and rate of change of vessel radius (M) serve as input quantities for the solution of equation 4.26, which produces as outputs the terminal arteriole instantaneous diameter (D_{ta}) and diameter to red cell ratio (v_{ta}). These two outputs then serve as inputs to block VII for the calculation of the terminal arterial resistance as a time function.

All output quantities thus obtained are then subject to an analog to digital conversion and are stored in memory of the digital computer along with the remaining preprogrammed parameters of the model. The digital control portion of the digital computer then increments the variable parameters of block I in accordance with the previously determined instantaneous values $R'(t)$, $C'(t)$, R_{ta} , and $\Delta\pi$. The simulation thus effects the simultaneous solution of the pertinent equations and regularly updates the variable parameters.

3. Implementation

All differential equations are programmed on the analog part of the computer in standard fashion and initialized prior

to program run. The active muscle contraction associated with the rhythmically active vessel and the diameter variation of the pre capillary sphincter are simulated by trapezoidal functions generated in the analog part, with plateau values and rates of rise and decay digitally controlled in accordance with in vivo values (see appendix B).

After an initialization process parameter variation is effected by first entering the digitally converted signals into the digital computer. The initial values entered correspond to those for zero active muscle stress and a terminal arteriole diameter equal to the average of its minimum-maximum range. Activation of the simulated muscle contraction and diameter variation then results in variation of both hemodynamic variables and parameters in the analog part of the simulation. The changing values of those quantities on which the model parameters depend are entered into the digital part of the machine, which then computes new values for the variable parameters in the analog simulation. The actual change in parameter values is achieved by altering the settings of so-called "digital control units" (DCU) in accordance with the control signals from the digital computer. The timing commands which allow the newly calculated parameter values to be entered into the analog part occur every 10 msec. Thus, every 10 msec the parameters are updated to reflect the composite solution obtained in the previous 10 msec. The choice of this sampling rate is used because the digital computer computation takes about 2 msec between sample

pulses. During this time, the integrators in the analog computer must be set in a hold mode. Thus, the sampling rate is limited by the machine design but is more than adequate for the simulation.

For realizing the time decay, δ , the signals which have to be delayed [$C'(t)$, $R'(t)$, $\dot{C}'(t)$, $Q_b(t)$, and γ] are sampled from the analog computer and stored in the digital memory. Starting with a constant sample frequency, the desired time delay is translated into a number (N) of array elements which then has to be shifted to get the values corresponding to the desired delay. The length of the array is determined by the number of vessel segments used, the desired time delay per segment, and the sample frequency. For the five segment rhythmically active vessel model, model N is five. The number of array places per array element depends on the number of variables which are to be delayed. For 5 variables, the total array length is thus $25N$. When the sampled values are stored in the array element j these values are directly set in the DCU's of the first section of the analog model. Then the values of the array elements $(j-N)$, $(j-2N)$, $(j-3N)$, and $(j-4N)$ are set into the DCU's of, respectively, the second, third, fourth, and fifth sections. The various circuit diagrams and detailed programming aspects have recently been extensively documented (Mäy, 1973).