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Transcoronary Intravascular Transport Functions Obtained via a Stable Deconvolution Technique¹

T. J. Knopp, W. A. Dobbs², J. F. Greenleaf³, and J. B. Bassingthwaight⁴

Department of Physiology and Biophysics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

Abstract

Following left atrial injection of indocyanine green in closed-chest, anesthetized dogs, 60 simultaneous input–output pairs of dilution curves were sampled via identical catheter sampling systems from the aortic root, $C_{in}(t)$, and the coronary sinus, $C_{out}(t)$. Assuming that $C_{out}(t)$ was the convolution of a transport function, $h(t)$, and $C_{in}(t)$, a new deconvolution technique was used to solve for the $h(t)$'s which was not sensitive to noise, recirculation, or the form of $h(t)$.

The 60 transcoronary $h(t)$'s were observed to be unimodal, right-skewed frequency distribution functions with mean transit times, $\bar{t}$, ranging from 3 to 7 sec. The relative dispersions (standard deviation, σ , divided by $\bar{t}$) averaged 0.38 ± 0.05 , the skewness averaged 1.40 ± 0.37 and the kurtosis averaged 6.1 ± 1.8 ; this means that the $h(t)$'s are more sharply peaked than Gaussian distributions. The fact that parameters were statistically independent of the mean transit time implied the constancy of the shape of the various $h(t)$'s and this was verified by the coincidence of the $h(t)$'s plotted as a function of $t/\bar{t}$. This "similarity" of the $h(t)$'s strongly suggests that changes in the transit time through any particular vascular pathway of the coronary bed are in proportion to the changes in other parallel pathways.

INTRODUCTION

Because intravascular dispersion is influenced by such a multiplicity of factors, both within single vessels (diffusion, turbulence, mixing and eddy formation, and the velocity profile) and within an organ bed (variations in path lengths and in regional flows and volumes), one can anticipate that different organ vascular beds will have different dispersive characteristics. Descriptors of individual vascular beds are important not only in order to formulate descriptions of humoral transport throughout the whole body, but they are also essential components of quantitative descriptions of the transport of substrates, metabolites, and drugs to and from individual organs. This study was undertaken to define the intravascular dispersion that results in a single traversal of the coronary bed extending from the root of the aorta to the coronary sinus.

Transport functions, the probability density functions of transit times through a system, have been described for single vessels (Bassingthwaight *et al.*, 1966a, 1967) and across various organs (Coulam *et al.*, 1966; Knopp *et al.*, 1969; Maseri *et al.*, 1970) and generally have

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²NIH postdoctoral fellow. Present address: Department of Pharmacology, CIBA-GEIGY, Summit, N. J. 07901.

³NIH postdoctoral fellow; now receiving NIH Cancer Development Award.

⁴Supported by an NIH Career Development Award. Present address: Center for Bioengineering, University of Washington, Seattle, Washington 98195.

been found to be simple unimodal density functions which can be characterized by their mean transit times, $\bar{t}$, their relative dispersion, $\sigma/\bar{t}$ (where σ is the standard deviation of the density function) and their skewness. This characterization seems to hold whether the transport functions had been obtained in terms of specific simple models (Bassingthwaighte *et al.*, 1966a, 1967; Knopp *et al.*, 1969), via Fourier transforms (Coulam *et al.*, 1966), or via numerical deconvolution (Maseri *et al.*, 1970). Even so, in undertaking the examination of the coronary vascular bed, we felt it important to utilize a technique which would assuredly provide an estimate of $h(t)$ that was independent of any specific unimodal model. Thus we have evolved a rather general approach which has previously been presented and tested only in a preliminary fashion (Greenleaf *et al.*, 1968; Knopp *et al.*, 1969). The approach to the experiments is based on the observation that it is futile to attempt to produce an ideal impulse injection giving flow-proportional labeling at the entrance to the coronary bed. The alternative used was to inject at a point upstream from the inflow into the mid-left atrium, allowing mixing during passage through the mitral and aortic valves and the left ventricle and then to sample the blood in the aortic root at the level of the coronary arteries to obtain an inflow concentration-time curve, $C_{in}(t)$, without disturbing the coronary bed, while simultaneously sampling the coronary sinus to obtain the output curve, $C_{out}(t)$. In a linear, stationary system, the relationship between $C_{out}(t)$ and $C_{in}(t)$ is defined by the transport function, $h(t)$, the probability density function of transit times across the organ, as expressed by the convolution integral

$$C_{out}(t) = \int_0^t C_{in}(\tau) h(t - \tau) d\tau, \quad (1)$$

where τ is a variable used only for the integration. When $C_{in}(t)$ and $C_{out}(t)$ are known, then estimates of $h(t)$ can be obtained by deconvolution, and the adequacy of the estimate can be tested by convoluting $C_{in}(t)$ with $h(t)$ to see if the result is a curve closely matching the true $C_{out}(t)$.

EXPERIMENTAL METHODS

Preparation of the Animal

The experiments were performed on three dogs anesthetized with 30 mg/kg sodium pentobarbital, intubated, and artificially ventilated at 40 breaths/min, so that nonstationarities at respiratory frequencies would not compromise the calculation of $h(t)$, as they would if the rate were only 10/min (Bassingthwaighte *et al.*, 1970). An arterial pressure cannula was introduced into the left femoral artery. An aortic sampling catheter was introduced by needle puncture of the right common carotid artery, and the tip was threaded into a position within the aortic root at the level of the ostia of the coronary arteries. The coronary sinus catheter was introduced by a cut-down on the left jugular vein and threaded into the coronary sinus. Proper placement of the catheters was confirmed by X-ray examination and by observation after injection of Renovist (E. R. Squibb and Sons, New York) into the coronary sinus catheter.

To demonstrate that the coronary sinus sample was not contaminated by blood refluxing from the right atrium, we ascertained that indocyanine green injected into the inferior vena cava appeared at the coronary sinus catheter later than at the aortic root catheter. A catheter (No. 6 Lehman, 100 cm) was threaded through an 11 in. No. 19 transseptal needle in the right jugular vein into the mid-left atrium for dye injection. It was filled with indocyanine green dye, 1.25 mg/ml, and approximately 0.4 ml boluses were injected in less than 0.5 sec using a pneumatic injection syringe at 8.5 lb per square inch pressure. The resulting dye-dilution curves were sampled from the aortic root, $C_{in}(t)$, and coronary sinus, $C_{out}(t)$. In

general, the methods were similar to those described earlier (Knopp *et al.*, 1969) for obtaining the transpulmonary transport functions.

The sampling catheters were carefully matched to have identical responses to step change in dye concentration at the catheter tip, as far as was possible, and their mean transit times were always within 0.2%. This was necessary in order to avoid correcting each dilution curve for the catheter transport function as discussed previously (Bassingthwaighte, 1966a). The catheters were No. 6F Teflon tubing (i.d. = 0.075 mm, o.d. = 2 mm, length = 45 cm) with a volume of 0.8 ml. Blood was sampled through the catheters and attached densitometers (XC100A, Waters Co., Rochester, Minn.) using a Harvard dual syringe pump (Harvard Apparatus Co., Dover, Mass.).

The dye solution was made up by dissolving 50 mg of indocyanine green dye (Cardio Green, Hynson Wescott and Dunning, Baltimore, Md.), then adding physiological saline to 37 ml, and bringing the final volume to 40 ml by adding 3 ml of the dog's blood; in the past this has produced optically stable dilutions (Bassingthwaighte *et al.*, 1964). Repeated calibrations during these experiments differed by not more than 1.5% and confirmed that stability was adequate. Calibrations were done by using a control of undyed blood and four different dye concentrations in blood three times during each animal experiment: at the beginning, in the middle, and at the end. These were done on both arterial and venous blood to avoid errors due to differences in oxygen saturation or to differences in hematocrit during the experiment, as was shown to be necessary for precise quantitation (Edwards *et al.*, 1963). The calibration data were analyzed essentially as described previously (Bassingthwaighte *et al.*, 1964) for these densitometers, which provide a Beer's law relationship between detector output and dye concentration over the range 0 to 20 mg per liter. The densitometers were set up carefully so that their calibrations were independent of the level of background dye in the blood (Edwards *et al.*, 1963).

For analysis, analog tape recordings (Sanborn Model 3924B) were made of airway pressure, arterial pressure, injection syringe travel, aortic and coronary sinus dilution curves, and densitometer calibrations. The indicator-dilution curves were digitized at 50 samples per second after filtering with a low-pass filter with a 10-cps cutoff at 6 db per octave, then reduced to 150 samples over a recording period of 24 to 35 sec. In one animal manual digitization was performed by using 3.5 samples per second from the photokymographic recording.

In order to provide a range of shapes of input curves and to vary coronary blood flow, in one animal (6069) curves were obtained during infusion of two micro-grams/min of isoproterenol (Isuprel) (three curves) or 0.1 ml of levoterrenol (Levophed) (three curves) or 0.1 mg/min of acetylcholine (four curves) into the arch of the aorta to alter peripheral resistance.

Theoretical Approach

A deconvolution technique has seemed particularly important in examining the coronary vascular bed, because the dispersion produced by the injection of tracer, either in the aortic root or in a single coronary vessel, would inevitably be large compared with the transport function itself. Therefore, in these experiments we adhere to the principle that the most accurate measurements of the transport function of the bed are obtained by avoiding a dispersive and disturbing injection into the inflow; we avoided it by injecting a bolus somewhat upstream to the inflow site (into the left atrium) and sampling from the root of the aorta to obtain the concentration-time curve $C_{in}(t)$ and from the coronary sinus to obtain the curve $C_{out}(t)$. Correction for catheter dispersion may be avoided without influencing the determination of the transport function simply by using rapid sampling systems with

identical impulse responses at the two sites, as has been done previously (Bassingthwaight *et al.*, 1966a, 1967; Coulam *et al.*, 1966; Knopp *et al.*, 1969).

Our original intention was to develop a one-pass technique, without iterations, providing $h(t)$. The previously used Fourier transform technique (Coulam *et al.*, 1966) theoretically should have been such a method, but random, relatively high-frequency noise plus problems in dealing with the nonperiodic curves resulted in the need to use three or more iterations to attain reasonable descriptions of $h(t)$, and even then the $h(t)$'s very often showed unrealistic oscillations in their tail portions. Straightforward numerical deconvolution had proven unusable for obtaining refined descriptions, again principally because of unavoidable small amounts of noise in the data which led to marked oscillations with the tails of the $h(t)$'s. Maseri *et al.* (1970) apparently successfully used a straightforward numerical deconvolution method for characterizing transpulmonary transport functions when the recorded dilution curves were represented by concentrations averaged over successive 1-sec intervals. However, our test of this method showed that only by using an initial value of $C_{in}(t)$ well along the upslope [beyond 30 to 50% of the peak, which caused deformation of the upslope of the calculated $h(t)$] could severe oscillations of the tails be avoided, and there tended to be large errors in the calculated form of the tail, as has been observed also by Gamel *et al.* (1973). The Z transform method of Neufeld (1971) appears less susceptible to noise and to input and output curve truncation than the Fourier transform technique, and it can solve for transport functions rapidly, providing reasonably accurate mean transit times. Transport functions obtained by the Z transform method, although providing good fits to the experimental data, show nonuniqueness in transport function shape that is related to noise, sampling density, and curve truncation which makes it difficult to compare transport functions visually and impossible to compare them in terms of higher moments.

The principle of our new method is to obtain an expression for $h(t)$ in terms of a weighted sum of fitting functions of differing forms, the $h_i(t)$'s. The analytical approach is designed to obtain values for the weighting vector, $\mathbf{f}$ ($f_1, f_2, f_3, \dots, f_N$), given a prechosen set of $h_i(t)$'s. In a linear system, the output function is the convolution of the input function with the transport function

$$C_{out}(t) = C_{in}(t) * h(t), \quad (1)$$

where the $*$ denotes the convolution integration. Equation (1) holds in spite of dye recirculation, provided that the recirculated dye is reflected in $C_{in}(t)$. We wish to find the weighting value, f_i , for each $h_i(t)$ such that Eq. (1) will hold with

$$h(t) = \sum_{i=1}^N f_i \cdot h_i(t), \quad (2)$$

where

$$\sum_{i=1}^N f_i = 1. \quad (3)$$

This allows us to derive $C_{out}'(t)$, which we desire to be identical to the recorded dilution curve $C_{out}(t)$, using the equation

$$C_{\text{out}}'(t) = \sum_{i=1}^N [f_i \cdot h_i(t) * C_{\text{in}}(t)]. \quad (4)$$

To avoid repeated convolutions and long computation times, matrix θ was obtained, where

$$\theta_i(t) = h_i(t) * C_{\text{in}}(t). \quad (5)$$

Equation (4) can then be rewritten in matrix notation:

$$C_{\text{out}}'(t) = \theta(t) \cdot \mathbf{f}. \quad (6)$$

$\mathbf{C}_{\text{out}}$, the vector form of $C_{\text{out}}(t)$, and the θ_i 's were interpolated so that each consisted of 150 values in time. An error, E , was minimized in the iterative solution for the vector $\mathbf{f}$ and was defined as the sum of the squares of the difference between $\mathbf{C}_{\text{out}}$ and $\mathbf{C}_{\text{out}}'$:

$$E = \sum [C_{\text{out}}(t) - C_{\text{out}}'(t)]^2 = (\mathbf{C}_{\text{out}} - \theta \cdot \mathbf{f})^2. \quad (7)$$

Theoretically, $\mathbf{f}$ can be obtained from Eq. (7) with E minimized directly through matrix inversion of $\theta^T \theta$ (the premultiplication of matrix θ by its transpose, θ^T , is a square matrix which can be inverted):

$$\mathbf{f} = (\theta^T \theta)^{-1} \theta^T \mathbf{C}_{\text{out}}. \quad (8)$$

This was attempted, but in nearly every trial θ was found to be singular (using 48 bit, floating point arithmetic). This prohibited the solution for $(\theta^T \theta)^{-1}$ and necessitated the use of an iterative technique. Consequently, a steepest descent technique was used to minimize the error, E , of Eq. (7). Successive adjustments to $\mathbf{f}$ were indicated by the projection of θ on $\mathbf{C}_{\text{out}} - \theta \mathbf{f}$ using

$$-\nabla_f E = 2[\mathbf{C}_{\text{out}} - \theta \mathbf{f}] \theta^T. \quad (9)$$

$\nabla_f E$ is the derivative of fitting error, E , with respect to the vector $\mathbf{f}$ and all elements of $\nabla_f E$ go to 0 when a least-squares fit is obtained. The adjustment scheme for $\mathbf{f}$ was

$$f_{i(p+1)} = f_{i(p)} + \beta \nabla_f E_{i(p)}, \quad (10)$$

permitting $f_{i(p+1)} \geq 0$, where p is the index for the iteration and β is a convergence rate factor. β was chosen for each iteration by assuming that E is a quadratic function of β , solving for E at three different values of β , then choosing a final β as that where $dE/d\beta$ is zero (the point at which E is a minimum). This steepest descent technique has been thoroughly discussed by Bekey (1964); the present approach differs only in the method of obtaining values for β .

The simplest form for the h_i would be delayed delta functions with widths equal to DELT (the time interval used to digitize the experimental data), areas equal to 1.0, and delays equal to i times DELT. This yields a weighting function, the array of $\mathbf{f}_i$'s, that is identical to $\mathbf{h}$ but

requires that the number of fitting functions, N , be equal to the number of elements of C_{in} and C_{out} , resulting in very long computation times to reach a final solution. Choosing h_j as a more dispersed function allows a reduction of N , and thus greatly reduces the computation time. The relative dispersion for a particular fitting function was defined as its standard deviation, σ_j , about its mean time, $\bar{t}_j$. Figure 1 shows the $h(t)$'s and f 's for one input–output pair of dilution curves, using lagged normal density fitting functions (Bassingthwaighte *et al.*, 1967) with skewness, β_1 , equal to 1.0 and different values of the relative dispersion, $\sigma_j/\bar{t}_j$, for each solution. N for these data and all those which follow was 20 with the $\bar{t}_j$'s distributed geometrically between $\bar{t}_{min}$ and $\bar{t}_{max}$; that is, $\bar{t}_j = \bar{t}_1 A^j$, where $j = 1$ to N , A is a constant, and $\bar{t}_1$ is $\bar{t}_{min}$, the shortest fitting function mean time. The $\bar{t}_{min}$ and $\bar{t}_{max}$ were selected individually for each curve pair, C_{in} and C_{out} , such that increasing the range would not alter the resulting fit or the vector f . This particular form for the h_j 's was chosen since lagged NDC's with skewnesses of about 1.0 had been shown to be suitable for the arterial circulation (Bassingthwaighte, 1966a) and might conceivably be descriptive of transport functions through individual pathways or groups of pathways through the coronary microvasculature; this study cannot answer the question of whether they are or not, as discussed below.

The testing of different values for N showed that increasing the number of fitting functions to above 20 provided no further refinement in the goodness of fit. The results in Fig. 1 show that the form of h is seen to be only mildly dependent on $\sigma_j/\bar{t}_j$, but f was more influenced.

As another test of the independence of h from h_j , the Gaussian distribution was substituted for the lagged normal distribution for five pairs of indicator curves. In each case, the transport function obtained with the Gaussian distribution was nearly identical to that obtained with the lagged normal distribution; however, the f 's were somewhat more right-skewed. Had the fitting functions been chosen as delta functions, then f and h would be identical; the case in which the dispersions of the lagged normal density h_j was smallest, $\sigma_j/\bar{t}_j = 0.08$, shows a result not very different from this. The use of dispersed h_j appears to have little effect on the resolution of the technique unless the value for $\sigma_j/\bar{t}_j$ is quite large. Resolution of very high-frequency components is primarily limited by the form of the input function, C_{in} , since the energy spectrum of the calculated h cannot contain energy at frequencies for which there is no energy in the input curve. This has been shown by Gamel *et al.* (1973), who found that high-frequency noise, added to h , did not affect the computed C_{out} because of the filtering effect of the convolution of h and the input curve. Figure 1 showed that the form of h was not very different with relative dispersions of 0.08, 0.12, and 0.16; although for best fits we should have used 0.08, we arbitrarily chose to use 0.16, with $\beta_1 = 1$, since we surmised that this might be physiologically more appropriate. (The mean transit time for the lagged normal density function, the convolution of a Gaussian function and an exponential function, is the sum of the mean times of these two functions, and the standard deviation for the lagged normal function is the square root of the sum of the squares of the standard deviations of the Gaussian and exponential functions.)

RESULTS

Twenty-five pairs of indicator–dilution curves were obtained from a dog weighing 21 kg, 21 from a second weighing 22 kg, and 14 from a third (26 kg). Each experiment lasted less than 6 hr. Autopsy examination at the end of the experiments showed appropriate catheter placement and no cardiac abnormalities.

Examples of the indicator–dilution curves, C_{in} and C_{out} , recorded with this system are shown in Fig. 2. The transcoronary transport functions, h , displayed on the same time base are typically unimodal and right-skewed. In each case, the convolution of h with C_{in} is

given by C_{out}' , which is seen to fit the experimentally recorded output curve, C_{out} , very closely. The upper panel shows a better than average fit, with a coefficient of variation of 0.017 (the reciprocal of the mean concentration of C_{out} times the standard deviation of $C_{out} - C_{out}'$), whereas the average was 0.041 (range = 0.010 to 0.095). An example of an average fit with a coefficient of variation of 0.042 is shown in the bottom panel; in general, the fits were good through all phases of the dilution curve, including recirculation, with the variations being random in nature.

Transcoronary transport functions obtained over a range of coronary flow rates occurring spontaneously and induced by drug infusion are shown in Fig. 3 (left panels). These 60 curves showed, for each of the three dogs, a diminution in peak height and increased breadth with longer mean transit times. The shapes of the h 's, however, were quite similar over the full range of mean transit times. This is demonstrated by plotting the curves normalized with respect to mean transit time in the panels on the right side of Fig. 3, where the curves are seen to be roughly coincident, as is especially well seen in the upper two panels. The similarity of the normalized curves is reflected by the small standard deviations found in the statistical assessments of the curves; relative dispersion, $\sigma/\bar{t}$, was 0.38 ± 0.05 ($N = 60$), the skewness (third central moment to the power of $2/3$ divided by the variance) was 1.40 ± 0.37 , and the kurtosis (the square root of the fourth moment divided by the variance) was 6.14 ± 1.80 . (The kurtosis is 3.0 for a Gaussian distribution.) The ratio of appearance time to mean transit time, $t_d/\bar{t}$, was 0.40 ± 0.02 , $N = 60$, and the ratio of the time to the peak of h to the mean transit time, $t_p/\bar{t}$, was 0.76 ± 0.07 . Thus the relative dispersion for the whole organ is seen to be greater than that for a branched artery ($\sigma/\bar{t} = 0.18$) (Bassingthwaighte, 1966a), but less than that for the lung ($\sigma/\bar{t} = 0.46$) (Knopp *et al.*, 1969).

Of particular interest is the deviation of the form of h from simple unimodal models, which clearly could not provide nearly as good descriptions of h . The commonly used unimodal density functions such as the lagged normal density curve (Bassingthwaighte *et al.*, 1966a, 1966b), a gamma variate (Gomez *et al.*, 1965), or the log normal density function all have downslopes which are virtually indistinguishable from a single exponential in the tail region below 30% of peak height. The lagged normal density functions describing arterial transport functions (Bassingthwaighte, 1966a) had skewnesses of about 1.0, in accordance with a monoexponential downslope. But the present study gives estimates of h with skewnesses around 1.4, the difference being due to the prolonged tails; these can be seen particularly well in the left panels of Fig. 3. The high values for kurtosis of 6.1 have a similar basis: The long tail causes a high value for peakedness. This deviation from monoexponential downslopes can be expressed in another fashion: How much of the area of h would lie to the right of a monoexponential equation fitted to early portions of the downslope. When the region of the downslope between 70 and 30% of peak height is used for the fit, then roughly 2 to 12% of the area remained in the tail above the monoexponential extrapolation. As can be seen from Fig. 3, this was greater for dog 2069 (lower panels) than for dog 3069 (upper panels).

DISCUSSION

The application of any deconvolution technique is appropriate only if the system under study has the properties of linearity and stationarity. A linear response to injections of indocyanine green dye has been demonstrated for dye transport through the dog aorta (Bassingthwaighte *et al.*, 1967) and across the lung (Knopp *et al.*, 1969), and is to be expected in any mass conservative system with passive transport processes. No work in the literature suggests the existence of a carrier-mediated transport process or saturable binding site for indocyanine green in the myocardial capillary membranes. On this basis, linearity with respect to dye concentration was assumed for the myocardial capillary bed. Although the coronary bed is

nonstationary with respect to flow, the frequency of fluctuations in flow is high enough not to interfere with the analysis, cardiac frequencies being effectively filtered out by the low-pass filter characterized by h , as described in an earlier study on the effects of unsteady flow on dye-dilution curves (Bassingthwaighte *et al.*, 1970). In these experiments the cardiac cycle had a period of approximately 0.3 sec while the mean transit time through the coronary bed was approximately 5 sec. Therefore, we feel that the obvious high-frequency nonstationarity does not invalidate this technique for determining h , just as it did not invalidate our earlier approaches to obtaining intravascular transport functions (Bassingthwaighte *et al.*, 1966a, 1967; Knopp *et al.*, 1969).

This deconvolution analysis, using multiple fitting functions, has the advantage over some other deconvolution methods that the system input and output functions need not be forced into periodicity; that is, the tails of these curves need not return to their starting values. The determination of the fitting function weighting is easiest and fastest when the fitting functions are orthogonal; that is, when no h_j can be expressed as a linear combination of the others. For instance, N terms of a Fourier series would be obtained using the parallel pathway technique if orthogonal trigonometric fitting functions were selected.

The family of lagged normal density curves that we have used as fitting functions have not been proved mathematically to be orthogonal; however, since all have the same shape (relative dispersion and skewnesses) but have mean transit times differing by discrete, moderately large time intervals, the frequency content of any $h_j(t)$ is distinctly different from that of all the others. Thus the $h_j(t)$'s, even if not exactly orthogonal, at least contain components which are.

The Transcoronary Transport Function

Because coronary blood flow is not constant through the sampling interval, the transcoronary transport function requires a special interpretation. A transport function represents the distribution of transit times at a given instant in time, as has been described for linear but nonstationary systems with flow-dependent transport functions (Bassingthwaighte *et al.*, 1970). Since coronary blood flow changes markedly between systole and diastole, the transcoronary transport function is interpreted as the time averaged transport function over the sampling interval. If the heart rate, the systolic and diastolic intervals, and other flow parameters remain constant through the sampling interval, then h would represent the mean density function as a time-weighted average of the set of distributions of transit times over a cardiac cycle. This interpretation appears well justified since fluctuations in concentration at cardiac frequencies can be shown, by methods discussed previously (Bassingthwaighte *et al.*, 1970), to be substantially filtered out by the dispersion of h itself.

The shapes of the descending limbs of the transport functions shown in Fig. 3 are not monoexponential, but if exponential analysis were applied they would be resolved into two or more components. Dilution curves recorded from the aorta have shown similar late, slowly decreasing tails (Bassingthwaighte *et al.*, 1967); such shapes may have been partly attributable to incomplete mixing at the injection site in the left ventricle. In the present case, where h should be independent of the forms of C_{in} and C_{out} , the nonmonoexponential form can only be attributed to the coronary bed itself. An alternative explanation that non-representative sampling distorted either C_{in} or C_{out} and, resulted in abnormalities of h seems unlikely since this might produce either shortening or lengthening of the tail, rather than a consistent lengthening.

The observations were made at two fixed positions, inflow and outflow, at a variety of flows. The lengths of the flow streams probably do not change with flow. Under these

circumstances, one can expect the standard deviation, σ , of $\mathbf{h}$ to be proportional to the mean transit time, $\bar{t}$, whether the flow is laminar or turbulent, so long as the flow characteristics do not go through a transition as flow is changed. The constancy of the shapes of the transport functions, demonstrable by normalizing with respect to $\bar{t}$, as in the right panels of Fig. 3, indicates that the relative dispersion, $\sigma/\bar{t}$, the skewness, and the kurtosis are all quite constant over a wide range of mean transit times. This basic feature, the “similarity” of the transport functions, was found in the kidney (Gomez *et al.*, 1965) and over a limited range of flow in the lung (Knopp *et al.*, 1969) and in the leg-arterial system (Bassingthwaighte, 1966a) and can be expected to be a feature of any vascular bed in which there are no dramatic changes in geometry at different flows.

Comparison of the Transcoronary Transport Function with Other Transport Functions

Figure 4 shows the relationship of the transport function dispersion to mean transit time for a variety of organs (Bassingthwaighte *et al.*, 1966a, 1967; Knopp *et al.*, 1969). Although considerable overlap of the data is seen, it is also obvious that consistent differences do exist between organs. The multiple pathway organs tend to have a greater relative dispersion than do the single vessels—a direct implication that different pathways have different mean transit times and flows.

In the lung, flow inhomogeneity is further substantiated by the nonlinear relationship of dispersion and mean transit time ($\sigma/\bar{t}$ is greater with long mean transit times). Since the studies in single vessels (Bassingthwaighte *et al.*, 1966a, 1967) showed no change in velocity profile with mean transit time, one might assume this to be true for individual pathways in the lung; if so, then the nonlinear relationship seen in the lung is probably due to a change in the distribution of pathway flows. Regional flow heterogeneity in the lung has also been observed with ^{133}Xe flow-tagging techniques (Anthonisen *et al.*, 1966) and is recognized to be a complex function of pulmonary artery pressure, left atrial pressure, alveolar pressure, and the direction and magnitude of the force due to acceleration.

The Weighting Factors, f_i

Also of interest are the families of weighting factors, the f 's. These could be interpreted as magnitudes of regional flows, through regions with similar transit times, if each $\mathbf{h}_i$ represented the transport function of an anatomically separate group of pathways having the same $\bar{t}_i$ and dispersive characteristics. We do not know the exact forms of regional transport functions, but they are most likely right-skewed and must have lower relative dispersion than the transport function for the total organ. For the description of the transcoronary transport functions, fitting functions were selected that would most reasonably approximate the transport function for a single blood pathway through the coronary bed. The assumption of a unimodal right-skewed distribution for $\mathbf{h}_i$ is based on the work of Bassingthwaighte (1966a), who described dispersion in the human leg artery with the lagged normal density function; Knopp *et al.* (1969), who used this function to describe plasma dispersion in the lung; and Gomez *et al.* (1965), who used the log normal function to describe dispersion in the human kidney. Lagged normal density functions were arbitrarily chosen to describe the individual pathway transport functions, although there is no question that gamma variates or log normals will do as well; and the choice has no influence on the shape of the calculated $\mathbf{h}$'s. (Sets of log normal density functions were also used to calculate $\mathbf{h}$'s, but this redundant information will not be reported.)

If the dispersive characteristics of turbulent systems were to apply to each pathway, then the dispersion would be proportional to the square root of the distance traveled—that is, proportional to the square root of mean transit time—rather than having a constant proportionality (Taylor, 1953). If the differing $\bar{t}_i$'s were proportional to path lengths, such an

assumption would be incorporated by using $\sigma_i = K(\bar{t}_i)^{\frac{1}{2}}$, so that the relative dispersion of the $\mathbf{h}_i$'s diminished with increasing $\bar{t}_i$'s. In this study the use of a square-root relationship would induce a twofold difference in $\sigma_i/\bar{t}_i$'s between the pathway transport function having the shortest mean transit time and that having the longest. Although Reynold's numbers for the coronary vasculature are low, nevertheless, there are pulsatile mixing changes in aortic pressure and even local arterial reversed flow with pulsatile intramyocardial tension development. However, lacking specific knowledge, we assumed $\sigma_i/\bar{t}_i$ to be a constant. No data are available on dispersion in small vessels, so we chose the shape and relative dispersion of the $\mathbf{h}_i$'s to be similar to those found for an artery of the human leg (Bassingthwaight, 1966a) which is a single but branched vessel. In these experiments one cannot discern whether the $\mathbf{f}$'s are closely related to the distribution of relative regional blood flows in the heart, because no paired measurements of regional flow were made, but we hoped that we could discern whether the distributions of $\mathbf{f}$'s were reasonably close to the distributions of flows determined in other experiments.

An example of the $\mathbf{f}_i$'s obtained in the solution for one h is shown in Fig. 5. At the bottom of the picture the individual $\mathbf{h}_i$'s multiplied by their scaling factor, f_i , are shown; the $\mathbf{h}_i$'s have constant relative dispersion ($\sigma_i/\bar{t}_i = 0.16$). The $\mathbf{f}_i$'s, normalized by dividing by the difference in mean transit times between adjacent members of the family of $\mathbf{h}_i$'s, $\Delta\bar{t}_i$, are plotted at the points of mean transit time of their respective $\mathbf{h}_i$'s. The smooth $\mathbf{h}$, which is the sum of the $\mathbf{f}_i \cdot \mathbf{h}_i$'s, is seen to have a larger relative dispersion than any of the individual $\mathbf{h}_i$'s, so it is not surprising that its shape is essentially independent of the choice of $\mathbf{h}_i$.

A critical test of the transport function as an indicator of the heterogeneity of regional flows has not, as yet, been performed. The question is whether the fitting-function-weighting factors, $\mathbf{f}$, obtained in these studies provide a reasonable description of the probability density function of regional myocardial blood flows. While keeping in mind that the experiments are not precisely similar, a comparison with the data of Yipintsoi *et al.* (1973) on nonworking isolated blood-perfused heart can be made for the purpose of giving a preliminary test to an idea. In theory, the deposited tracers are deposited in regions of the myocardium in amounts proportional to the blood flow and inversely proportional to the mean transit time for that region. The same constant of proportionality relates the weighted average of regional depositions to the total organ flow and the inverse of the total organ mean transit time. The normalized distribution, $\bar{t}\mathbf{f}$, an average of those found for the 25 transport functions of one dog, is plotted as the thick continuous line in Fig. 6. Plotted along with this curve are frequency distributions for the reciprocals of the fractional deposition density for four deposited tracers, each normalized with respect to its mean density in the whole heart, derived from the data of Yipintsoi *et al.* (1973). The diffusible tracers, ^{131}I -antipyrine (I-Ap) and ^{42}K , show a narrower distribution, mainly an absence of very high density of deposition (no values in the low range of $\bar{t}/c_i$, which represent the highest deposition or flow); this is attributable to incomplete extraction of ^{42}K and early washout of I-Ap. The microspheres, of both 15 and 35 μm diameters, show a broader dispersion of densities, which has been shown to be due to preferential deposition in regions of high flow (Yipintsoi *et al.*, 1973), especially the subendocardium (Yipintsoi *et al.*, 1973; Utley *et al.*, 1974). From the arguments given by Yipintsoi *et al.* (1973), the true distribution of regional flows should be between the distributions for microspheres and those for diffusible tracers, and so it is encouraging to see that the solid line of $\bar{t}\mathbf{f}$ lies in this region. This suggests that our choice of shape of the assumed $\mathbf{h}_i$'s with $\sigma_i/\bar{t}_i = 0.16$ is probably not too far from the correct relative dispersion.

Further study is needed to show more precisely the ability of the technique to determine fractional flow distributions, following which its ability to indicate pathological conditions

could be investigated. The presence of ischemic regions would result in increased skewness of the transport functions and perhaps secondary peaks in the weighting function; however, general ischemia would be noted only by an increased mean transit time; complete obstruction to a region would go undetected by a transport function technique. Although the information contained in the transport function can be expected to reveal supranormal degrees of heterogeneity in large regions of an organ, it is yet to be shown whether this technique is sufficiently sensitive to allow diagnosis where other methods fail.

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Fig. 1.

Transcoronary transport functions calculated from a single pair of input–output curves using five different values for the relative pathway dispersion. The coefficient of variation between C_{out} and C_{out}' was 0.015 to 0.021 with the smallest relative dispersion giving the best fit. The curves of $h(t)$ are ordered, that associated with a pathway dispersion, σ_i/t_i , of 0.24 having the highest values early on the upslope (at about 3 sec) and the lowest peak. With $\sigma_i/t_i = 0.08$, the curves of $h(t)$ and $f(t_i)$ are nearly coincident—lowest peaked $f(t_i)$ and highest peaked $h(t)$ —as is to be expected when the relative dispersion approaches the limit at zero, for $h(t)$ approaching the Dirac delta function.

Fig. 2.

Two sets of dilution curves sampled from the aortic root, $C_{in}(t)$, and coronary sinus, $C_{out}(t)$ and the calculated transcortical transport functions, $h(t)$. The calculated output given by convolution of the recorded aortic root curve and the calculated transport function, $C'_{out}(t)$ the X 's, show close approximation to the observed coronary sinus dilution curve, $C_{out}(t)$. The mean transit times are 6.1 and 3.6 sec for the top and bottom panels, respectively.

Fig. 3.

Transcoronary transport function for three dogs. Left panels: Transport functions expressed as a function of time. Right panels: Transport functions are normalized with respect to the mean transcoronary transport time. The number of curves is 25 for dog 3069, 21 for 6069, 14 for 2069.

Fig. 4.

The dispersion of the probability density functions of intravascular transit times in four different vascular beds are roughly proportional to the mean transit times. The closed circles show the 60 values obtained in this study on the coronary beds of three dogs. The open circles are for 54 transport functions in the aortas of four dogs (Bassingthwaighe *et al.*, 1967), and the open triangles for 144 transpulmonary transport functions in four dogs (Knopp *et al.*, 1969). The crosses are for 57 transport functions between the external iliac and dorsalis pedis arteries of five men (Bassingthwaighe, 1966a). The relative dispersion, the slope of the relationship, for the coronary bed is generally less than that for the lung but is considerably more than for a peripheral artery.

Fig. 5. Transcoronary transport function, $h(t)$; pathway transport functions, $f(\bar{t}_i) \cdot h_i(t)$; and normalized weighting factor, $f(\bar{t}_i) / \Delta \bar{t}_i$, found for one pair of aortic root and coronary sinus sampled dilution curves.

Fig. 6.

A typical normalized transcoronary pathway weighting function in one dog (solid, bold line) is compared to the deposition fractions of two diffusible tracers and two sizes of microspheres in another dog. The abscissa can be considered equivalent to a reciprocal of relative regional flows, that is, the average flow divided by the local flow; the curves plotted can be considered as estimates of this distribution of reciprocal flows. The diffusible tracers (^{131}I -Ap and ^{42}K combined as the dashed line) and the microspheres (for both 35 and μm diameter spheres combined as the dotted line) would ideally be deposited with relative concentration, $C_i/\bar{C}$, precisely in proportion to the relative regional flow per unit volume, $F_i/\bar{F}$. Deviations from ideality cause larger microspheres to show preferential deposition in high-flow regions (small values of abscissa) and diffusible tracers to have earlier washout and reduced deposition in high flow regions. (The data are taken from the middle panel of Fig. 4 of Yipintsoi *et al.* (1973) for an experiment where the flow was similar to that in the present experiments. Differences between 15 and 30 μm microspheres, and between ^{42}K and

I-Ap, were much smaller than the difference shown in our present figure.) Since the data from the present experiments (solid line) lie between those for the diffusible tracers (dashed line) and those for the microspheres (dotted line), it seems likely that these curves of $f(\tilde{t}_i)$ give a fair approximation of the correct distributions, and suggests that definitive experiments can be done to provide reasonably precise estimates of the shape of the $h_f(t)$'s.

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