Published in final edited form as:

Prog Cardiovasc Dis. 1977 ; 20(3): 165–189.

Physiology and Theory of Tracer Washout Techniques for the Estimation of Myocardial Blood Flow: Flow Estimation From Tracer Washout

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The purpose of this article is to present a general conceptual approach to blood–tissue exchanges of solutes with particular emphasis on washout techniques used for the estimation of flows in the heart. The focus will be on the estimation of *clearance* of tracer from the organ and on the limitations to the accuracy of the estimates. Clearance is defined, in the classical fashion, as the apparent flow of effluent fluid in which the concentration is equal to the average concentration in the heart; except under exceptional circumstances, it will be equal to or less than the blood flow. Both probabilistic (stochastic) and deterministic approaches to transorgan transport will be considered. The stochastic description has the virtue of being very general and serves as a good introduction to the design and analysis of experiments, while the deterministic approach provides a mechanism for interpreting the data in terms of specific physical models. The approaches are not mutually exclusive: deterministic physical models are simply special cases of the more general stochastic approach, and combinations are common. The stochastic approach follows that of Zierler,¹ who has expressed the concepts in terms nicely descriptive of experimental data. Experimentally, much follows from Chinard et al.²

An overly simple analog to a tracer washout curve from an organ can be produced by injecting tracer into a mixing chamber in which the concentration of tracer is uniform throughout its volume at each instant. Then the washout is entirely determined by the flow; i.e., the *clearance* (ml/min) *equals the flow* (ml/min), and when the flow is constant, the clearance is constant. But this situation almost never occurs in reality, because instantaneous mixing or diffusion is not possible over regions larger than a few microns. Most commonly, there are barriers that tracers must permeate, or there are parallel and more or less independent pathways for flow streams to take, so that overall uniformity of concentration following a single injection is not possible (except when a very long time is allowed for a steady state to be reached). *With variation in flow, clearance will change in the same direction as the flow*, but not necessarily in proportion. This more complex situation is diagrammed in Fig. 1, following Renkin's³ concept.

At low flow, clearance is entirely flow-limited, and there should be no diffusional retardation to washout. At very high flows, clearance is entirely limited by extravascular diffusion or capillary membrane permeation. At middling flows, the washout is limited by both extravascular diffusional velocities and intravascular convective velocities. Tracer washout can be used for estimation of flow only when the washout is wholly flow-limited, that is, at the lowest flows.

The basic diagram of Fig. 1 will be explained, modified, and extended in the process of providing greater generalization and, hopefully, more accurate interpretation. It is the starting point of the conceptual framework for examining washout curves in the heart and in other organs.

PHYSIOLOGIC ANATOMY OF MYOCARDIAL MICROVASCULATURE

In washout processes, we consider principally the use of tracers that escape from the vascular system during transcapillary passage; therefore, one must consider how the microvascular anatomy affects the washout process. Our main interests are in the arrangement of the capillaries between myocardial cells and the degree of success in minimizing extravascular diffusional resistances, and in the geometric relationships between arterioles, venules, and the tissue, keeping in mind the possibility of diffusional shunting (by-passing capillaries).

Myocardial Capillary Anatomy

The structure of myocardial microvasculature is, as in other organs, defined by the arrangement of the functional cells—the syncytium of contractile striated muscle cells. These cells run in parallel in large groups. The capillaries parallel the cells with a density of about one per cell, or 3000/sq mm cross-section.⁴ The general arrangement is shown in Fig. 2 for the dog heart.

It is clear that such capillary regions cannot easily be regarded as mixing chambers. The distances for extravascular diffusion are vastly different in the radial and axial directions: the average half-intercapillary distance for radial diffusion is 9μ , but the axial lengths are 400–1000 μ . Accordingly, even if extravascular radial diffusion is so fast that radial concentration gradients are negligible (a local “uniformly mixed region”), axial gradients can be expected to persist for long times.

Models of the Capillary Arrangement

We can regard Krogh cylinder type models, such as those shown in Fig. 3, as being roughly analogous to the myocardium, although still oversimplified. There are additional complexities, such as the capillary branching, the interconnections between capillaries, the increase in surface area from arteriole to venule, the variations in flows, lengths, etc., which cannot be wholly dismissed. However, the simple model of Fig. 3A can be fitted to data on solute transport through the heart,⁵ showing that it provides a fairly good description. The countercurrent arrangement (Fig. 3B) would be most applicable to the washout of highly diffusible tracers which, like oxygen,⁶ may exhibit exchange between arterioles and venules. The shapes of Xenon washout curves are apparently influenced by such a phenomenon,^{7–9} but it is difficult to quantitate the relative influences of countercurrent exchange and of heterogeneities in local velocities and distances.

THEORETICAL APPROACHES

It is of greatest importance to consider the whole organ, including inflow and outflow vessels, and the location of the organ within the circulatory system. For example, the interpretation of curves of tracer emissions from the *heart* is somewhat complicated because of the rapid recirculation of tracer that has escaped into the outflow and returned to the inflow, and because the total systemic flow passes through the cavity of the heart but not through its microvasculature.

For a beginning, let us define the theoretical approaches in the simplest situation, as if the heart were an organ with a single inflow and a single outflow.

The acquisition of experimental data follows the principles illustrated in Fig. 4: one ordinarily measures the indicator contained in the organ, $q(t)$, obtained as the residue function, $R(t)$, or the concentration–time curve in the venous outflow, $C_v(t)$. The relationships between these and the cumulative fraction $H(t)$ of the tracer escaped from the organ are well defined for the idealized organ; but since no organ provides an ideal arrangement, the possibility of using two or more detection methods simultaneously should always be considered.

Analysis of a Linear Stationary System

In Fig. 4, the organ is diagrammed as a constant volume, V , with a constant inflow and outflow, $F(\text{ml/sec})$; the system is considered to be linear and stationary, as defined by Zierler.^{1,10} When a sudden slug of quantity, m_i , of tracer is injected into the inflow, the quantity of tracer, $q(t)$, contained in the volume, V , can be estimated by external detection of the radiation. When the detection is of equal efficiency for tracer throughout V , then the residue function, $R(t)$, can be taken directly from the recorded signal that is proportional to $q(t)$:

$$R(t) = \frac{q(t)}{q_0} \text{ or } \frac{kq(t)}{kq_0} \quad (1)$$

where k is the efficiency of detection, and q_0 is the amount in the system at time zero and is equal to m_i .

A venous outflow detector (intravascular detector, or a flow-through detector when cannulation is possible) provides a signal proportional to $C_v(t)$.

The unit impulse response or transport function, $h(t)$, is the frequency function of transit times or the probability density function of transit times. It has the shape of the concentration–time curve, $C_v(t)$, that would be obtained by flow-proportional sampling at the output if indicator were injected in ideal fashion¹¹ at the inflow, i.e., if the input were the ideal impulse input, $\delta(t)$, and if there were no recirculation. Under such conditions:

$$h(t) = F \cdot C_v(t) / m_i \quad (2)$$

where F is the flow (ml/sec), $C_v(t)$ is concentration in the outflow (g/ml or counts/min/ml), and m_i is the dose in grams or cpm, of indicator injected at $t = 0$ into the inflow. The subscripted term $h_N(t)$ will be used for transport functions of a nonpermeant reference molecule when used in combination with a test molecule, as in studies concerning tracer extraction during transcapillary passage. From $h(t)$, the other overall stochastic functions can be determined, as in Fig. 5.

$H(t)$ is the cumulative residence time distribution function (dimensionless) of the system, representing the fraction of injectate collected at time t in a bucket into which all the outflow is emptying. It is also the response to a unit step input and is the area of $h(t)$ up to any particular time t :

$$H(t) = \int_0^t h(t') dt' \quad (3)$$

where t' is a dummy variable used for the time integration.

$R(t)$, the residue function (dimensionless), is the complement of $H(t)$, i.e. $R(t) = 1 - H(t)$. It represents the fraction of injectate remaining in the organ at time t following indicator entry at $t = 0$. It is the probability of a particle residing in the organ for time t or longer. We will use $R(t)$ frequently to measure the mean transit time of the organ, $\bar{t}$, since:

$$\bar{t} = \int_0^{\infty} R(t) dt \quad (4)$$

A general definition of a fractional escape rate, FER, is the rate of loss of tracer, $-dq/dt$, divided by the residual amount, $q(t)$:

$$FER = \frac{-dq/dt}{q} \quad (5)$$

The FER is the clearance per unit volume of the heart. $\eta(t)$ is the emergence function (fraction/sec), the specific fractional escape rate following impulse injection:

$$\eta(t) = h(t)/R(t) \quad (6)$$

It is the fraction of the particles residing in the system for t seconds, which will exit in the t^{th} second. In chemical engineering, it is known as the intensity function,¹² and in population statistics or renewal theory, as the risk function, the death rate of those living at age t . Other useful forms of $\eta(t)$ are:

$$\eta(t) = \frac{-dR/dt}{R} \quad (7A)$$

$$= -d \log_e R/dt \quad (7B)$$

$$\eta(t) = \frac{h(t)}{1 - \int_0^t h(\lambda) d\lambda} \quad (8)$$

$$= \frac{C_v(t)}{\int_0^{\infty} C_v(t) dt - \int_0^t C_v(\lambda) d\lambda} \quad (9)$$

Equation 7B shows that $\eta(t)$ is the logarithmic slope, which would be obtained by the local slope around time t on a semilog plot. Use of the slope of $R(t)$ has the disadvantage that one must calculate a derivative from inevitably somewhat noisy data. Equation 9 is used when one records outflow concentration-versus-time curves, $C_v(t)$, and necessitates excluding recirculation from the estimation of the area under the curve to time equals infinity. A way of avoiding the influence of errors concerning the tail of $h(t)$ is to use a combination of techniques, as represented by equation 6. At any time prior to recirculation, the integral of $h(t)$ is $H(t)$ or $1 - R(t)$:

$$1 - R(t) = \frac{\int_0^t C_v(\lambda) d\lambda}{\int_0^\infty C_v(t) dt} = \int_0^t h(\lambda) d\lambda \quad (10)$$

which may then be used to calculate $\eta(t)$:

$$\eta(t) = \frac{h(t)}{R(t)} = \frac{C_v(t) / \left[\int_0^t C_v(\lambda) d\lambda (1 - R(t)) \right]}{R(t)} \quad (11A)$$

$$= \frac{C_v(t) \cdot [q_0 - q(t)]}{\left[\int_0^t C_v(\lambda) d\lambda \right] \cdot q(t)} \quad (11B)$$

where $C_v(t)$ is obtained by intravascular sampling or continuous detection and $q(t)$ by external detection.

When a system is linear and stationary, the relationship between the arterial input concentration–time curve, $C_A(t)$, and the output curve, $C_v(t)$, is completely defined by $h(t)$ and is described by the convolution integral:

$$C_v(t) = \int_0^t h(t - t') \cdot C_A(t') dt' = C_A(t) * h(t) \quad (12)$$

where t' is a variable used in the integration; in the abbreviated expression the asterisk denotes convolution. A portrayal of the convolution integral applied to dilution curves has been published.¹³ Thus, $h(t)$ describes the deformation, dispersion, and delay that transform $C_A(t)$ into $C_v(t)$; $h(t)$ is the time domain description of the behavior of a linear operator, the deforming process within the organ. An organ system being, so far as tracer is concerned, mass conservative, behaves simply as a low-pass filter with unity gain; high-frequency fluctuations in $C_A(t)$ will be damped out, and the damping will be greater for tracers with larger volumes of distribution. The filter characteristics may be examined by taking the Fourier transform of $h(t)$; the filters are not ordinarily first order, as is obvious from Fig. 5, and will often show slopes of 12db/octave or so. The cutoff frequency will be lower for those tracers with larger volumes of distribution within the organ.

Nonstationary Systems

Nonstationary systems, organs with fluctuating flow, can sometimes be characterized in spite of the nonstationarity by using linear operators with a suitably time-varying form. This is simplest when the shapes of the impulse responses or of the residue functions at varying flows are all *similar* (having the same relative dispersions, skewnesses, etc.) so that the varying flows can be described by a proportionally varying cutoff frequency for the linear operator, as have been used by Bassingthwaighte, Knopp and Anderson¹⁴ for examining the errors inherent to standard dye dilution practice. The condition required for similarity is that the indicator transit times be governed by flow and volume of the system, but not influenced by diffusional processes, whose rates would be unchanged by changing flow. The ability to characterize a nonstationary system well enough to treat it in this fashion is severely limited,

since both the form of the impulse response, $h(t)$, for the system in a stationary state *and* the variation in flow or volume as a function of time must be known.

Under conditions where fluctuations in flow about some mean value occur rapidly compared to the duration of the impulse response, the lack of stationarity may not produce much error in the estimation of flow or volume.^{10,13,15} But when the fluctuations are slow, the errors may be very large.¹⁴ This generality applies whether one is using the slug injection technique and recording $h(t)$ or using external detection for $R(t)$. If the flow changes from one rate to another during the recording of the information from which the calculations of flow or volume must be made, then at best the estimate can be said to represent something in between the two sets of conditions.

Estimation of Blood Flow

Outflow dilution curve—The calculation of flow from a coronary sinus dilution curve obtained following an impulse injection of dose m_i into the coronary artery is straightforward when there is no recirculation; the total mass of tracer emerging from the organ must equal that which was injected.

$$m_i = F \int_0^{\infty} C_v(t) dt \quad (13A)$$

and the flow, F , is:

$$F = m_i / \int_0^{\infty} C_v(t) dt \quad (13B)$$

In tracer studies, m_i is usually expressed at cpm or curies, and $C_v(t)$ has units of cpm/ml or Ci/ml. This gives the area under the curve of $C_v(t)$ (the integral in equation 13) the units cpm · sec/ml and F the units ml/sec.

When recirculation occurs early so that recirculated tracer summates with the primary pass tracer, as in Fig. 6, then the classical technique of Hamilton, Moore, Kinsman, and Spurling¹⁶ can be applied in order to obtain an estimate of the true area of the curve of indicator passing through the organ only once. The technique to be applied is to fit a single exponential curve to the downslope of $C_v(t)$ for the portion of the curve prior to recirculation of tracer, and to extrapolate it through the time when recirculation has occurred and down to a level to about 1% of the peak of the curve. Then the primary pass curve is considered to be the recorded curve prior to recirculation and to be the extrapolated curve for later times. Then equation 13 can be applied to this constructed total curve. This can probably be done with reasonable accuracy, since the shapes of the impulse responses of the coronary vascular bed have not been shown to differ greatly from shapes that could be fitted with an exponential downslope.¹⁷

However, even though the extrapolation may be adequate, this technique does not provide accurate estimates of coronary blood flow from intracoronary artery injections. There are very limited circumstances under which one can use this impulse injection technique for the estimation of total coronary blood flow. The problems stem from the fact that there is neither one inflow nor one outflow; not only are there two coronary arteries, but the left main coronary artery branches so quickly that there is little chance for total cross-sectional mixing within the main coronary artery itself. The theory requires that the indicator be injected into the inflow in proportion to the flow through each element of the cross-section of the entering flow stream. Clearly, this cannot be accomplished for the right and left coronary arteries simultaneously, and the question remains whether it can be accomplished

for even one of the coronary arteries. Injections of small amounts of radiocontrast media into coronary arteries can be seen to stream along one side of the vessel, thus giving a strong hint that flow-proportional labeling across the cross-section of the coronary artery is not very likely.

Actually, if only the estimation of the flow is needed, and not mean transit time or intravascular blood volume, then the requirement for flow-proportional labeling across the inflow may be relaxed; but what is still necessary is that there be mixing somewhere in the bed between inflow and outflow. This leads to the question of whether or not there could be thorough mixing of all the coronary venous drainage. Which would suffice for flow estimation. The answer is no: the microvasculature supplied by the right coronary artery drains partly into Thebesian veins, emptying into the right ventricle or atrium, and partly into the lower end of the coronary sinus. This is a physical situation in which there is really no possibility for complete mixing of the total coronary outflow.

The remaining question is whether or not the technique might conceivably be used for flow through the left main coronary artery. Tracer must be injected into the left main coronary artery without loss into the aorta (which can be checked by sampling from the left radial artery or a femoral artery). If there were mixing within the left main coronary artery, then all that is required is that the outflow dilution curve, $C_v(t)$, should be sampled at a point upstream from the point of contamination with blood from the unlabeled right coronary artery, for example, high in the great cardiac vein. In this circumstance, equation 13B could be used for the estimation of left coronary artery flow. Even if mixing were not adequate between the injection site and the first branch of the left main coronary artery, there is still a possibility for estimating the left main coronary flow. This requires that there be sufficient mixing in the outflow from the coronary venous bed draining the cognate bed of the left main coronary artery and its branches to allow adequate sampling at a point upstream to any admixture of blood supplied via the right coronary artery. Thus, a catheter placed not very deeply into the coronary sinus might be used to obtain the dilution curve; the absence of contamination from the right coronary artery would have to be checked by making tracer injection into the right coronary artery while sampling from the same point, the required condition being that no tracer be obtained in this catheter prior to recirculation. (It should be emphasized that these conditions are defined for the estimation of flow but are not adequate for the estimation of mean transit time or intravascular volumes.

Estimation of blood flow: Residue function—In the standard application of residue function analysis for the estimation of organ blood flow, the technique provides an estimate of flow per unit volume of tissue rather than an absolute flow in milliliters per minute. This is not really a handicap since, for the most part, what is of interest is the adequacy of delivery of substrate and of removal of metabolites from the tissue. Thus, it is the flow per gram of functioning tissue or per unit of volume of tissue that is important rather than the absolute flow. This can be regarded as an advantage of the residue function technique over the outflow dilution technique described above.

The technique is based on the estimation of mean transit time of tracer through the organ, as diagrammed in Fig. 7.

$$F/\lambda V = \frac{1}{t} = \frac{1}{\int_0^\infty R(t)dt} \quad (14A)$$

Here, V is the volume of the organ (ml), F is the flow through the organ (ml/sec), and λ is an apparent partition coefficient, the volume of distribution of the tracer within the organ

divided by the total organ volume. For an intravascular label, such as ^{131}I -albumin, λ would be its volume of distribution, the intravascular volume divided by the total myocardial volume, about 0.10–0.15 ml/ml. For antipyrine or for other tracers that distribute approximately in the total water space of heart, λ is approximately 1.0. (The estimate of λ could be obtained from this type of experiment if F and V were measured, but ordinarily it is derived from estimation of the steady state volume of distribution.) One should be aware that the partition coefficient may be dependent on the hematocrit, as has been shown so well for xenon by Carlin and Chien.¹⁸

The residue function is derived from the time course of the quantity of tracer within the tissue; m_i is the amount of tracer injected into the inflow to the organ at time zero, and $q(t)$ is the quantity of tracer contained in the tissue at time t . In theory, the amount m_i injected instantaneously is detected as $q(t = 0)$ or q_0 . In practice, q_0 and $q(t)$ are recorded with a detector efficiency that is not 100%, but the exact counting efficiency, k , is not critical to the analysis, since only the relative amount at a particular time need be known (as shown in equation 1) so that equation 14A may be written:

$$F/V = \frac{\lambda k q_0}{\int_0^\infty k q(t) dt} = \frac{\lambda q_0}{\int_0^\infty q(t) dt} \quad (14B)$$

Zierler¹ has described a useful mechanism for obtaining the absolute flow, F , by taking a sample from the venous outflow, as shown in Fig. 8.

Recirculation is a problem in residue function analysis just as it is for intravascular recording of dilution curves. For this reason, Hoedt-Rasmussen and Lassen¹⁹ introduced a modification that we tested on the coronary circulation.²⁰ The modification, shown in Fig. 9, is designed to avoid having to record the tail of the washout curve for infinite time; the height of the curve at a particular time of stopping the recording, T , is used to provide a measure of the indicator still retained within the organ:

$$\frac{F}{\lambda V} \doteq \frac{1 - R(T)}{\int_0^T R(t) dt} \quad (15A)$$

The right side of equation 15A is approximately equal to the reciprocal of the mean transit time. The expression is exact if the residue function itself is a single exponential. Although monoexponentiality is very rare, the approximation is quite reasonable.²⁰ The rationale of the correction can be seen without reference to an analytical deduction: the subtraction of $R(T)$ from the numerator of equation 15A reduces the size of the numerator. The integration from 0 to T in the denominator reduces the size of the denominator compared with integrating to time infinity. Thus, one can see that the modifications in numerator and denominator tend to keep their ratio the same. The greater the deviation from a monoexponential, $R(t)$, the poorer is this approximation. In practice, this equation can be written as follows:

$$F/V \doteq \frac{\lambda(1 - R(T))}{\int_0^T R(t) dt} \quad (15B)$$

$$\doteq \frac{\lambda(q_0 - q(T))}{\int_0^T q(t)dt} \quad (15C)$$

In the above equations, we have looked on F as being overall flow of blood and V as being the organ volume. Because the velocities of red cells are somewhat higher than average plasma velocities during transcapillary passage, and because a number of tracers (for example, xenon) have mean transit times that are dependent on the hematocrit, one needs to be aware that equation 14 should more correctly be written as:

$$\frac{\lambda_r F_r + F_p}{\lambda_r V_r + V_p + \lambda_E V_E} = \frac{q_0}{\int_0^\infty q(t)dt} \quad (16)$$

Here, λ_r is the erythrocyte partition coefficient, the ratio of the concentration of tracer in the red cell to that in the plasma at equilibrium; λ_E is the ratio of solubility in extravascular tissue to that in plasma; and V_r , V_p , and V_E are the volumes of red blood cells, plasma, and extravascular space in ml/ml of tissue. Taking this view, it can be seen that the unsubscripted partition coefficient, λ , in equations 14 and 15 is a weighted λ that is susceptible to being hematocrit-dependent whenever the tracer enters the erythrocytes. When the tracer does not enter erythrocytes, then it can be seen from equation 16 that F in equation 14 would be the plasma flow, but also that the λ would still be secondarily hematocrit-dependent, since it would depend on the ratio of plasma to extravascular tissue volumes that would be influenced by having more or fewer red cells in the intravascular space. These points are brought out so that refinements in equation 14 can be introduced when the experimental situation demands it.

APPROACHES TO DISTINGUISHING FLOW VERSUS DIFFUSION LIMITATION TO WASHOUT

Residue function analysis is based on conservation of mass. This does not require that the rate of washout of tracer from the organ be governed solely by the flow, but only that the volume of distribution is the product of flow times mean transit time. However, any diffusional barriers to exchange will tend to prolong the tail of the curve, making the integration less accurate and more susceptible to recirculation. Slow diffusion within the extravascular region or slow permeation of a membrane tends to slow the entry of tracer from the blood into the extravascular region and similarly to retard the washout from an extravascular region into the effluent blood, reducing the accuracy.

Tests for flow-limitation are based on the logic that the physical process of diffusion outside of the bloodstream should not be affected by events within the vasculature. Suppose that at a given blood flow rate, the washout of tracer is impeded by slow diffusion or permeation, which means that there are local concentration gradients. If flow is slowed, then, presuming tissue geometry remains constant, relatively more time is available for diffusion to occur, the concentration gradients become smaller, and the washout process is governed more nearly completely by flow. This changes the shape of the washout curve, mainly by reducing the fraction of indicator coming out slowly as a long low tail on R(t) or h(t). On the other hand, when flow is increased, then any diffusional process will be relatively more retarding, causing the diffusion-limited tracer to separate more from any flow-limited tracer and increasing the relative length of the tail. Presumably the diffusional process does not change at all in its time course, but, if flow is low enough or local diffusion (which includes

permeation) is fast enough, then there will be local diffusion equilibration, and the influences of diffusion will not influence the rate of solute transport into the outflow in the least. Theoretically, if the flow can be made high enough, diffusional limitation to efflux should always come apparent; if there is a diffusion limitation, the situation is represented by the middle or right-hand regions of Fig. 1, where clearance increases less than in proportion to increases in flow.

When a particular tracer is wholly flow-limited in its exchange within that particular organ over a wide range of flow, then the washout curve is relatively compact, there is no long tail of a diffusion-limited component, and one can apply the extrapolation of Fig. 6 and 9 and the approximation of equation 15 with reasonable confidence and accuracy.

The techniques for discerning whether or not there is diffusional limitation to washout are simple in theory and only moderately complex in application. The methods for doing this can be divided into two groups. First, one can use a single tracer at a variety of flows, and second, there are techniques involving looking for separability of two or more tracers at different flows. The second approach is the stronger one, but the single-tracer technique is simpler and has proven useful in applications to the heart. The single-tracer technique is based on the supposition that the impulse responses, $h(t)$, or the washout curves, $R(t)$, have “similar” shapes at different flows.

Tests for Similarity of Washout Curves at Different Flows

Testing of a single indicator at a variety of flows is based on the idea that if there is any diffusional limitation (whether it be due to large intratissue diffusion distances or to low permeability of a membrane), the relative influences of flow and diffusion *must* be changed by changing flow. If, for any given organ, it can be shown that the dispersive characteristics of the organ vascular bed for a given tracer are constant over a wide range of flows (similarity), then any experiment that demonstrates nonsimilarity in the shapes of the tracer dilution or washout curves at two different flows provides evidence of diffusion-limitation to washout. A stronger point is that whenever similarity can be demonstrated over wide-range flows, one can be sure not only that there is no diffusion-limitation to exchange but also that the relative dispersion of intravascular tracer transit times is constant. Consider a system in which there is constant proportionality of distribution of flow. Such a system might have turbulent or laminar flow. The simplest example is a system (Fig. 10) consisting of a number of parallel pathways of differing transit times, each having piston flow and each carrying a constant proportion of the total flow. (Piston flow defines the velocity to be the same at all points in a cross-section of the tube.) Indicator injected at point A in such a system will be dispersed spatially in the same fashion at all flows but at a rate governed by the total flow rate, F . It is obvious that, under these conditions, when an impulse input is made at A, the *spatial* distribution, $C(x)$, of concentrations along a distance axis, X , will be the same when the centroid is at B, no matter what the flow rate is. However, the *temporal* distribution at point B, $C(t)$, is a function of the spatial distribution *and* of the flow rate. Let the curve at the lower left panel of Fig. 10 represent $h_1(t)$, when the flow is stationary at F_1 ml/sec. The amount of indicator and the time for it to travel from A to B through pathway D is given by the rectangle at time t_{D1} , and through pathway E takes transit time t_{E1} . Doubling the flow from F_1 to F_2 (right lower panel) halves each pathway transit time, so that $t_{D2} = 0.5 t_{D1}$ and $t_{E2} = 0.5 t_{E1}$.

In this idealized circulatory network in which there is constant proportionality of distribution of flow, the transport functions, $h(t)$, at different flows are related by:

$$h_2(t) = \frac{\bar{t}_1}{\bar{t}_2} \cdot h_1\left(\frac{\bar{t}_1}{\bar{t}_2} \cdot t\right) \quad (17)$$

where $\bar{t}_1/\bar{t}_2$ scales the time t (in the brackets) and the magnitude so that the areas under $h_1(t)$ and $h_2(t)$ are both unity.

For any system, the mean transit time is the volume of distribution of the indicator, V , divided by the flow:

$$\bar{t} = V/F \quad (18)$$

and therefore:

$$\frac{\bar{t}_1}{\bar{t}_2} = \frac{V_1/F_1}{V_2/F_2} \quad (19)$$

Then $h_2(t)$ can be expressed from $h_1(t)$ substituting into equation 17:

$$h_2(t) = \frac{V_1/F_1}{V_2/F_2} \cdot h_1\left(\frac{V_1/F_1}{V_2/F_2} \cdot t\right) \quad (20)$$

and when V is constant and only flow changes, then:

$$h_2(t) = \frac{F_2}{F_1} \cdot h_1\left(\frac{F_2}{F_1} \cdot t\right) \quad (21)$$

The scale factor $\bar{t}_1/\bar{t}_2$ in equation 17 and F_2/F_1 in equation 21 preserves unity area for $h(t)$, while shrinking or expanding the time scale.

In general, similarity at different flows is demonstrated if plots of $\bar{t} \cdot h(t/\bar{t})$ or of $R(t/\bar{t})$ versus $t/\bar{t}$ are superimposed on each other. For the concentration–time curves, recalling that $h(t) = F \cdot C(t)/m_i$, (equation 2), then:

$$C_2(t) = C_1\left(\frac{\bar{t}_1}{\bar{t}_2} \cdot t\right) \quad (22)$$

and for the constant volume system:

$$C_2(t) = C_1\left(\frac{F_2}{F_1} \cdot t\right) \quad (23)$$

Equations 22 and 23 show that for a system with stable dispersive properties, a change in F doesn't affect the peak heights of $C(t)$ but does change the spread of the curve, the areas being inversely related to F . Similarly, $C(t_{D2}) = C(t_{D1})$ and $C(t_{E2}) = C(t_{E1})$ while $t_{D2} =$

$F_1 t_{D1}/F_2$ and $t_{E2} = F_1 t_{E1}/F_2$. This may be viewed merely as normalization of the time scale of $t/\bar{t}$.

The model illustrated in Fig. 10 is a generalized streamline flow model. The parameters of the spread of $C(t)$ are in constant proportion to $\bar{t}$. These relationships will apply to any constant-volume streamline flow model over any range of flows so long as the requirement for constant proportionality of flow in each stream is fulfilled. They (and also equations 17, 21, and 23) apply equally well to any turbulent or disturbed flow system of constant volume in which the mean velocity profile is unchanged by flow changes. It is important to realize that *streamline flow is not necessarily implied by observations of similarity*. The generalized flow model has been discussed because it is simple and because streaming flow is probable in the vascular system, even though true laminar flow is not, because of the presence of erythrocytes. Any type of turbulent flow whose spatial dispersion is related linearly or nonlinearly to the distance traveled and not to the flow will give similar results.

Similarity has been demonstrated for transport within the arterial system of the human leg over a six-fold range of flows¹⁵ and, with somewhat less precision, in the aorta.²¹ This is to be expected so long as changes in flow do not change the velocity profile within the vessel.

Similarity has been demonstrated for *transorgan* transport functions in the kidney by Gomez et al.,²² in the lung over a very limited range of alveolar and left atrial pressures by Knopp and Bassingthwaighe,²³ and in the coronary bed by Knopp et al.¹⁷ Data from the latter study are plotted in Fig. 11, showing a fair degree of similarity. For similarity to apply across an organ bed, unchanged volume is not a requirement, but if the intravascular or extravascular volume changes or a new section of capillary bed opens up, the distribution of flows through this new region should be similar to those in the sections already open. The main requirement for similarity is that there be no influence by diffusional processes and that the transport be entirely limited by the flow. We will return to this point when examining the processes of blood-tissue exchange of diffusible tracers.

Deviations from similarity are notable in the lung. The data of Knopp and Bassingthwaighe²³ showed greater transpulmonary dispersion at low flows than at high flows. Maseri et al.²⁴ showed that it was the level of pulmonary arterial pressure that influenced the spread rather than the flow, for $h(t)$ s obtained at the same pulmonary artery pressure but different flows did show similarity, whereas $h(t)$ s at the same flow with different perfusing pressures showed less spread in $h(t)$ at high pressures than at low.

Similarity of Residue Functions

The transformation of residue functions to test for similarity is done by scaling time on the abscissa relative to the mean transit time. No vertical scaling is needed, since the initial value is always unity. This is demonstrated in Fig. 12 where hypothetical $R(t)$ s are drawn for four flows; the system is assumed to have a constant volume in this particular instance (although this isn't necessary in general), so that scaling of the abscissa in proportion to mean transit time, and therefore to flow, causes all the curves to become superimposed, as they are in the right panel.

Experimentally, iodoantipyrine (I-Ap) has been shown to be flow-limited in the heart²⁵ and in bone²⁶: the residue function curves were superimposable by plotting $R(t)$ versus $t/\bar{t}$. Nine washout curves from one heart are shown in the lower panel of Fig. 12. Such data justify the estimation of flow per unit volume of time from the earlier parts of incomplete washout curves.

The data on antipyrine and xenon washout from the heart²⁰ fit this concept fairly well, except that there is a suggestion that the xenon curves are not wholly flow-limited. The ¹³³Xe washout curves are slightly faster in the earliest portions and slower in the tails. The slow tails may be explained by the greater solubility of xenon in the fat of the heart, but the only mechanism that we can put forth to explain the beginnings of the curves is a diffusional shunting of the xenon from inflow to outflow vessels short-circuiting the capillary bed to some extent. This also explains the prolongation of the tails, as will be shown later.

Test for Flow-Limitation by Failure to Separate Two Tracers of Differing Diffusibility

For this test to be useful, the tracers must penetrate the extravascular space, permeating the capillary membrane and diffusing through the interstitial space. The logical basis of the approach is that if it can be shown that two tracers of differing molecular weight are injected together and, at one flow can be shown to have identical outflow dilution curves, and also have identical outflow curves at a much higher or much lower flow through the same organ, then their transit through the organ must have been wholly flow-limited at both flows; if there had been any diffusion-limitation to one of them at the higher flow, the curves would have separated. By going to a sufficiently high flow, the tracer of lesser diffusibility in the tissue must be the first to have its transit slowed by the diffusional component of the transfer process. That is, the clearance would come into the intermediate range shown in Fig. 1 for one tracer before it would for the other tracer.

The test can be done as simply as is described here only if the two tracers have the same volume of distribution in the organ. Also, since a diffusional process outside of the vessel must be involved before the test is pertinent to tracer washout studies, the test is not usefully applied using a pair of tracers that are limited to the vascular space even if their diffusion coefficients differ.

When the volumes of distribution for a pair of tracers differ, as is usually the case, then the same technique of transformation can be used as was applied for the tests of similarity with a single tracer, scaling of the abscissa with respect to the mean transit time. This was neatly demonstrated by Goresky²⁷ for the liver using several flow-limited tracers simultaneously; his data also required a shift of the apparent zero time to a time later than the actual injection time in order to account for the volume and dispersion in the inflow and outflow vessels before and beyond the capillary bed.

Perhaps the most direct test of flow-limitation is the simple one of comparing a potentially useful tracer with an intravascular tracer such as ¹³¹I-albumin. When this is done for ⁴²K, as is shown in Fig. 13, the relative change in shape of the vascular and permeating tracer dilution curves at the different flows is clearly seen. The instantaneous extraction, $E(t)$, gives a quantitative measure of the change in the fraction of tracer participating in the diffusional transfer across the capillary membrane. The instantaneous extraction, as introduced by Crone,²⁸ is calculated from the two normalized impulse responses, $h_R(t)$ for albumin (reference nonpenetrating) and $h_K(t)$ for the permeant, diffusible tracer, potassium:

$$E(t) = \frac{h_R(t) - h_K(t)}{h_R(t)} \quad (24)$$

In Fig. 13, it can be seen that the effect of increasing the flow is to reduce the extraction of potassium; it decreased from 62% at $F/\rho V$ of 0.70 ml/g/min to 51% at the higher $F/\rho V$ of 1.19 ml/g/min. (The density, ρ , is about 1.06 g/ml in dog hearts.²⁹) These data are similar to those of Ziegler and Goresky.^{30,31}

When this same experiment is performed using tritiated water, ^3HHO , or iodoantipyrine instead of potassium, the maximum extractions come out to be about 88%–90% (unpublished data obtained by Tancredi, Yipintsoi, and Bassingthwaighte), and the values are apparently not at all influenced by the flow. This was to be anticipated from the earlier experiments of Yipintsoi et al.,²⁵ using similarity testing for iodoantipyrine, but these are the only experiments that have been done to confirm the deduction of flow-limitation from similarity testing by using an independent technique, the double-tracer test.

From these various experiments we conclude that iodoantipyrine is the indicator of choice for estimating myocardial flow from washout curves using external detection. Beta-emitting tracers can be found that are flow-limited in the heart over the physiologic range, such as ^{14}C -antipyrine, and probably a number of the monohydric or dihydric alcohols used by Perl et al.³² in their studies on the kidney may be suitable. It would also be most useful to find an adequate noniodinated gamma-emitting tracer with a volume of distribution similar to that for water and antipyrine. For those who have a cyclotron capable of producing ^{11}C or ^{15}O , this problem is close to solution, but as will be discussed, H_2^{15}O , like ^{133}Xe , is not quite ideal for the heart in that it shows some degree of countercurrent exchange, which shows up as a modest diffusion-limitation.

COUNTERCURRENT EXCHANGE AND DIFFUSIONAL SHUNTING

At high flows through dog myocardium, from 2.0 up to 3.8 ml/g/min, antipyrine and tritiated water show no separation,²⁵ but at low flows, the water outflow dilution curves tended to show a higher earlier peak than did the antipyrine curves. Since the antipyrine dilution curves showed similarity over the whole range, and since the separation occurred at low but not high flows, the likeliest explanation appears to be a diffusional shunting of the water. This might occur between inflowing arterioles and effluent veins, since these travel together throughout the myocardium, particularly in the subendocardial regions,⁴ but could also occur between neighboring groups of capillaries flowing in opposite directions, such as those diagrammed in Fig. 3. In either situation, at high flows the amount of diffusional shunting between regions could be such a small fraction of the total tracer traversing the system that it would escape detection, but at low flows, the fraction would not only be higher but also the Convective transport would be relatively slower and later, allowing the shunted tracer to show up as a high early peak. When one is using the residue detection technique, this phenomenon shows up as a rapid early washout, a steep initial slope. As a result, this early slope tends to give an *overestimate* of the average flow through the organ. Such a form can be seen in the curves of Fig. 14 that were derived from a countercurrent exchange model. (We should point out that Rose, Goresky, and Bach³³ hold a different view, namely, that water exchange is retarded by permeation of the sarcolemma of the myocardial cells, and attribute the high early peak of the water outflow dilution curve to unextracted THO, which failed to permeate the capillary endothelium and sarcolemma, whereas we would attribute it to a small diffusional shunt component, as argued above.)

Modification of the Clearance–Flow Diagram

This concept of diffusional shunting is not encompassed by the clearance–flow diagram in Fig. 1, but requires a modification in a particular range of flows, as is suggested by Fig. 15. The left region of Fig. 1 is now divided into three regions: I is for global flow-limitation, a first order uniform mixing chamber; II is a region where diffusion between inflow and outflow influences the fractional escape rate or clearance; and in region III, there is local blood–tissue diffusional equilibration, and therefore, flow-limitation to washout, which is not influenced by diffusional transport from inflow to outflow. Regions IV and V are the partially and completely diffusion-limited regions represented in the middle and right regions of Fig. 1.

At the very low flows, region I in Fig. 15, there is sufficient time available for diffusion to occur in all directions within the tissue so that there are no intratissue concentration gradients. This would be the perfect first-order mixing chamber in which clearance equals flow. With conditions lying within region I, the clearance of intratissue tracer will be constant with rate constant, F/V , so that the washout curve is a simple monoexponential. This is the only circumstance in which washout will be both flow-limited and monoexponential, and there is much doubt that the heart could be viable at flows low enough to be in region I.

Region II of Fig. 15 is a region where diffusional shunting influences the rate of appearance of tracer in the outflow. If tracer entering the arterial inflow is highly diffusible and if the time required for diffusion from inflow to outflow (through vascular or extravascular pathways) is comparable to the time required for convection, then at *early* times detectable amounts of tracer may reach the outflow by diffusion. It may summate with tracer arriving there via the flow pathway or may even precede it, as suggested by the left upper diagram. However, at *later* times, tracer that is deep within the tissue tends to be retained by the same diffusional shunting, since in this case the tracer concentration gradient is from the outflow region toward the inflow region; the tracer tends to recirculate within the organ, as suggested by the left lower diagram. In this latter case, the clearance is much less than the flow. Perhaps the best example of this is seen in the experiments of Setchell et al.,³⁴ where they showed that the rate of ^{85}Kr washout from the ram's testis was almost purely monoexponential for nearly four orders of magnitude diminution of $R(t)$. The interlacing rete of venous outflow and arterial inflow vessels maximizes countercurrent exchange of heat (thereby keeping the testis cool) and undoubtedly also maximizes the shunting of ^{85}Kr , slowing the washout and diminishing $\eta(t)$.

Because of the possible clinical importance of countercurrent diffusional shunting of highly permeable substances, such as xenon and oxygen, in the partially ischemic myocardium, particularly in the subendocardial regions, the phenomena occurring in region II will be described in more detail. The subendocardial region is particularly subject to the influence of any diffusional shunt, because the arterial inflow and venous outflow vessels travel together in triads (as shown in Fig. 2) from the endocardium to where the major arteries and veins are situated on the epicardium. The diagrammatic representation in Fig. 15 (left) is appropriate in this situation, particularly so because the capillaries are very long (~1 mm) and end-to-end diffusion slow, and long compared to side-to-side intercapillary distances (17–20 μm) and venule-to-arteriole distances (15–50 μm), as shown by Bassingthwaighte et al.⁴ and Henquell et al.³⁵

Let us consider region II in more detail for the situation following a bolus injection of a highly diffusible tracer into the coronary artery inflow. The average, or steadystate, value of the fractional escape rate, $\eta(t)$, will always be $F/\lambda V$ for any tracer whose diffusional characteristics put it into regions I, II, or III. (λ is the tissue–blood partition coefficient and V the organ volume, as in equation 15.) Then we can consider the observed clearance or $\eta(t)$ relative to that which would be expected were there no diffusional shunting. The situation is complicated by the reality that $\eta(t)$ is never constant in the heart, but rises rapidly to a peak just after washout begins and then diminishes gradually.⁸ Consider the behaviour at two flows, F_a and F_b , in Fig. 16. F_b falls in a region where it has been ascertained that there is no difference between iodoantipyrine and ^3HHO washout; therefore, the fractional escape rate at any particular phase of washout at flow F_b can serve as a reference standard for $\eta(t)$ at the lower flow F_a .

The left panel of Fig. 16 emphasizes region II; the actual size of the region and shapes of the curves depends very much on the geometry of the organ as well as on the nature of the

tracer. But in all situations, the clearance is a monotonically increasing function of the flow; there is no situation in which an increase in flow leads to a decrease in clearance. However, for a change in flow near the upper end of region II, at a time when tracer is entering the inflow (upper curve, left panel), it can be seen that the ratio of clearance to flow decreases as flow increases, or that the slope of the line decreases. Conversely, during the late phase of washout (lower curve), an increase in flow increases the ratio of clearance to flow; clearance increases more than in proportion to flow.

The right panel of Fig. 16 illustrates the comparison of the $\eta(t)$ s at flows F_a and F_b , where they are scaled by their mean transit times, $\bar{t}$ or $\lambda V/F$. At early times t_1 and t_2 , the diffusional shunt from the inflow region to the outflow adds to the otherwise expected escape rate; at late times t_4 and t_5 , the shunt from outflow region to inflow region retains some tracer and reduces the escape rate.

Quantitation of Diffusional Shunting

The type of normalization shown in Fig. 16 leads toward a definition of the degree of diffusional shunting. One can see at any particular relative time, $t/\bar{t}$, that when there is a reference situation, such as F_b , where no shunting occurs then a ratio can be used to describe the fractional or percentage diffusional shunting or retention:

$$\frac{\bar{t}_a \cdot \eta_a(t/\bar{t}_a)}{\bar{t}_b \cdot \eta_b(t/\bar{t}_b)} > 1: \text{diffusional shunting}$$

$$\frac{\bar{t}_a \cdot \eta_a(t/\bar{t}_a)}{\bar{t}_b \cdot \eta_b(t/\bar{t}_b)} < 1: \text{diffusional retention}$$

and S , the percent shunt at time $t/\bar{t}_a$, is:

$$S(t/\bar{t}_a) = 100 \left[\frac{\bar{t}_a \cdot \eta_a(t/\bar{t}_a)}{\bar{t}_b \cdot \eta_b(t/\bar{t}_b)} - 1 \right] \% \quad (25)$$

where negative values indicate percent retention. The maximum value of the function defined in equation 25 is highly dependent on the geometry of the vasculature and so will not provide a good general description of the degree of shunting. The integral of equation 25 up to the time of the crossover at t_3 will give an average value for the percent shunt:

$$\% \text{ Diffusional shunt} = - \frac{100 \bar{t}_a}{t_3} \int_0^{t_3/\bar{t}_a} S(t/\bar{t}_a) d(t/\bar{t}_a) \quad (26)$$

An alternative to equation 26 is to use the normalized residue functions, similar to those in Fig. 14 (upper panel), taking the area between the $R(t)$ s for a reference tracer not participating in the diffusional shunting (e.g. iodoantipyrine, analogous to a high flow) and the test tracer (analogous to the curve at low flow) up to the time of the crossover, and dividing by $\bar{t}$. Since an area has the dimension of time, this provides a measure of the shunting. The area between the tails of the two $R(t)$ s is equivalent, since the $\bar{t}$ of the system is not affected by the presence of diffusional shunting; however, as in Fig. 14, this area is very extended and thus difficult or impossible to measure. The “shunt” area divided by the whole area gives a quantitative measure of the shunt:

$$\begin{aligned}
 \% \text{ Shunt} &= \frac{100 \int_0^{t_c} (R_{\text{ref}} - R) dt}{\int_0^{\infty} R_{\text{ref}} dt} \\
 &= \frac{100}{t} \int_0^{t_c} (R_{\text{ref}}(t) - R(t)) dt
 \end{aligned}
 \tag{27}$$

where t_c is the time of the crossover, and $R_{\text{ref}}(t)$ and $R(t)$ are the residue function for the reference tracer and the shunting tracer. This formula should be more suitable than equation 26, since the crossover times will differ for $\eta(t)$ and $R(t)$ as suggested by the comparison of the upper and lower panels of Fig. 14.

Awareness of the possibility of diffusional shunting is important so that it may be considered when interpreting washout curves. The increased initial rate of washout can be mistaken for evidence of high flow or evidence for increased heterogeneity, which may not be easy to distinguish from shunting when appropriate testing has not been done.

Region of Local “Radial” Flow-Limitation to Washout

In region III, the washout is flow-limited, but in a less general way than considered in Fig. 1, and in a different fashion than described for region I. Region III is considered to define local rather than global flow-limited exchange between blood and tissue. This can be most easily seen by considering a capillary–tissue region that is much longer than it is wide. A Krogh cylinder (Fig. 3A) is a good example but is unnecessarily simplified—all that is required is that permeation and radial diffusion locally at right angles to the general direction of flow is very fast, obliterating any radial concentration gradients, compared to diffusion along the length of the system from entrance to exit. (This was the conceptual model used by Goresky, 27 it is the Sangren-Sheppard³⁶ model with infinite capillary permeability.) The concentration profiles in such a system are uniform radially at any particular point along the capillary, but there may be large axial or source-to-sink gradients, as seen in Fig. 17.

Not all organs will show regions I, II, and III, even for a single capillary–tissue element. Region I will presumably exist if the tissue can survive at flows so low as to allow complete axial and radial diffusional equilibration. Region II will exist, no matter what the geometry, whenever source-to-sink (para-axial) convection and diffusion are of the same order of magnitude, as shown by Perl and Chinard.³⁷ But region III cannot exist except under rather restricted circumstances, namely that convective velocity is large compared to diffusive velocity in the source–sink direction and small compared to the local radial diffusive velocity. The heart is not unique in this respect; for example, the liver operates principally in region III for all extracellular tracers,^{27,38} but it is not obvious that skeletal muscle has the same possibility—intereapillary distances there are much larger than in either the heart or the liver. Our chosen reference tracer demonstrating flow-limited washout in the heart is antipyrine labeled with iodine for external detection or ^{14}C for beta-counting. Other gamma-emitting flow-limited tracers should be explored, seeking to avoid the problems in using iodine and to obtain a shorter biologic half-life.

Regions at Partial and Complete Diffusion-Limitation to Washout

In region IV, where exchange is partially flow-limited and partly diffusion-limited, the clearance fails to increase in proportion to the flow. This region extends from the upper end of the flow-limited region III, where F/PS (flow divided by permeability-surface area product) is very small, to the lower end of region V, where PS/F is very small and where permeation, PS , or radial diffusivity completely limit the washout. Since flow changes of two or three orders of magnitude are ordinarily impossible in a functioning tissue, the region represents the clearance–flow relationship for a variety of solutes of differing radial

diffusivity (permeation or radial diffusion). Small lipophilic substances in the heart tend to fall into region III, and small hydrophilic solutes, such as urea and potassium, are at the lower end of region IV. Figure 13 shows that the transcapillary extraction of potassium decreased with increasing flow, as expected for substances in region IV. (The corollary is that potassium deposition will have reduced sensitivity for defining regional blood flow.) Larger molecular weight hydrophilic solutes, such as vitamin B₁₂ (mol wt, 1356) and insulin (mol wt, 6000), are at the upper end of region IV, where F/PS is higher and exchange between blood and tissue is limited by the time taken for transport across the capillary endothelium. For these and larger substances, such as myoglobin (mol wt, 30,000), there may also be some interstitial radial diffusion limitation in the tissue, as in Fig. 18, in addition to the permeability limitation at the capillary endothelium.

For hydrophilic solutes the size of albumin (mol wt, 70,000) and upwards, the heart is essentially in region V. Albumin extraction during single transcapillary passage is less than 1%, low enough that one cannot confidently distinguish albumin removal by surface absorption on the endothelium or by trans-endothelial permeation.

Solutes, substrates, and metabolites involved in beat-to-beat cellular functions in the heart mainly lie in region III and the lower range of region IV. Exceptions are O₂ and CO₂, which probably fall into region II. It is conceivable that diffusional shunting of O₂ may contribute to the compromise of the subendocardial regions when flow to this region is slowed.

EFFECTS OF HETEROGENEITY OF FLOW ON WASHOUT

The concepts described thus far were expressed in terms of single capillary–tissue regions or an organ composed of a multitude of like regions behaving independently and in parallel. The behavior of an aggregate organ composed of *unlike* independent units in parallel is more complex, but it is mathematically treatable. Diffusional interaction between unlike units tends to be analytically intractable, but the local behavior is akin to the phenomenon of diffusional shunting. Detailed consideration of heterogeneity is a rapidly developing phase of research in this field. The heterogeneity in flow is the first of the several probable heterogeneities (permeability, volumes of distribution, intercapillary distances, etc.) to be explored. Variation in regional myocardial blood flow is familiar to those who have used microsphere deposition techniques in animals or Anger camera approaches to obtaining xenon washout curves from multiple sites in clinical situations.

The true extent of the heterogeneity is difficult to estimate: obviously, the smaller the regions examined the greater will be the apparent dispersion. With microspheres, the statistical problems introduced by cutting the pieces smaller and smaller occur simply by virtue of the inability to represent relative flow quantitatively by a smaller and smaller integer number of spheres with some statistical probability of being deposited in proportion to flow.³⁹ In the limit, a very small piece of tissue either does or does not contain a sphere, which can scarcely convey graded information. The technique developed by Yipintsoi et al. merits special consideration for use as a standard for estimating heterogeneity.⁴⁰ They cut the hearts into four or five slices from apex to base. Each slice of left ventricle was cut into 8 wedges at 45° angles, and each wedge cut into 10–12 sections from endocardium to epicardium, as shown in Fig. 19. The density of deposition of microspheres is represented by the thickness of the shading lines in the figure.

The extent of the heterogeneity is better seen in Fig. 20, showing deposition densities of 9-μ microspheres (injected into left atrium) in one slice of the mid-left ventricle from an anaesthetized baboon. Note the tendency toward greater density in the subendocardial regions; this is typical of the data from anaesthetized baboons but is not so clearly evident in awake animals at rest, during mild and moderate exercise, and during low and high levels of

heat stress. (There was no systematic difference between 9- μ and 15- μ microspheres in this animal; in general, to reduce any tendency for maldistribution due to the use of larger microspheres, we prefer the smaller ones, but have used the 15- μ microspheres extensively to minimize costs.)

These distributions are best seen as probability density functions of relative flows (relative deposition densities). In Fig. 21, six distributions are shown for the left ventricle of one awake baboon, each obtained by left ventricular injection of microspheres in a different steady state of cardiac output and absolute level of coronary blood flow at rest and during heat stress. Two observations are relevant: (1) the distribution of flows ranges from just about 0.3 to over 2 times the mean myocardial blood flow, and (2) the distributions have approximately the same shape in each situation. The latter observation suggests that the basis for similarity of transcortical transport functions (as shown in Fig. 11) may simply be that the distribution of flows in a given heart is very nearly constant over a wide range of circumstances. This idea is supported by data from other baboons in this series: the distributions in a given baboon appear to be characteristic; when a distribution is skewed left or right at rest, it remains so during graded levels of heat stress or exercise. It would be surprising if this were so in a pathologic state, such as partial coronary obstruction and ischemia, but it might well hold true for normally perfused areas of myocardium in such disease states.

But the critical message provided by the distributions in Fig. 21 is the wide range of regional flows in a *normal* awake primate. This kind of information must be used in interpreting externally detected washout curves. The regions are large enough that there is little or no diffusion between regions, so that washout from a region is independent of other regions. Three factors are fundamental to the externally observed residue function curves: (1) the amount of tracer delivered to each region, which can be expected to be proportional to the relative regional flow, f_i , in region i ; (2) the regional residue function itself, $R_i(t)$, for a flow-limited tracer; and (3) the efficiency of external detection from the i^{th} region times the volume of that region, a combined factor, K_i . Putting these together by summation over N independent regions gives an expression for the overall residue function obtained via a detector NaI crystal or each of a set of detector crystals:

$$R(t) = \sum_{i=1}^{i=N} K_i f_i R_i(t) \quad (28)$$

Note that f_i is dimensionless, being the local flow in ml/sec/ml tissue divided by the mean coronary blood flow. This equation is highly relevant in any circumstance where a detector is receiving signals from a variety of depths within the myocardium or from more than a very small and superficial region. The information on regional flow is contained within the $R_i(t)$ and in the f_i .

If tracer is injected close to the myocardial capillary bed so that the time to reach each of the regions is small, then the combined factor, $K_i f_i$, can be isolated, since $R_i(0) = 1$, so that:

$$R(0) = \sum_{i=1}^{i=N} K_i f_i = 1.0 \quad (29)$$

In this situation, it can be seen that the f_i cannot be specified uniquely, although if N is small, the efficiency component of K_i known, and some restricting information available on

the possible f_i s it will be possible to make some estimates. This problem is conceptually identical to that of estimating microsphere deposition density by external detection, although with microspheres there is much more time to obtain better counting statistics. (Probably the best approach to solving this is 3-dimensional reconstruction from images in several planes. See the review by Gordon, Herman and Johnson.⁴¹)

A stronger approach is to combine the information in the f_i s with that in the $R_i(t)$ s. This can be done if similarity, as defined earlier in Fig. 12, holds for the various regions. It is not known whether this is true or not; those who use multiexponential analysis have assumed that similarity holds, which I suspect is correct, and have made the additional assumption the $R_i(t) = e^{-t/\tau_i}$, where τ_i is the time constant and equals $\lambda V_i/F_i$, which I feel is generally incorrect, although changes in washout rates will be directionally appropriate. One may safely write an equation assuming similarity and without assuming any particular form for the $R_i(t)$ s:

$$R(t) = \sum K_i f_i R'(f_i t) \quad (30)$$

where $R'(t/\tau_i)$ or $R'(f_i t)$ defines the shape of each of the similar residue functions. The use of the f_i as a scalar for time is based on the additional assumption that the ratio of intravascular to extravascular volumes is the same in each region, a point on which more information is needed. When the shape of $R'(t)$ is known, then the determination of the distribution of f_i s is a relatively straightforward optimization task of the sort described by Knopp et al.¹⁷ When $R'(t)$ is undefined, then the task is more difficult, but not impossible, because the bounds on the possible shapes for $R(t)$ are the monoexponential mixing chamber and the piston flow forms shown in Fig. 7. In this case, the optimization must involve not only the f_i s but also two or three shaping parameters for the family of $R_i(t)$ s.

It is conceivable that a further simplification might be reasonable, one which would greatly reduce the number of parameters to be optimized. The method necessitates a further assumption, the form of the probability density function of flows, the f_i s: assumption of a Gaussian distribution would mean determining two parameters—the mean and the standard deviation; permitting left or right skewed density functions would add a third parameter. Thus, when optimizing the shapes of $R'(t)$ and the distribution of f_i s only four to six parameters would need defining, far fewer than the number of data points available from a washout curve. Nevertheless, even if such an approximation gave excellent fits to the data, the resolution in defining the f_i s would remain dependent on the accuracy of estimation of $R'(t)$, and the question to be explored is the sensitivity of the f_i s to errors in $R'(t)$. Because of the bounds on $R'(t)$ (Fig. 7), the sensitivity may not be very great; in addition, there are good possibilities for narrowing the bounds on reasonable shapes for $R'(t)$, thereby reducing the sensitivity and increasing the accuracy of the flow estimation.

SUMMARY

The time course of washout of tracer from the myocardium provides an estimate of the flow per unit volume when the blood–tissue exchange is flow-limited. Methods of testing for the flow-limitation and for the absence of influences of low permeability or diffusion on the washout include the uses of paired or multiple tracers and the examination for similarity of the shapes of the residue function or washout curves at varied coronary blood flows. A conceptual framework for these studies is provided by a clearance-flow diagram for the myocardium where capillaries are long compared to radial intercapillary distances. This anatomic–physiologic framework coupled with a probabilistic, general analytical approach and with various experimental approaches to tracer studies of mass transport through the

heart provides a general basis for methods of estimating myocardial blood flow in the whole organ and in its component regions.

Acknowledgments

Discussion with Dr. Tada Yipintsoi over the past several years has contributed immeasurably to the expression of these concepts. Thanks are extended to Sylvia Danielson who prepared the manuscript and to Hedi Nuts for the illustrations. Dr. G. A. Holloway, Jr., provided most helpful criticisms. Dr. David Williams developed the shading for Fig. 20.

Supported in part by NIH Grants HL 19135 and HL 19139.

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Fig. 1. Clearance-flow diagram, following Renkin.³ The thin line of identity, where clearance equals flow, signifies that washout is completely flow-limited.

Fig. 2. Microvasculature of the dog left ventricular myocardium. The vessels are filled with a white elastomer (Microfil, MV 112, Canton Biomedical Products, Inc., Boulder, Colo. 80302) and the tissue rendered transparent by replacement of the water with alcohol, then methyl salicylate. In the left to lower region is an arteriole accompanied by two venules, a typical triad. Capillaries are long and generally parallel, but have branches and interconnections. (Reproduced by permission.⁴)

Fig. 3. Adaptations of Krogh cylinder models to the myocardial microvasculature. (A) The traditional concurrent flow model composed of hexagonal axisymmetric columns of equal length. With concurrent, identical flows in adjacent capillaries having coincident entrances and exits, there are no concentration gradients across the interfaces between regions and no net fluxes between hexagons. (B) A combination of concurrent flows in each of two groups flowing in countercurrent fashion. The exact coincidence of starting and ending points is unrealistic but quantitatively may be representative, since capillary lengths are long compared to the length over which the sudden branching from the arterioles and the confluence into the venules occur.

Fig. 4.

Diagram of experimental approaches to measuring the response of a system to a slug injection of tracer of dose m_i . The left lower striped cylinder represents an idealized gamma detector providing a signal proportional to the amount of indicator, $q(t)$, contained in the organ of volume V at time t , and which gives the residue function $R(t)$. The uppermost detector provides a signal from the outflow, proportional to the effluent concentration–time curve and to $h(t)$. Only in an idealized nonrecirculating system can $H(t)$ be directly estimated by measuring the cumulative amount of indicator having left the organ and being collected in the chamber in front of the detector on the right.

Fig. 5. Relationships between $h(t)$, $H(t)$, $R(t)$, and $\eta(t)$. The curve of $h(t)$ is given by a lagged normal density curve⁴² having a relative dispersion of 0.33 and a skewness of 1.5. However, the theory is general and applies to $h(t)$ s of all shapes. (Figs. 5–9 are similar to figures published in *Seminars in Nuclear Medicine*.⁴⁵)

Fig. 6.

Tracer dilution curve with monoexponential extrapolation. The curve of tracer passing the sampling site for the first time (not recirculating) is termed the *primary curve*. The extrapolation is exponential, following Hamilton et al.¹⁶ and is an approximation. The equation for flow applies to the primary curve.

Fig. 7.

Three residue function curves, $R(t)$, may have quite differing shapes (A, B, and C) but have the same area beneath the curve, $\int_0^\infty R(t) dt$, and give the same estimate of flow per unit volume. Curve A represents a uniform mixing chamber; curve C represents a "piston flow" system, with all transit times the same.

Fig. 8.

Combined intravascular and external detection. External detection provides $\bar{t}$ by equation 14A and the slope dR/dt at a particular sampling time t_s . Sampling from the venous outflow from the organ at t provides the concentration, $C_v(t_s)$. The combination allows estimation of F , F/V , and therefore of V . The main source of difficulty in applying this technique is ascertaining the time delay between the organ and the sampling site in the outflow.

Fig. 9. Truncation of the integration of $R(t)$ to provide an approximate value for $F/\lambda V$ when recirculation masks the terminal portion of the curve. The approximation is exact when $R(t)$ is monoexponential.

Fig. 10.

Diagrammatic representation of the effect of a doubling of flow rate in a system with a constant relative distribution of transit times, as would occur in a stable laminar flow system. When the flow is doubled, the area of the dilution curve is halved, and the transit time through any particular path (*D* or *E*) between *A* and *B* is also halved. In such a system, the various measures of the breadth of concentration–time curves are linearly related to the mean transit time (see text).

Fig. 11.

Transcoronary transport functions for plasma protein-bound indocyanine green obtained at varied flow rates ($\bar{t}$ from 5.3 to 9.1 sec) in the dog. The similarity of the curves indicates flow-limited intraorgan distribution of the dye and constancy of the relative distribution of flows. The ordinate is the fraction emerging per mean transit time at each time t , and unity on the abscissa is 1 mean transit time. (Data from experiments of Knopp et al.17)

Fig. 12.

(A) "Similarity" of a family of residue function curves can be tested by plotting curves obtained at differing flows (left) each against time divided by its own mean transit time. Superimposition of the curves indicates similarity and that solute washout is flow-limited (right). (B) 125 Iodoantipyrine washout curves obtained by external γ -detection of a blood-perfused isolated heart after bolus injection into the cannulated aortic root at various flows. F/W is the flow ($\text{ml/g}^{-1}/\text{min}^{-1}$) listed in order of the times at which $R(t) = 0.5$. Broken lines, $F/W > 2$; solid lines, $1 < F/W < 2$; dotted lines, $F/W < 1 \text{ ml/g}^{-1}/\text{min}^{-1}$. The range was narrow and the order apparently random, therefore, the curves demonstrate similarity.

Fig. 13.

Effect of flow and venous ^{131}I -albumin and ^{42}K curves and ^{42}K extractions. Venous concentration-time curves for ^{131}I -labeled albumin [$h_R(t)$] and $^{42}\text{K}^+$ [$h_K(t)$] were normalized to fraction of injected dose, as in equation 2. At high flow (left), a greater fraction of injected dose is recovered in a shorter period, and curves are less temporally dispersed than at low flow (right). Fractional extractions [$E(t)$, broken lines] increase to maximum ($E_{\max}$) at or slightly before time of peak of $h_R(t)$. $E_{\max}$ is higher at a low flow and persists for approximately 4 sec before a decrease in $E(t)$ is seen. (Reproduced by permission.⁴³)

Fig. 14.

Numerical solutions for the residue functions obtained from a countercurrent exchange model, similar to that of Fig. 3B, at two different flows. The curves have been normalized by abscissa scaling in proportion to $\bar{t}$, so that they would be identical if there were no diffusional shunting between inflow and outflow. Note that prolongation of the tail at the lower flow. The corollary of early shunting is late retention: tracer that is in the depths of the tissue will have a tendency to be shunted from outflow to inflow and so be retained longer in the tissue than would occur if the washout were solely flow-limited.⁷

Fig. 15.
Source-to-sink diffusion. Influences of diffusional transfer of tracer between inflow and outflow on clearance.

Fig. 16.

Influence of diffusional shunting on clearance following an impulse injection into the arterial inflow. (A) Clearance–flow relationship at various times after tracer injection. These relationships exist only momentarily following a sudden injection, but each would apply in the steady state if the relative local concentrations were stable. Thus, at time t_1 , tracer is principally in the inflow region, and at time t_5 , tracer is deep within the tissue, as suggested by “early” and “late” in Fig. 15. (B) Normalized emergence functions at two flows: F_a , where shunting is apparent and at a higher flow, and F_b , where convective transport is rapid and diffusional shunting negligible.

Fig. 17.

Local radial concentration equilibration and negligible axial diffusional transport from entrance to exit means flow-limited exchange of tracer, region III of Fig. 15. Flow in the capillary is from left to right; relative brightness indicates relative concentrations in capillary and tissue after an impulse injection at the upper end of the capillary 0.3 sec earlier. Solution of convection-diffusion model of Bassingthwaighte, Knopp, and Hazelrig⁴⁴ with $D_R \gg D_x$ radial diffusivity much greater than axial.

Fig. 18. Concentration profiles in capillary–tissue model with a significant capillary permeability barrier and additional radial diffusion limitation. Response to impulse injection of tracer at the input 0.5 sec earlier. Flow in capillary is from left to right. Solution of convection–diffusion model of Bassingthwaighe, Knopp, and Hazelrig⁴⁴ with capillary velocity = 0.1 cm/sec, $PS/F = 2$, and radial diffusive velocity = diffusion coefficient/cylinder radius = 0.04 cm/sec. The lower panel shows the concentration–time curve at the outflow.

Fig. 19. (A) Frontal view of dog heart. (B) Coronal rings of left ventricle: top ring is base of heart. Arrows point to position of major coronary vessels on these rings. (C) Diagram of the division of one left ventricular ring into 8 segments and into 12 concentric cylinders from endocardium to epicardium. (Reproduced with permission from the American Heart Association.⁴⁰)

Fig. 20.

Relative deposition densities of 9μ microspheres in a 1-cm thick mid-left ventricular slice of an anaesthetized baboon heart, demonstrating higher densities (flows) in the subendocardial region. The densities relative to the mean density for the heart are shown by the shading according to the calibration scale. Gradations are at 0.13 times the mean flow for the whole heart, so that in this slice, the range was from 0.6 to 1.9 times the mean myocardial flow. The relative areas are proportional to the mass of each piece, there being six pieces from endocardium to epicardium. (Data from experiments with R. B. King, J. R. S. Holes, L. B. Rowell, and O. A. Smith.)

Fig. 21.

Frequency functions of relative deposition densities of microspheres in the whole left ventricle of one awake baboon, interpreted as regional flows relative to the mean myocardial flow. Six situations are represented, two at rest, two at moderate heat stress (low), and two at severe heat stress (high). The coronary blood flows were: control, 2.33 and 2.31 ml/g⁻¹/min⁻¹; low heat stress, 1.4 and 1.9; and high heat stress, 2.0 and 3.0. The relative dispersions of the six distributions were 0.25 ± 0.03 . (Experiments with R. B. King, J. R. S. Hales, L. B. Rowell, and O. A. Smith.)