Evaluation of the Early Extraction Method of Determining Capillary Permeability by Theoretical Capillary and Organ Models

By David G. Levitt, M.D., Ph.D.

ABSTRACT
The early extraction method of measuring capillary permeability was evaluated with theoretical models of capillaries and organs. The organs consisted of feeder lines and a capillary bed that was either homogeneous or heterogeneous with respect to capillary length or flow. The capillary permeability of the model organ determined by the early extraction method was compared with the actual permeability of the capillaries from which the organ was constructed. The main results of this analysis are: (1) If all the capillaries are identical and if the extravascular volume of distribution of the diffusible indicator is at least three times as large as the capillary volume, then the early extraction method provides a satisfactory measure of the capillary permeability. (2) If the capillaries are identical but the extravascular volume is about the same size as the capillary volume, then the early extraction method can lead to a qualitative underestimate of the permeability, namely assigning a significant diffusion limitation to a substance which is actually flow limited. (3) If the capillaries are not identical, either through differences of flow or length, then the early extraction method can again lead to the assignment of a significant diffusion limitation to a substance which is actually flow limited.

ADDITIONAL KEY WORDS

indicator dispersion

capillary heterogeneity

The purpose of this paper is to develop a model that can be used to describe the early organ washout curves of a diffusible substance and to use this model to evaluate the experimental method of measuring capillary permeability based on the early extraction value (Eo method). In the Eo method, first used by Crone (1) and Martin and Yudilevich (2), a substance assumed not to diffuse across the capillary wall (nondiffusible) and a diffusible tracer substance are injected simultaneously into the artery, and the relative concentration of the diffusible to the nondiffusible indicator (C_{diff}/C_{nondiff}) in the venous effluent is measured. The extraction at time t is defined by $E(t) = 1 - [C_{diff}(t)/C_{nondiff}(t)]$. It can be shown that for a single capillary (under certain assumptions, see below) the following relationship holds:

$$E_o = 1 - e^{-PS/F}$$

where $E_o$ is the value of $E$ at the time of the first appearance of the nondiffusible indicator, $P$ is the capillary permeability (per unit area), $S$ is the capillary surface area, and $F$ is the rate of capillary blood flow. The method of Yudilevich and others consists of extrapolating $E(t)$ for the entire organ back to the appearance time of the nondiffusible indicator to determine $E_o$ for the organ and calculating $PS/F$ from equation 1. It is then assumed that this value of $PS/F$ is representative of the average capillary permeability of the organ.

There are several obvious difficulties with this method. First, even if all the capillaries are identical and satisfy equation 1, it is difficult to measure the venous concentration ratio for the first appearance of the tracer. Equation 1 assumes that there is no backflow from the extravascular to vascular space and therefore the measurement must be made.
early enough so that backflow is insignificant. Qualitatively, it is clear that the smaller the extravascular space, the sooner backflow will become important. At least two experimental factors limit the accuracy of the measurement of the early part of the curve. First, samples of at least 1-second duration are usually collected to obtain enough material to analyze, and therefore the outflow is averaged over at least 1 second. Also the very early outflow contains indicator at an extremely low (possibly undetectable) concentration, and therefore the analysis is less reliable. The usual experimental approach to this problem is to extrapolate the first three or four time periods back to the first appearance of the indicator to determine $E_n$. A second, and probably more important, difficulty with the $E_n$ method is the effect of any inhomogeneity in the capillary bed. Since the measurement of permeability depends entirely on the very early outflow, one is actually measuring the permeability of those capillaries which have the shortest transit time. In general, one would expect that the capillaries with the shortest transit time would have $PS/F$ values smaller than average, since they would tend to have higher flows and smaller volumes (surface areas). In the extreme case of a shunt, the first appearance of the indicator would have a $PS/F$ of zero, and thus even a very small shunt could completely invalidate the method.

In this paper, an attempt is made to quantify these two sources of error. To evaluate the importance of backflow, a model of the capillary will be presented for which equation 1 is satisfied exactly. Then a model of the organ will be constructed in which all the capillaries are assumed to be identical and the pre- and postcapillary feeder lines produce a dispersion of the indicator similar to what is actually observed in the dog heart. The validity of the experimental extrapolation procedure will then be tested by comparing the actual permeability of the capillaries from which the organ is constructed with the permeability determined by the $E_n$ method. Also, to examine the effect of capillary heterogeneity, an organ will be constructed in which the capillaries vary either in length or in flow rate and the actual permeability again compared with permeability determined by the $E_n$ method.

The capillary model used in this analysis is especially significant because it will be shown that it is an "ideal" model with respect to the $E_n$ method. That is, if any other reasonable capillary model is used in the organ in place of this ideal model, the permeability calculated by the $E_n$ method will deviate more from the actual permeability than if the ideal capillary model were used. This implies that for those organ models made up of ideal capillaries in which the $E_n$ method is not valid, it will also be invalid if that organ is made up of any other reasonable capillary model.

1. Single Capillary Model

This model was first used by Sangren and Sheppard (3). It is assumed that (a) the capillaries are uniform cylinders, and flow through the capillary is block flow; (b) radial diffusion in both the tissue and capillary space is assumed to be infinitely rapid, while axial diffusion in both spaces is zero; (c) there is no exchange between capillary units. The differential equation for the concentration of material in the capillary ($C_p$) and tissue ($C_T$) is:

**Capillary:**
\[ -F \frac{\partial C_p}{\partial t} - 2\pi r P (C_p - C_T) = A_c \frac{\partial C_p}{\partial t} \]  

**Tissue:**
\[ 2\pi r P (C_p - C_T) = A_T \frac{\partial C_T}{\partial t} \]

where $A_c = \text{cross-sectional area of the capillary}$, $r = \text{radius of capillary}$, $A_T = \text{cross-sectional area of tissue (extravascular) space}$, $F = \text{blood flow rate}$, and $P = \text{permeability (per unit area)}$. Sangren and Sheppard solved these equations for a "delta input" (unit impulse). The solution for the concentration leaving a capillary of length $L$ after a step input is (see ref. 4, p. 393):

\[ C_p(L,t) = 1 - \left[ e^{-\frac{t}{t'}} \int_0^{t/t'} e^{-\sigma} I_0(2\sqrt{\alpha \sigma}) d\alpha \right], \]  

where
\[ t' = \frac{2\pi r P}{A_T} \left( t - \frac{A_c L}{F} \right). \]
and  is the zero order modified Bessel function. It can be shown that for \( t = \frac{A_c L}{F} \) (the appearance time of the nondiffusable indicator) \( \frac{C_{att}}{C_{nonatt}} = e^{-PS/F} \) and therefore this capillary model satisfies equation 1 exactly. Values for the function in brackets in equation 3 have been tabulated by Brinkley (5). A square-wave input will be used as an approximation to the short arterial injection which is used experimentally. The solution for a square-wave input of duration \( T \) can be obtained simply by adding the solution for two step inputs of opposite sign separated by an interval \( T \).

It can be shown that if \( t \) is expressed in units of \( \frac{A_c L}{F} \) (the traversal time for the nondiffusable indicator), then the shape of the venous outflow curve becomes a function of two parameters: \( PS/F \), the permeability to flow ratio, and \( A_c/A_T \), the ratio of the capillary to tissue area. Figures 1 through 3 show the capillary outflow concentration curves for values of \( A_c/A_T \), of 1.0, 0.33, and 0.1 and for values of \( PS/F \) varying from 0.7 to 4.0 for a square-wave input of height = 1 and a duration \( t = 1 \) (in units of \( \frac{A_c L}{F} \)). This input shape is chosen because it simplifies the calculations and the presentation of the results and it is a rough approximation of the experimental input. Since the permeability measurement is based only on the very early outflow and all results are normalized by the nondiffusable indicator, the general results of
this analysis do not depend on the particular input shape chosen. However, when actual organ outflow curves are used (see below) it must be assumed that this input approximates the experimental input. As can be seen in Figures 1 through 3, the nondiffusible indicator (shown by the dotted lines) travels through the capillary without any change in shape and therefore leaves the capillary with the same shape as the input. Its appearance time, that is, the delay in traveling through the capillary, is equal to one capillary traversal time.

For values of $PS/F$ of 2.0 or less, the curves can be roughly described as an initial peak, which has the same appearance time as the nondiffusible indicator, followed by a relatively smaller tail due to back diffusion from the tissue to the capillary. However, for $PS/F$ of 4.0 or larger, this description is no longer applicable because most of the diffusible solute outflow is now in the tail region. Figure 4 illustrates the capillary outflow curves as $PS/F$ varies from 5.0 to 500 for an $A_c/A_T$ of 0.1. It can be seen that as $PS/F$ increases beyond 5.0, the peak becomes shifted to a point at about $t = 11.5$ (in units of $A_c L/F$) and the peak concentration becomes higher with increasing values of $PS/F$. As $PS/F$ approaches infinity, this capillary model be-
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comes identical with the completely flow-limited model used by Goresky (6) to describe results in the dog liver. The outflow curve for an infinite permeability (flow limited) is indicated in Figure 4 by the dotted line. It may be surprising that even for a value of PS/F as large as 500, the outflow curve of a single capillary still has a significantly different shape than that of the completely flow-limited capillary.

The curves in Figure 4 are plotted as a function of the number of capillary passage times \( A_eL/F \). To plot the curves as functions of cumulative flow \( (Ft) \) instead of time, the abscissa in Figure 4 is simply multiplied by \( F \). The curves still have the same shape, but now the abscissa is in units of \( A_eL \) (the capillary volume), which is independent of flow. A flow-limited substance is one for which the outflow concentration curve plotted as a function of cumulative flow \( (Ft) \) is independent of flow rate \( (F) \). Applying this definition to the curves in Figure 4 would imply that with this model the outflow curve for a substance with a value of PS/F as large as 500 could still be distinguished from the flow-limited case \( (PS/F = \text{infinity}) \). However, an \( E_0 \) of 0.99 \( (PS/F = 4.5) \) could not be distinguished experimentally from a substance which was completely flow limited \( (E_0 = 1) \) by the \( E_0 \) method. Therefore, one experimental limitation of the \( E_0 \) method is its inability to distinguish different values of permeability once they become greater than 5. This example is interesting because, as is shown in Figure 4, although the outflow curve for a

FIGURE 3
Outflow curve of a model capillary with \( PS/F = 4.0 \).

\[
\frac{PS}{F} = 4.0
\]

\[
\text{Non-Diffusible}
\]

\[
\frac{A_e}{A_i} = 0.1
\]

\[
\frac{A_e}{A_i} = 0.33
\]

\[
\frac{A_e}{A_i} = 1.0
\]

\[
\text{Time (in units of capillary traversal time: } A_eL/F)
\]

\[
\text{Concentration}
\]
$PS/F$ of 5 is markedly different from that for a $PS/F$ of infinity, the actual capillary clearances differ by only 1%, and therefore this difference is not significant for the organ itself.

It is useful to make some very rough calculations of the range of validity of this capillary model. To simplify the calculations, the cylindrical tissue space of thickness $R$ will be replaced by a rectangular slab of the same thickness. Probably the most stringent requirement of the model arises from the fact that it is assumed that diffusion in the radial direction (perpendicular to the capillary) is very fast relative to the rate of capillary flow. If the concentration just outside the capillary is suddenly raised from zero to a fixed concentration, the rise in concentration at the outer edge of the tissue produced by diffusion can be determined. If, as an approximate fit to the model, it is required that the concentration at the outer edge reaches a concentration equal to 90% of that at the capillary edge in a period of time less than 10% of the capillary transit time, the following relationship can be derived (ref. 4, p. 101):

$$DT/R^2 > 10,$$

where $T = A_c L/F$ is the capillary passage time and where $D$ is the diffusion coefficient in the tissue and will be assumed to be $10^{-5}$ cm$^2$/sec. If, as a reasonable set of values for cardiac muscle, it is assumed that the blood...
flow equals 1.2 ml/g/min and the capillary volume is 2% of the heart weight. It follows that \( T = 1 \) second. With these assumptions, it follows from equation 4 that \( R \), the thickness of the tissue, should be less than 10 \( \mu \) or the intercapillary distance should be less than 20 \( \mu \).

Another requirement of the model is that diffusion in the axial direction is slow compared to the capillary flow rate. If the tissue concentration at the entrance to the capillary is suddenly raised from zero to a fixed value, the rate of axial diffusion through the tissue can be determined. It can be shown that if the concentration reached in the tissue at a point 0.2 \( L \) from the entrance due to diffusion is to be less than 5% of the fixed concentration at the entrance in the time it takes the blood to travel this distance (0.2 \( L \)), the following relationship must be satisfied (ref. 4, p. 101):

\[
DT/L^2 < 0.001, \tag{5}
\]

where \( L \) = capillary length. For a capillary transit time of 1 second, the capillary length must be greater than 1 \( \text{mm} \). Most capillaries will approximately satisfy these requirements, within the rough limits of the calculation. A more detailed calculation is necessary to quantify the validity of this model. Furthermore, this model assumes that there is no exchange between neighboring capillary beds, and this error probably far exceeds the other errors. Also, this model is "ideal" for the \( E_0 \) method and, therefore, to the extent it is not satisfied by the actual tissue, the \( E_0 \) method will also be incorrect.

II. Evaluation of \( E_0 \) Method for Model Organs

To determine capillary permeability from the venous outflow curve of an entire organ requires detailed information about (1) the distribution of capillary flow rates, (2) pre- and postcapillary transit times, (3) the geometry and distribution of tracer within each capillary tissue unit, and (4) the kinetics of exchange of tracer between capillary units. However, even in the best of studies, all that is independently measured is the distribution of transit times for the nondiffusible and diffusible indicators. Therefore, as Zierler (7) has emphasized, the average capillary permeability cannot be unequivocally determined by the methods currently used.

All Capillaries Identical.—To evaluate the \( E_0 \) method it is necessary to construct the diffusible and nondiffusible organ outflow curves for the given organ model. It would be desirable if this could be done without making detailed assumptions about the distribution of flow rates, path length, and amount of indicator dispersion in different segments of the feeder lines. That is, if a given set of model capillaries is assumed, then the nondiffusible organ outflow curve contains all the information about the feeder lines that is needed to construct the corresponding diffusible outflow curve. It is shown in the appendix that this can be done only for the special case in which all the capillaries have identical outflow curves. Since, as was shown above, equation 1 is satisfied exactly by the model capillaries and if all the capillaries are identical, then it will be satisfied exactly by the model organ, and the \( E_0 \) method will be theoretically correct for this model. However, as was discussed early in this paper, there are some experimental difficulties in correctly measuring \( E_0 \). This special case, therefore, serves as a model to test the experimental procedure of extrapolating the first few collection periods back to the first appearance of tracer to determine \( E_0 \).

It can be seen from equation 3 that the requirement that all capillaries have outflow curves of the same shape implies that \( PS/F \) and \( \tau P/A_T \) (\( \tau_c = \) capillary radius) are the same for each capillary. It can easily be shown that

\[
2\pi\tau_P/F = \frac{PS}{F} \frac{A_c}{A_T}, \tag{6}
\]

and since \( PS/F \) and \( \tau_P/A_T \) are assumed to be the same for all capillaries, the capillary traversal time \( (A_c/L/F) \) and the ratio of capillary to tissue area \( (A_c/A_T) \) can vary

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1Personal communication from Dr. J. A. Johnson of this department. This value of 2% for the capillary volume is based on the early volume of distribution of \( ^{131} \)I albumin determined by tissue analysis of the perfused rabbit heart.

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Figure 5 shows a plot of the ratio of the concentration of the diffusible to the non-diffusible indicator in the venous outflow as a function of time $[1-E(t)]$ for a model organ made up of capillaries with an average $A_c/A_T$ curve and the model capillary outflow curve. This relationship is derived in the Appendix (equation 6A). The convolution was performed by approximating the curves by square waves of 1-second duration (see Appendix). This approximation results in an averaging of the outflow curves over a period of 1 second, which is probably as good as can be obtained with the actual experimental detection equipment. More rapid sampling would significantly affect only the first and second collection period and would not appreciably change the extrapolation based on the first three periods.

Figure 5 shows a comparison of the actual PS/F of the capillaries which make up the organ with the PS/F calculated by the $E_0$ method.
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The value of 0.33 was used because it corresponds to what is probably the minimum volume of distribution that would be expected for an extracellular tracer. If the extrapolation procedure is satisfactory for this value of $A_c/A_T$, it will be satisfactory for any smaller value.

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In this section, a quantitative calculation of the error in the Ea method for two special types of heterogeneity will be shown.

In the first type it will be assumed that PS, Ac, and At are the same for each capillary, but that F varies from capillary to capillary. A distribution of F which greatly simplifies the calculation will be considered, that is, \( n(F) = A/F \), where \( n(F) \) is the number of capillaries with flow \( F \) and where \( A \) is a constant. That is, the number of capillaries with flow \( F \) is inversely proportional to \( F \). The contribution of capillaries with flow \( F \) to the indicator in the total outflow of the capillary bed is equal to the product of the concentration leaving the capillaries \( [C(F,t)] \) times the flow of that capillary \( (F) \) times the number of capillaries having that flow \( (A/F) \). The total outflow can be written as the integral over all the capillary flows:

\[
F_{\text{total}} C_{\text{total}} = \int_{F_1}^{F_2} A \frac{1}{F} C(F,t) dF = A \int_{F_1}^{F_2} C(F,t) dF. \tag{9}
\]

Values of the function \( C(F,t) \) can be obtained directly from the solution for the single capillary, and the integration in equation 9 can then be performed graphically. It was assumed that there was a 10-fold range of flows, that is, \( F_m < F < 10 F_m \), where \( F_m \) is the minimum capillary flow and the average capillary traversal time was set equal to 1.0, the value used in the previous section. It turns out for this case that \( 0.4 < A_c L/F < 4.0 \).

Figure 8 shows the concentration leaving the whole capillary bed with this kind of heterogeneity as a function of time for the nondiffusible indicator and for a diffusible indicator with an average PS/F of 10 and infinity, and with \( A_c / A_F = 0.33 \). Since the
Outflow curve of heterogeneous capillary bed. Capillary flow varies over a 10-fold range in such a way that the capillary traversal time varies from 0.4 to 4.0 with an average of 1.0. For the curve with an average PS/F of 10, the range of PS/F of the capillaries is from 4 to 40. The input is a square wave of duration of one average capillary traversal time.

Diffusible outflow curve varies from capillary to capillary because of the heterogeneity of PS/F, the diffusible organ outflow curve cannot be constructed from the organ outflow curve of the nondiffusible indicator as was possible for the homogeneous case (see Appendix). It will be assumed that the $E_0$ method provides an adequate estimate of the ratio of the concentration of the diffusible to nondiffusible indicator leaving the capillary bed averaged over the first second. This underestimates the actual error in the method.

From Figure 8 it can be shown that the average concentration ratio for the first traversal time (1 second) after the appearance of the nondiffusible indicator leaving the capillary bed averaged over the first second. This underestimates the actual error in the method. From Figure 8 it can be shown that the average concentration ratio for the first traversal time (1 second) after the appearance of the nondiffusible indicator for a capillary bed with an average PS/F of 10 is about 0.1, which would correspond to a calculated value of PS/F of about 2.3. It is interesting to note that the actual PS/F of the capillaries varies from 4 to 40 for this bed, and therefore the value of PS/F calculated by the $E_0$ method is even less than the smallest value of capillary PS/F for the heterogeneous capillary bed. This is the result of the averaging over a period of a second which is inherent in the experimental procedure. It can be seen that for an organ with this type of capillary heterogeneity, a substance which is primarily flow limited (average PS/F = 10) for the whole organ, would be interpreted as having a significant diffusion limitation (PS/F = 2.3) by the $E_0$ method.

The second type of capillary heterogeneity to be considered is similar to that postulated by Goresky (6) to explain the dispersion of indicator in the liver. This assumes that $P$, $F$, $A_c$ and $A_T$ are the same for each capillary, but that $S$ varies because of variation in capillary length ($S = 2\pi r_L$). Again, a particularly simple distribution will be used for calculation purposes. It will be assumed that any length between zero and $L_m$ is equally probable:

$$n(L) = \begin{cases} 1 & 0 < L_m < L \\ 0 & L_m < L \end{cases}$$

where $A$ is a normalizing constant. As before, the total concentration leaving the capillary bed is given by

$$F_{\text{total}}C_{\text{total}} = AF\int_0^{L_m} C(L, T) \, dL. \quad (10)$$

As before, values for the function $C(L, T)$ can be obtained from the solution for the single capillary and the integration in equation 10 can be performed graphically. The average traversal time is again set equal to 1.0 as for the two previous models. Figure 9 shows the concentration leaving the capillary bed as a function of time for the nondiffusible indicator and for the diffusible indicators with an average PS/F of 10 and infinity and with $A_c/A_T = 0.33$. Clearly, if $E$ is extrapolated back to the appearance time, a value of PS/F = 0 would be found (as though the substance were nondiffusible) since those capillaries with the shortest transit time have an $L$ (and $S$) equal to zero. The inset of Figure 9 shows the ratio of the diffusible to nondiffusible indicator as it leaves the capillary as a function of time. Experimentally, one actually obtains an average of the concentra-
Outflow curve of a heterogeneous capillary bed. Capillary length varies from 0 to 2 L with an average of L. For curve with an average PS/F of 10, the range of PS/F of the capillaries is from 0 to 20. The input is a square wave of duration of one average capillary traversal time. The inset shows the ratio of the diffusible to the nondiffusible indicator for the early times.

For a substance which is completely flow limited (average PS/F = infinity) the $E_0$ method would yield a value of PS/F of no more than about 1.4. Thus both types of capillary heterogeneity result in a qualitative error in the determination of PS/F, assigning a significant diffusion limitation to a substance which is primarily flow limited.

As shown in the analysis of the homogeneous capillary bed, the $E_0$ method is completely dependent on the early part of the venous outflow curve. Thus any effect which makes this early part of the curve not representative of what is actually occurring in the average capillary, such as capillary heterogeneity, will invalidate the method. Another factor which can disturb the early part of the curve is a difference in the degree of the Taylor dispersion of the nondiffusible and diffusible indicator due to their greatly different diffusion coefficients (9). Lassen and Crone (10) have recently shown that this effect may be significant in studies on the cerebral circulation.

"Ideal" Character of Capillary Model.—The model of the single capillary used in this analysis is obviously not very realistic. However, it represents the model most favorable for obtaining valid values of PS/F by the $E_0$ method. This is because the two major assumptions of the model (rapid radial diffusion and negligible axial diffusion in the tissue space) both favor the accuracy of the $E_0$ method. The assumption of zero tissue axial diffusion ensures that as the front of the input wave is carried along the capillary by the blood flow, it is always exposed to a tissue space with a zero tracer concentration, and it is this condition which is essential for the
validity of the determination of permeability from $E_o$. For example, in the extreme case of a well-mixed extravascular space, the diffusible indicator would shunt the capillary and appear in the outflow before the nondiffusible indicator and therefore completely invalidate the $E_o$ method. The assumption of rapid tissue radial diffusion is also favorable to the $E_o$ method. If the tissue space limits the movement of solute from the capillary, it is as if the actual tissue area ($A_r$) were reduced. As shown in the discussion of the organ outflow curves, when the tissue space becomes small enough ($A_r/A_T = 1.0$) the $E_o$ method will underestimate the actual permeability. A radial diffusion limitation would produce the same effect.

Since this model is the most favorable for the $E_o$ method, it follows that any deviation of the actual capillary from this model would result in a larger error and uncertainty in the values of $PS/F$ calculated by the $E_o$ method than is indicated by the model. In general, for those conditions in which the $E_o$ method underestimates the value of $PS/F$ of the model organ, it would probably underestimate the $PS/F$ of the actual organ even more.

Appendix

Construction of the Organ Outflow Curve of the Diffusible Indicator Given the Outflow Curve of the Nondiffusible Indicator

The organ will be assumed to be made up of $N$ parallel channels of flow, with each channel consisting of a capillary which is preceded and followed by a feeder line. Since the feeder lines and the capillary behave linearly with respect to concentration, their order can be changed and all the capillaries placed at the entrance to the organ without changing the overall effect of the channel. The organ can then be described as $N$ channels in parallel, with each channel consisting of a capillary with a transfer function for the diffusible indicator [$h_d(t)$] followed by the feeder line with a transfer function [$d_f(t)$], with each channel having a flow ($F_i$). It is assumed that the diffusible and nondiffusible indicators are injected simultaneously and therefore the input concentration to all the capillaries is given by the same function [$i(t)$] for both substances where $i(t)$ is a square-wave function (see equation 7A). It is again assumed that the nondiffusible indicator travels through the capillaries without any change of shape. To take advantage of the linearity of the system, the Laplace transform of organ process will be analyzed, with $s$ as the transform of time $t$, and $H_i(s)$, and $I(s)$ as the transform functions of $h_i(t)$ and $i(t)$, respectively.

The nondiffusible indicator leaves each model capillary with the same shape it entered, but delayed in time by $T_i = A_r L_i/F_i$. Thus in the transfer domain, the nondiffusible indicator leaves the capillary as the function $e^{-sT_i}I(s)$. This is then acted on by the dead-space transfer function $D_i(s)$, and the Laplace transform of the amount of indicator leaving this channel of the organ is given by

$$F_i e^{-sT_i}I(s)D_i(s). \quad (1A)$$

The Laplace transform of the total amount of the nondiffusible indicator leaving the organ per unit time is then

$$F_{\text{total}}C(s) = I(s) \sum_{i=1}^{N} F_i e^{-sT_i}D_i(s). \quad (2A)$$

It is assumed that $D_i(s)$ is the same for the diffusible and nondiffusible indicators. This neglects the possibility that differences in the diffusion coefficient of the solute can result in different degrees of dispersion for flow in small tubes as was described by Taylor (9).

For the diffusible indicator, the shape of the concentration curve leaving the capillary is given by a function of the form of equation 3 of the text; that is, a function which has a time delay. $T_i = A_r L_i/F_i$ (the same time as for the nondiffusible indicator), whose shape is determined by two parameters: $FS_i/F_i$ and $r_sP_i A_r$. If the transfer function of the capillary is given by $h_i(t-T_i)$ then the Laplace transform of the total organ outflow per unit time is given by

$$F_{\text{total}}C(s) = I(s) \sum_{i=1}^{N} F_i e^{-sT_i}H_i(s)D_i(s). \quad (3A)$$
To construct the diffusible outflow curve (equation 3A) the effect of the feeder lines \([D_i(s)]\) must be known for each capillary. It can be seen from equation 2A that only the sum of the \(D_i's\) can be obtained from the nondiffusible outflow curve. Thus, in general, even if the exact behavior of each capillary \([H_i(s)]\) and each capillary flow \((F_i)\) is known, the outflow curve of the diffusible indicator cannot be constructed with the information obtained from the nondiffusible organ outflow curve.

A special case in which the diffusible organ outflow curve can be constructed from the nondiffusible curve is for an organ in which the shape of the diffusible indicator curve leaving each capillary is identical \([H_i(s) = H(s)\) for all \(i\)]. Then equation 3A reduces to

\[
\text{dif} \quad F_{\text{total}}(t) = I(s)H(s) \sum_{i=1}^{N} F_i e^{-r_i s} D_i(s), \quad (4A)
\]

and the sum in this equation can be obtained from the outflow curve for the nondiffusible indicator. Using equation 2A and equation 4A it is apparent that

\[
\frac{\text{dif}}{\text{total}} \quad C(s) = \frac{H(s)C(s)}{\text{total}}. \quad (5A)
\]

Or, taking the inverse transform of equation 5A:

\[
\text{dif} \quad C(t) = \int_0^t h(\tau) C(t-\tau) \, d\tau; \quad (6A)
\]

that is, the organ outflow curve for the diffusible indicator is given by the convolution of the outflow curve of the nondiffusible indicator with the outflow curve of the diffusible indicator for the single capillary. It can be seen that for the single capillary model used in the text, the requirement that all capillaries have outflow curves of the same shape implies that \(rF/A_T\) and \(FS/F\) is the same for each capillary.

The convolution necessary in equation 6A was performed by approximating the \(h(t)\) obtained from the single capillary model and the \(C(t)\) used as the reference curve, nondif by a sum of square-wave functions of 1 second duration:

\[
h(t) = \sum_{k=0}^{n} A_k \delta(t-k), \quad C(t) = \sum_{j=0}^{E} B_j (t-j), \quad \text{nondif}
\]

where \(\delta(t-k) = \begin{cases} 1 & 0 < k < k + 1, \\ 0 & k + 1 < t \end{cases}\) (7A)

With this approximation, for \(t = n\) (where \(n\) is an integral number of seconds) equation 6A reduces to

\[
C(n) = \sum_{k=0}^{n} A_k B_{n-k}, \quad \text{dif}
\]

where \(A_k = 0\) for \(k > D\), and \(B_j = 0\) for \(j > E\). (8A)

This summation can be easily performed by hand.

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Evaluation of the Early Extraction Method of Determining Capillary Permeability by Theoretical Capillary and Organ Models

DAVID G. LEVITT

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