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Dispersion of Indicator in the Circulation*

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One of the first physicians to take an interest in the characteristics of flow in blood vessels was Poiseuille. His careful observations on the pressure-flow relationships for a viscous fluid passing through smooth cylindrical tubes led him to formulate empirically the equation:

$$Q=\frac{\pi R^4(P_1-P_2)}{8\eta L} \qquad \text{(equation 1)}$$

where Q = flow (ml/sec), R = radius (cm), P_1 and P_2 = (dynes/cm^2) at the beginning and end of the tube, respectively, η = viscosity (poise), and L = tube length (cm). The same equation can be derived from the Navier-Stokes equation by neglecting gravity and inertial effects, that is, by considering only the pressure difference and viscosity. This equation is only applicable when flow is “laminar” or “parabolic,” and this means only when there is absolutely steady flow of a Newtonian fluid.

Despite these severe restrictions, physicians and physiologists have tended to think of blood flow in similar terms. This view is obviously inadequate when applied to blood, a mixture of plasma and cells, being forced by a single-stroke pump, the heart, along arteries which are curved, elastic, tapering tubes with many branches. It is ridiculous to consider parabolic flow in capillaries because an erythrocyte often must bulge a capillary, like a mouse swallowed by a snake, in order to pass through. Flow within the great veins is also somewhat pulsatile.

The empirical model to be presented has its raison d'etre in the fact that it provides a good description of recorded indicator dilution curves and also of the transfer function of certain segments of the human circulation. This model, the lagged normal density curve, is stochastic, as all of the more useful models have been.[1,2] Its use as a transfer function illustrates how simple operational concepts, so familiar to engineers, can be applied to the circulation. It is hoped that similar methods may be used for the description of movement of drugs, hormones, or foodstuffs between any two points in the bloodstream. It may be possible to extend these methods to describe the movement of such substances from the bloodstream into the tissues where most of the body's chemical reactions take place.

Review of Indicator Dilution Theory

After an indicator dye is injected into the great veins or the heart, the resultant dye-blood mixture is sampled, either continuously or at frequent intervals, at some point downstream. The concentration-time curve (Figure 1) obtained will show an initial delay before the first dye particles reach the sampling site, then the concentration rises to a maximum, diminishes

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to a minimum, and again rises as dye recirculates to pass the sampling point a second time. In order to calculate the flow through the heart, where the dye has mixed with the blood, the area under that portion of the curve representing dye passing for the first time must be calculated. To exclude the recirculated indicator, the downslope of the curve is approximated by a single exponential line, which is extrapolated toward the base line. In systems in which there is no recirculation, this has been shown to approximate the primary curve quite well. Flow is calculated from the equation:

$$\text{Flow} = \frac{\text{amount of dye injected}}{\text{area of curve}} \qquad \text{(equation 2)}$$

One may also determine the average time for the indicator to pass from the injection site to the sampling site. This is done by calculating the first moment of the curve from the formula:

$$\text{Mean transit time} = \bar{t} = \frac{\int_0^\infty C(t) \cdot t \cdot dt}{\int_0^\infty C(t)\, dt} \qquad \text{(equation 3)}$$

If the distance between the points is known, then the average velocity may be found. The volume of fluid between the two points may be estimated by the formula, volume = flow × $\bar{t}$. If the two points are on a straight tube or if the injection and sampling points are situated so that all of the flow passes each, then the volume estimated is realistic. The indicator dilution method has been most important in the elucidation of abnormal routes of flow in patients with congenital and acquired heart disease, but I will not discuss this.

Mathematical Models

One needs no model to use indicator dilution curves for the measurement of cardiac output and mean transit times. These are estimated directly from simple measurements on the raw data. A model may be used in two ways: 1) to provide a concept of physicobiologic events; and 2) to provide simplicity of description of the observations. The best models do both.

Of previously considered models for the circulation, the random walk equation proposed and tested by C. W. Sheppard[1] is the most pleasing esthetically. Another model, distinctly less useful, is the log normal curve described by Stow and Hetzel.[2] Both of these models can be fitted to indicator dilution curves of the shape shown (Figure 1). The parabolic flow model can be rejected immediately. If the injected dye labelled a thin cross section of the bloodstream, then flow of the Poiseuille type should produce curves in which the dye appears in exactly one-half the mean transit time, rises immediately to the maximal concentration, and then disappears in inverse proportion to the square of the time from the injection. This obviously is not the case.

The Lagged Normal Density Curve

I propose a model composed of two processes: 1) a random dispersion of indicator about some average point in the flowing blood; and 2) a superimposed single exponential washout (Figure 2). This results in a skewed Gaussian distribution, the equation for which is:

$$C(t)=\frac{I/Q}{\sigma\sqrt{2\pi}}e^{-1/2\left(\frac{(t-t_c)}{\sigma}\right)^2}-\tau\frac{dC(t)}{dt} \quad \text{(equation 4)}$$

where: t = time; C = concentration of the indicator in the blood; I = amount of indicator injected; Q = flow at the site of mixing with the circulation; σ = standard deviation of the Gaussian distribution; t_c = centroid or median time of the Gaussian distribution; τ = time constant of the exponential; and e = base of natural logarithms. This model can be used to describe the shape of indicator dilution curves. It also can be used to describe the transfer function between points in the circulation, which is much more useful.[3] Under certain circumstances, one can calculate the velocity profile in a tube from the transfer function.

The Model as a Description of Recorded Indicator Dilution Curves

Consider the application of the model to the description of the recorded indicator dilution curve. Figure 3 shows indicator dilution curves recorded at the femoral and dorsalis pedis arteries of normal men after the injection of dye into the superior vena cava. In each panel, the recorded curves (open circles) have been fitted with the equation of our model (solid line), and it is apparent that a good match can be obtained. These curves are rather broad and prolonged because the dye has passed from the great veins, through the right heart, lungs, left heart, and out to the aorta before coming to the sampling site. The rapid injection of the dye causes some initial dispersion of dye in the blood at the injection site. Furthermore, the sampling system, which consists of a needle, tubing, and densitometer, causes additional slurring of the curve from what it is in the artery. All of these slurring features of the experiment result in low-frequency curves which are relatively easy to fit with our simple equation.

Curves recorded after injection into the aorta, low in the thorax, are shown in Figure 4. Although there was dispersion at the injection site and through the sampling system, the circulatory dispersion is much diminished by the proximity of the injection and sampling sites, and therefore the curves have much more rapid time components. The fits obtained are not quite as good (average coefficient of variation for these was .067, as compared with .047 for the curves recorded after injection into the superior vena cava), but still can be considered to be reasonable. In some of the examples shown (Figure 4), it appears that the curves are not fitted well in the lower part of the downslope, which might suggest that the model is unsatisfactory. On the other hand, the errors due to the injection and the sampling have a greater effect on the shape of the curve in this region.

When two injections are made a few seconds apart into the same site in the lower part of the aorta (Figure 5), the curves recorded at the femoral artery have a double peak, while those recorded at the dorsalis pedis artery are more slurred out and even may fail to show two distinct peaks. Such curves still can be matched by the model. To do this, two models are generated using the same parameters for the equation, except that the t_c for the second one is greater by the duration of the period between the injections. The amplitude of the two components is in proportion to the amount of dye given in each injection. Again, the model matches the recorded curves rather well and accounts for the loss of the distinctiveness of the two peaks as the dye becomes more dispersed in traversing the segment of artery through the leg.

The Model as a Transfer Function

The successful matching of recorded indicator dilution curves with the model does not prove its adequacy in describing dispersion in the circulation because of the aforementioned

additional dispersion due to the injection and to the sampling system. Two methods have been used to arrive at a method of describing more clearly the circulatory dispersion only.

The first of these utilized the lagged normal density curve as the parametric model. Dilution curves were recorded simultaneously at the femoral and dorsalis pedis arteries of normal men after single and double injections of dye into the central circulation (Figure 6). The sampling systems were made as nearly identical as was practicable. If sampling at a given site produces no disturbance in flow at that site and if the arterial segment between these two sites can be considered as a mathematically linear system, then the dispersion of indicator between these two sites is described by the transfer function of the segment. In such a case, the form of the input should not matter and, if physiologic conditions are constant, then the same transfer function should be obtained from the low-frequency curves recorded after injection into the superior vena cava as from the high-frequency curves recorded after injection into the aorta.

To ascertain the transfer function, the femoral (upstream) curve was considered to be the input to the segment and the dorsalis pedis curve to be the output. For trial purposes, a transfer function having the form of our model, the lagged normal density curve, is assumed. Then the convolution of the femoral curve with the assumed transfer function is calculated to produce a trial output curve. This trial output curve is compared with the recorded dorsalis pedis curve, the trial parameters are adjusted automatically by the computer, and the process is repeated until the theoretical and recorded output curves are very similar.

$$\text{The convolution integral, } g(t)=\int_0^t f(t-\lambda)h(\lambda)d\lambda \qquad \text{(equation 5)}$$

in which g(t) is the output function, f(t) is the input function, h(t) is the transfer function, and λ is a dummy variable of integration, may be calculated numerically by:

$$g_n=\sum_{i=1}^{i=n} f_i h_{(n-i+1)} \qquad \text{(equation 6)}$$

Representative results are shown in Figure 7.

The linearity of the arterial segment at a constant rate of flow of blood was tested in the following manner. Curves were recorded at the two sampling sites after injection of dye into the aorta. Less than one minute later, two doses of dye were injected, about four seconds apart, into the aorta and curves were recorded at the downstream sampling sites. If the physiologic situation remains constant, the transfer function also should remain constant. Figure 8 shows the results obtained with a normal rate of flow of blood through the limb. The transfer functions are slightly different for the two input forms, but the physiologic conditions were unsteady, as shown by the difference of 1.0 second in mean transit times. It generally was found that flow in the limb and transit time varied continuously under normal circumstances. However, when the flow was increased by the infusion of adenosine triphosphate, the transfer function obtained was the same following single or double injection (Figure 9). This strongly suggests that the arterial segment can be treated as a linear system, but that, under normal circumstances, conditions are not sufficiently steady to allow a conclusive test.

A second method of computing the transfer function of the arterial segment is to perform the calculation in the frequency domain:

$$H(s)=G(s)/F(s) \qquad \text{(equation 7)}$$

where F(s), G(s), and H(s) are the LaPlace and Fourier integral transforms of f(t), g(t), and h(t), respectively.

LaPlace transforms are not available for indicator dilution curves or for the lagged normal density curve, but the calculation can be performed in the time domain by rearranging equation 6 to give h(t) in the recursive form:

$$h_n=\frac{g_n-\sum_{i=1}^{i=n-1} f_{(n-i+1)}h_i}{f_1} \qquad \text{(equation 8)}$$

The transfer function calculated in this manner is in numerical terms and no model is needed for the description. This is an application of the approach suggested by Stephenson,[4] but it is not wholly satisfactory because of a tendency for the solution to oscillate if f_1 is small, if the curve is noisy, or if the time intervals between readings are not sufficiently small. The same method is useful for the correction of recorded curves for distortion due to the sampling system when the transfer function of the sampling system is known. This is determined by finding the derivative of the sampling system response to a step change in dye concentration at the input end.

A similar frequency domain method is now being used by Dr. Homer Warner.[5] He approximates the Fourier integral transform of f(t) and g(t) by a limited Fourier series and then divides, as in equation 7, to obtain h(t) also as a limited Fourier series. This solution also may oscillate, but the tendency can be minimized by calculating the Fourier series with a number of coefficients that are equal to, or an integer multiple or simple fraction (1/2, 1/3) of the number of data points.

Uses of the Transfer Function

Once the transfer function describing flow through a segment of the circulation is obtained, there are several uses to which it may be put. One use might be comparison of the transfer functions through the heart and lungs of normal subjects and of patients with valvular regurgitation. One would expect that the increased chamber volumes and the to-and-fro movement of the regurgitated blood would increase the dispersion. The data shown here demonstrate that dispersion is linearly proportional to mean transit time. If, in valvular regurgitation, there is a disproportionate increase in dispersion relative to mean transit time, this would allow differentiation between patients with regurgitation and those with large cardiac volumes secondary to other causes. The prerequisite for this type of analysis is constant proportionality (stationarity) of distribution of flow* through pathways in parallel; this may not be applicable to turbulent flow through the heart.

Another use is the calculation of the velocity profile. The method is illustrated in Figure 10 and requires certain assumptions. The assumptions are: that the artery is a cylinder of unit

*This is a generalization of the concept of stationarity as defined by Meier and Zierler.[6]

radius, that flow occurs as concentric cylindrical laminae of constant velocity, and that the velocity is highest in the center and diminishes toward the wall. Velocities relative to the mean velocity in the tube can be calculated for each lamina using the equations given in the figure. If flow were laminar, the transfer function would be the curve of the left upper panel in Figure 10. By approximating the curve with a histogram, each bar of which has a specific average transit time, the shaded profile in the left lower panel can be obtained. If the interval for each bar is sufficiently short, a smooth curve will result. A similar calculation is shown in the right panels for a nonparabolic transfer function. The velocity profiles in the arteries of the legs of two subjects are shown in Figure 11, and it is apparent that they do not represent parabolic flow. The fact that these profiles are similar to each other, in spite of wide differences in mean velocity, is strong evidence that there is constant proportionality (stationarity) of distribution of flow in the artery between the sampling points.

An extension of these methods to descriptions of the movement of indicator from an artery to a vein of an organ is certainly practical[7] and invites comparison with the description of transport of a diffusible indicator which rests momentarily in the tissue outside of the vascular system.[8] Such an approach has been used effectively by Goresky[9] in the elucidation of trans-sinusoidal exchanges in the liver.

Since linear equations are apparently applicable to the circulation when flow is constant, one may take advantage of this fact to measure regional blood flows. The example given by Nicholes, Warner and Wood[10] involved measuring the time-concentration curves of indicator in the superior vena cava, inferior vena cava, coronary sinus, and pulmonary artery. Knowing the transfer functions from the first three sites to the pulmonary artery, one can convolute these inputs with their respective transfer functions and then sum them with weighting factors on each, adjusting the weighting factors until the summation is the same as the recorded pulmonary artery curve. The weighting factors then represent the fraction of flow coming from each of the three inflows. This method has been used with some success in calculating flow in the coronary sinus.

Summary

A three-parameter equation, the lagged normal density curve, has been found to fit recorded indicator dilution curves, and is even better suited to the description of the transfer function in a segment of the circulation between two arterial sampling sites. From tests of the constancy of the transfer function when different forms of indicator dilution curves were recorded from the femoral and dorsalis pedis arteries, it was concluded that, when the flow is steady, the femoral artery segment probably can be considered to be a linear system.

An “average” velocity profile, ignoring the variations in flow profile during the cardiac cycle, has been calculated from the transfer function. It was found to be quite different from the parabolic flow profile. The lack of wide variation in the calculated velocity profiles is consistent with the concept of constant proportionality (stationarity) of distribution of flow through the artery even when the absolute flow rates vary greatly.

Acknowledgments

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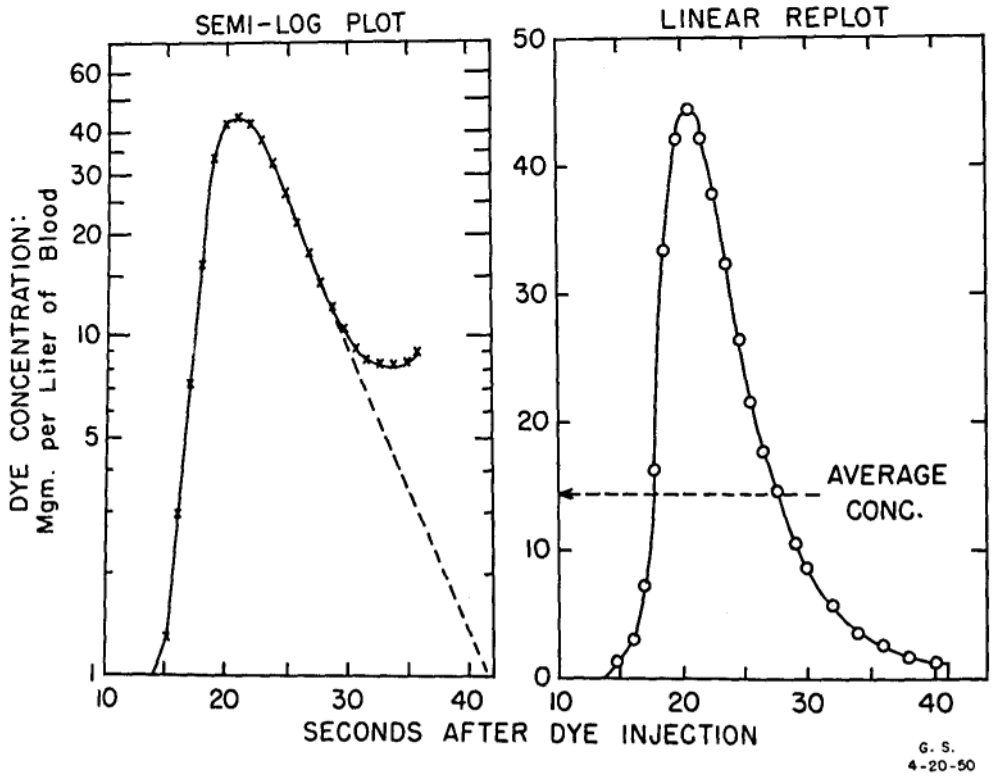

Figure 1.
Indicator dilution curves in the circulation. Left panel: Concentration plotted on semilog scale so that downslope could be approximated by a single exponential line and extrapolated to exclude recirculated indicator. Right panel: Linear replot of primary curve.

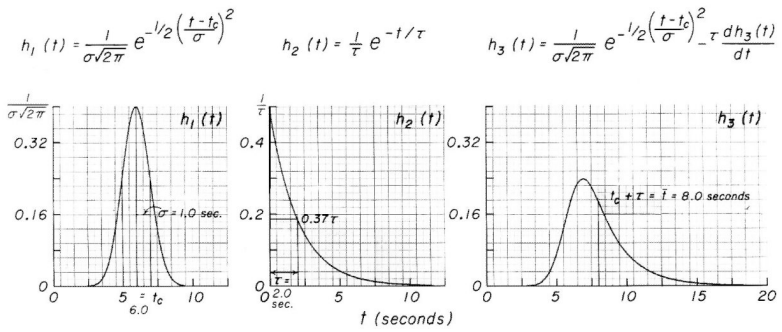

Figure 2.

Model for indicator dilution curves. Left panel: Gaussian distribution, or normal density curve. Middle panel: Single exponential. Right panel: Lagged normal density curve, which is the convolution of h_1 and h_2.

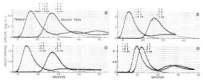

Figure 3.
Lagged normal density curves fitted to experimental curves recorded after injection of dye into the superior vena cava. Each panel consists of the curves recorded (open circles) from the femoral artery and the dorsalis pedis artery of normal men. The parameters, σ, τ, and t_c, of each model curve (solid line) and the coefficient of variation of the fit are given in the upper part of each panel.

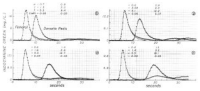

Figure 4.
Lagged normal density curves fitted to experimental curves recorded after injection of dye into the thoracic part of the aorta.

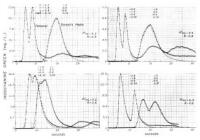

Figure 5.
Lagged normal density curves fitted to experimental curves recorded after two injections into the aorta a few seconds apart. $\Delta t_{Inj.}$ = time (seconds) between the two injections. R = ratio of volume of second injection to volume of first injection.

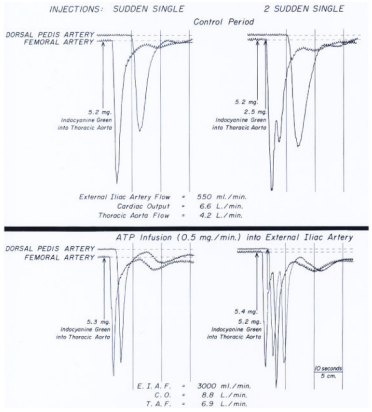

Figure 6.

Indicator dilution curves recorded at the femoral and dorsalis pedis arteries after injections of dye into the thoracic aorta. Top panel: At low rate of flow of blood in the limb, there is considerable slurring. The double peak recorded at the femoral artery (right upper panel) became so slurred that a single peak was recorded at the dorsalis pedis artery. Bottom panel: When the rate of flow of blood through the limb is high, because of infusion of adenosine triphosphate (ATP), there is little distortion of the peak.

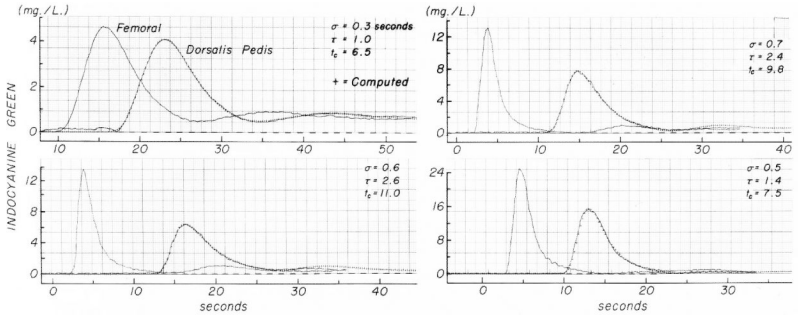

Figure 7.

Description of the dispersion process in an arterial segment by a lagged normal density curve. Each femoral curve has been convoluted with a lagged normal density curve having the three parameters listed. The result of the convolution is represented by the points superimposed on the recorded dorsalis pedis curve (continuous line).

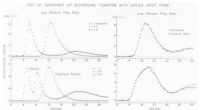

Figure 8.

Test of constancy of the transfer function at normal femoral flow rate. Left panels show curves recorded from femoral artery and calculated transfer function. Right panels show curves recorded at dorsalis pedis artery and computed output curve (upper panels, single injection; lower panels, double injection). The mean transit time ($\tau + t_c$) after the single injection was 14.5 seconds and after the double injection, 13.5 seconds. Because of the inconstancy of the mean transit time, this is not a valid test of linearity.

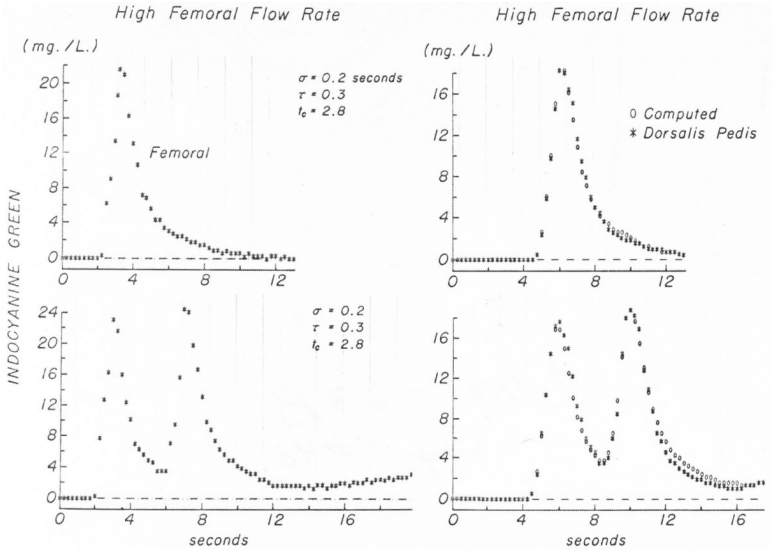

Figure 9.

Test of constancy of the transfer function at increased femoral flow rate (produced by infusion of adenosine triphosphate into the common iliac artery at a rate of 1.0 mg/min). Panels as in Figure 8. In this case the mean transit time remained constant. The transfer function is the same for the two forms of curves and is an indication that the arterial segment may be considered to behave as a linear system.

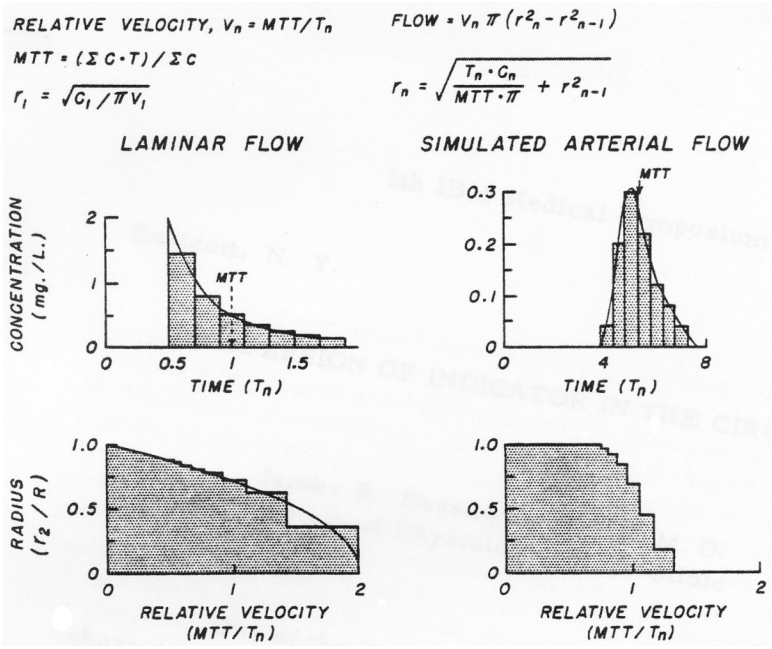

Figure 10.

Calculation of velocity profile. If the time interval used is sufficiently small, the calculation will result in relatively smooth profiles compared to those illustrated in the lower panels. All times are plotted and calculated relative to the mean transit time, MTT.

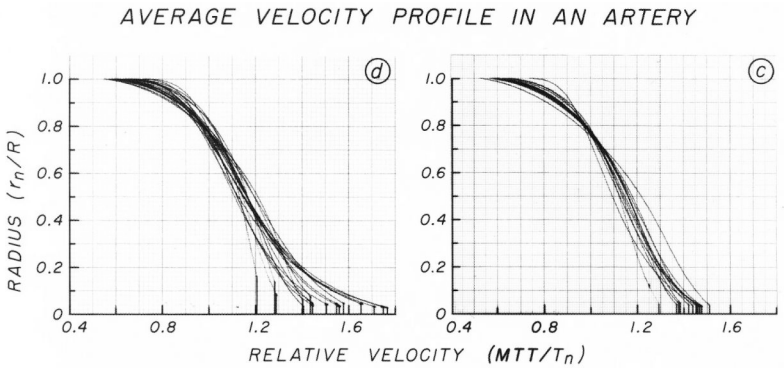

Figure 11.

Average profiles calculated for the arterial system of the legs of two normal subjects. There are 18 profiles for one subject (left panel) and 12 for the other (right panel); each profile was calculated from the transfer function between the femoral artery and the dorsalis pedis artery.