Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learn and Live℠

A Transfer Function Analysis of Coronary and Renal Circulation Calculated from Upstream and Downstream Indicator-Dilution Curves

CRAIG M. COULAM, HOMER R. WARNER, EARL H. WOOD and JAMES B. BASSINGTHWAIGHTE

Circulation Research 1966, 19:879-890
doi: 10.1161/01.RES.19.5.879
Circulation Research is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7330. Online ISSN: 1524-4571

A Transfer Function Analysis of Coronary and Renal Circulation Calculated from Upstream and Downstream Indicator-Dilution Curves

By **Craig M. Coulam, B.S., Homer R. Warner, M.D., Ph.D., Earl H. Wood, M.D., Ph.D., and James B. Bassingthwaighte, M.D., Ph.D.**

ABSTRACT

A method has been developed for computing the distribution of blood transit times (transfer function) from indicator-dilution curves recorded from upstream (aorta) and downstream (pulmonary artery, renal vein and coronary sinus) circulatory sites in mongrel dogs. The method employs a Fourier series transformation of the upstream and downstream curves and yields a time-domain transfer function which is independent of recirculating dye particles. Discontinuities, created in the upstream and downstream indicator curves by the termination of sampling (120 sec postinjection), are removed by a tail terminating procedure which employs normal and lagged normal density distributions. The transfer functions computed for the trans-renal and trans-coronary circulations and their relationship to the systemic circulation dispersion patterns are shown under control conditions (pentobarbital anesthesia) and during intra-aortic infusion of angiotensin, acetylcholine and adenosine triphosphate. These distribution patterns reflect the response of the vascular system to the drugs and demonstrate, to a limited extent, the role which different vascular beds have in the cardiovascular mixing process.

ADDITIONAL KEY WORDS cardiac output catheterization cardiovascular mixing circulation computer dye dispersion flow Fourier series transit rime anesthetized dog

• Until the present time most dye-curve analysis has been limited to the study of the downstream dye-dilution curve following an upstream slug or step injection (1). A slug injection is, in reality, an attempt to simulate a unit impulse—for if a true unit impulse could be made, the downstream dye curve would be the transfer function, or the true distribution of particle transit times. However, due to the impossibility of creating a true unit impulse and to the presence of recirculating dye, the transfer function cannot be recorded directly.

Theory

This paper presents a method of computing the transfer function which relates upstream and downstream dye-dilution curves and requires no assumptions regarding the effects of recirculating dye (2). The method is based upon the Fourier series transformation of a time-domain curve into the frequency-domain and characterizes the original curve as a series of sine and cosine terms that have characteristic amplitudes or coefficients (3). Equations 1 through 4 describe how the calculation of these characteristic coefficients, a(n) and b(n), are made.

From the Department of Biophysics and Bioengineering, University of Utah, Salt Lake City, Utah, and the Department of Physiology, University of Minnesota, Minneapolis, Minnesota and the Mayo Foundation, Rochester, Minnesota.

This work was supported in part by Research Crants 5 PO7 FR-00012 and HE 04664 and Fellowship Fl-CM-16,769 from the National Institutes of Health, U. S. Public Health Service.

Dr. Bassingthwaighte is a recipient of Research Career Development Award and Dr. Warner of a Research Career Award of the National Institutes of Health, U. S. Public Health Service.

Dr. Wood is a Career Investigator of the American Heart Association.

Accepted for publication August 17, 1966.

$$a(n)_F = \frac{2}{P}\int_{-\frac{P}{2}}^{\frac{P}{2}} f(t)\cos\frac{2\pi n}{P}t\,dt \quad n = 0,1,2\ldots,N \qquad (1)$$

$$b(n)_P = \frac{2}{P}\int_{-\frac{P}{2}}^{\frac{P}{2}} f(t)\sin\frac{2\pi n}{P}t\,dt \quad n = 1,2,\ldots,N \qquad (2)$$

where P = period or number of data points and $b(o)=0$.

$$F(n) = \sqrt{a(n)^2 + b(n)^2} \qquad (3)$$

$$\phi(n)_F = \tan^{-1}\frac{b(n)}{a(n)} \qquad (4)$$

In these equations f(t) is assumed to be a repetitive function with a period (P) equal to the time from indicator injection to the end of sampling (120 to 180 sec) and n is the harmonic-frequency index. F(n) is the vector sum of the sine and cosine components and $\phi(n)_F$ is the corresponding phase angle.

In general, the computation of the transfer function begins by transforming the upstream dye curve f(t) and the downstream dye curve g(t) into their frequency-domain representations, F(n) and G(n), respectively.

G(n)

$$\phi(n)_H = \phi(n)_G - \phi(n)_F \qquad (6)$$

$$a(n)_H = H(n)\cos\phi(n)_H \qquad (7)$$

$$b(n)_H = H(n)\sin\phi(n)_H \qquad (8)$$

$$h(t) = \frac{a(o)}{2} + \sum_{n=1}^{N}\left[a(n)_H\cos\frac{2\pi n}{P}t + b(n)_H\sin\frac{2\pi n}{P}t\right], \qquad (9)$$

where N = total number of coefficients used for forming curve.

H(n), the transfer function, is defined as the ratio of G(n) to F(n), and the phase angle as the difference between $\phi(n)_G$ and $\phi(n)_F$ (equations 5 and 6) (4). The quadrature components of H(n) are recovered using equations 7 and 8 and the inverse Fourier series, as given by equation 9, is used to transform H(n) into its time-domain equivalent h(t). Once h(t) is known, a check on its accuracy can be made by convolving it with the upstream dye-dilution curve and comparing the resulting curve with the recorded downstream curve. This comparison is made both visually through plots and numerically through use of a correlation coefficient. If h(t) is correct, these two curves will be superimposable. A summary of this procedure is shown in Figure 1.

However, to derive the transfer function of a system from a recording of its input and output signals, it is necessary that the recorded output curve be the result of the system having acted upon the entire recorded input curve. In the case of dye-dilution curves, this condition does not hold since sampling is discontinued at the same time on both the input (upstream) and output (downstream) curves. Thus, it is necessary to add to the downstream curve the "information" lost when the sampling was stopped.

The method used in this study to find the transfer function and the downstream curve termination employs an iterative approach. The method begins by terminating the upstream curve at the point in time where sampling was stopped, with a function which is proportional to the integral of a normal-density distribution (equations 10 and 11).

$$m(t) = \frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(t-t_0)^2}{2\sigma^2}} \qquad (10)$$

$$T_f(t) = K_i\left[1 - \int_{-\infty}^{t} m(t)\,dt\right] \qquad (11)$$

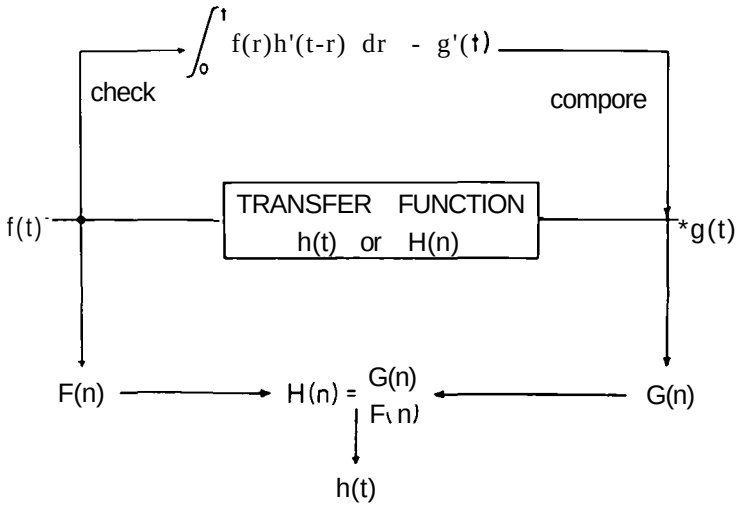

FIGURE 1

General block diagram of transfer function computation. The lower pathway shows the computation route; the upper pathway shows the check on the accuracy of the transfer function.

Here *a* and to characterize the normal distribution m(t), $T_f(t)$ is the terminating curve for f(t) and K_x is a scale factor equal to the last recorded value of f(t). The input curve is terminated by equation 11 in order to eliminate the spurious high frequency components which are generated by the abrupt step to zero concentration.

To find a first approximation to the termination for the output curve, it is necessary to assume a form for the transfer function which will represent the dispersion occurring across the circulatory bed (between upstream and downstream sites). This first transfer-function approximation is chosen to be a lagged normal distribution (5) as given by:

$$h(t) = m(t) - T\text{-}\wedge[h(t)], \qquad (12)$$

where T is the time constant of a first order lag. Now had there been no terminating tail placed on the input curve, the termination for the output curve, $T_g(t)$, would be given by:

$$T_g(t) = K_2[1 - \int_{-\infty}^{\infty} h(t)dt], \qquad (13)$$

where K2 is a scale factor equal to the last recorded value of the output curve. However, since the upstream curve was terminated, it is necessary to convolve equation 11 with equation 13 in order to generate the appropriate downstream termination as shown in:

$$T_g(t) = \int_{-\infty} T_f(x)T_g(t-x)dx, \qquad (14)$$

where x is a dummy variable of integration. The results of this convolution are then placed on the end of the recorded downstream curve. Next, using these terminated upstream and downstream curves and equations 1 through 9, a second approximation to the transfer function h(t) is found. Since this h(t) is more nearly the correct transfer function than the last h(t), it is used to find a new downstream terminating tail $T_g(t)$, and then the whole process is repeated. This iterative procedure is stopped when the correlation between the recorded downstream curve and the calculated downstream curve is ≻0.999, or when a specified number of iterations have been made (see Fig. 2 for a block diagram of the computation process).

Another problem pertains to the number of harmonic terms that are to be used in the transfer-function computations. Since the transfer function is not known, neither is the number of harmonics needed for its description. However, the following conditions wil]

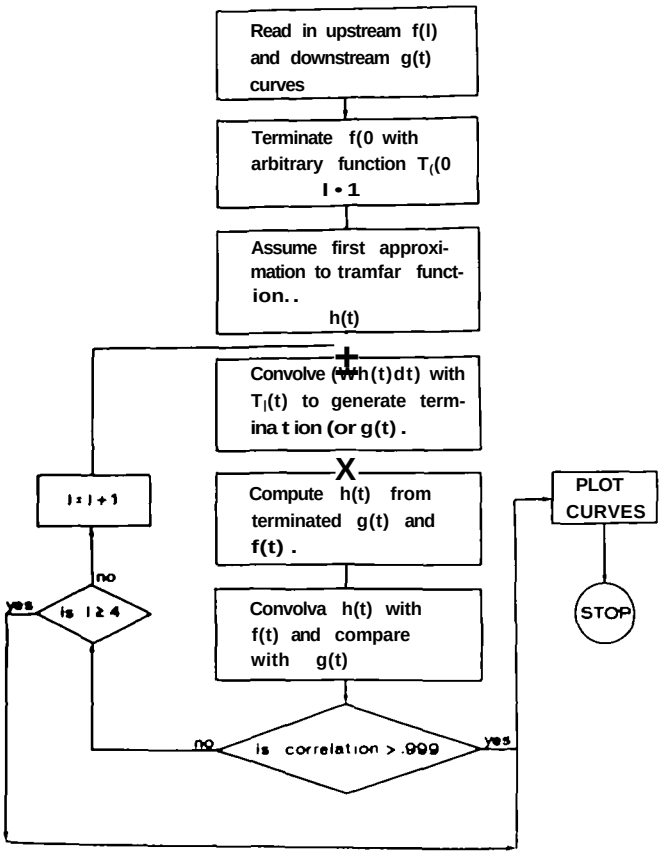

FIGURE 2

Diagram of the iterative transfer function computation method.

always hold. First, since the circulatory pathway acts as a low-pass filter, the number of significant harmonic terms found in the input signal will determine the maximum number of harmonics that can be used in the computation of the transfer function. Second, if the number of harmonics found in the input curve, say n, is *less* than the number of harmonics needed to completely describe the transfer function, and if those n transfer-function harmonics (found from equations 5 through 8) are then used to generate h(t) (equation 9), h(t) will contain oscillations in its tail portions. In order to eliminate these oscillations, it is necessary to create as narrow and as sharp an upstream curve as possible, for this adds additional harmonic terms to the upstream curve description. An example of using too few harmonic frequencies in the transfer function computations is shown in Figure 3, lower portion. Here, a simulated dye curve (lagged normal distribution with recirculation) was generated on the analog computer. This "upstream" curve was then passed through a network which had a known linear transfer function containing no tail oscillations to generate a "downstream" curve. In Figure 3, upper portion, the input curve was chosen so that it contained more significant harmonics (50) than did the transfer function (40). In this case, no oscillations appeared in the transfer-function tail when it was computed from the "upstream" and "downstream" curves. In Figure 3, lower portion, however, the input curve contained only 30 harmonic terms. After it was passed through the same system and the transfer function was calculated from the "upstream" and the resulting "downstream" curve, oscillations appeared in the transfer-function tail. Thus, if the up-

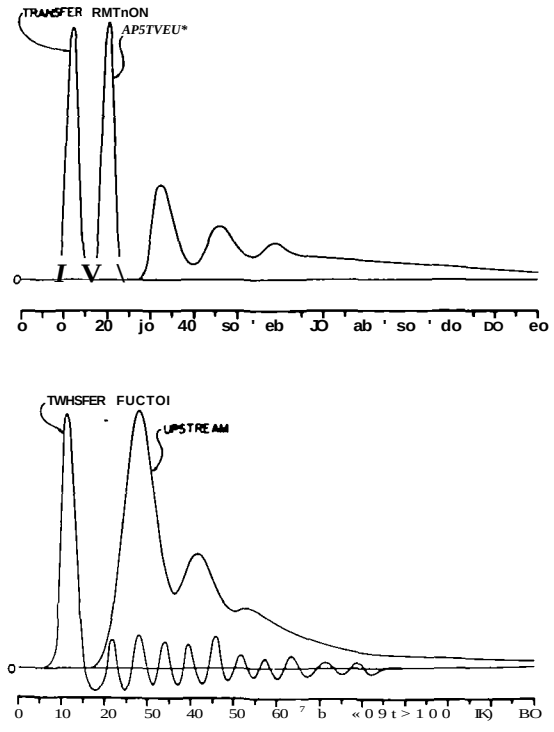

FIGURE 3

Examples of transfer functions computed from theoretical upstream and downstream dilution curves in which too few (lower) and a sufficient number (upper) of harmonic terms were available from the upstream curve for describing the transfer function. The oscillations in the tail of the transfer function shown in the lower portion are the result of using too few harmonic terms in its description.

stream curve does not contain the number of harmonics needed to completely describe the transfer function in the frequency-domain, then the transfer function in the time-domain will contain terminal oscillations. It should be mentioned that even in such a case as this, convolution of the upstream curve with the transfer function will accurately recreate the recorded downstream curve providing no error is made in the transfer-function calculations. Thus, the comparison of the recorded and computed downstream curves is a measure of both the accuracy of the computation process and of the validity of the transfer function for the number of harmonic terms used. A correct transfer function description can be assumed only if the number of harmonics found in the upstream curve description is greater than the number of harmonics necessary to generate the transfer function and if the correct terminations of upstream and downstream curves have been used.

Experimental Methods

Dye curves were obtained from mongrel dogs, ranging in body weight from 18.0 to 23.5 kg, anesthetized with morphine sulfate (5 mg/kg of body weight) iv followed by nembutal (20 mg/kg of body weight) iv and studied without thoracotomy. Five mg of indocyanine green dye was injected rapidly from a pneumatically powered, solenoid-controlled syringe into a distal pulmonary artery (see catheter labeled injection in Fig. 4). The sampling apparatus consisted of no. 6 teflon catheters (length, 100 cm; internal diameter, 1.16 mm) connected to Water's Model X-250 densitometers. The sampling catheters had nearly identical internal volumes of 1.2 (1.1 to 1.3) ml. The total dead space of the sampling systems was 1.9 ml. The upstream or input curve was sampled at the aortic arch, thus allowing the blood and dye to mix in the lungs and left heart before reaching the upstream sampling site (6, 7). Simultaneously with the upstream sampling, downstream or output curves were obtained by withdrawing blood at the same constant rate (9.9 ml/min) through nearly identical sampling systems from the coronary sinus, renal vein and pulmonary artery proximal to the injecting catheter. The tip of the coronary sinus catheter was advanced far enough into the sinus so that no contamination with right atrial blood could be demonstrated in dilution curves recorded from this site following injections of 5 mg of indocyanine green into the inferior vena cava. The outputs of the densitometers were filtered using a 2 cycles/sec cutoff, were digitized at 4 samples/sec and fed directly to a digital computer. All curves were recorded in parallel on FM magnetic tape. The normal physiological state of the animals was altered in some cases by constant rate infusion of drugs into the ascending aorta (lowest aortic catheter tip shown in Fig. 4). The following drugs were used: angiotensin (1.5 mg/ml at 1.25 ml/min), acetylcholine (1.5 mg/ml at 0.5 ml/min) and adenosine triphosphate (1 mg/ml at 1.23 ml/min).

Results

Figures 5 and 6 show the results of some transfer functions computed on 1 of 5 dogs. The aortic or input curve is represented as dashed line. The output curve, recorded from the coronary sinus (Fig. 5) or the rena.1

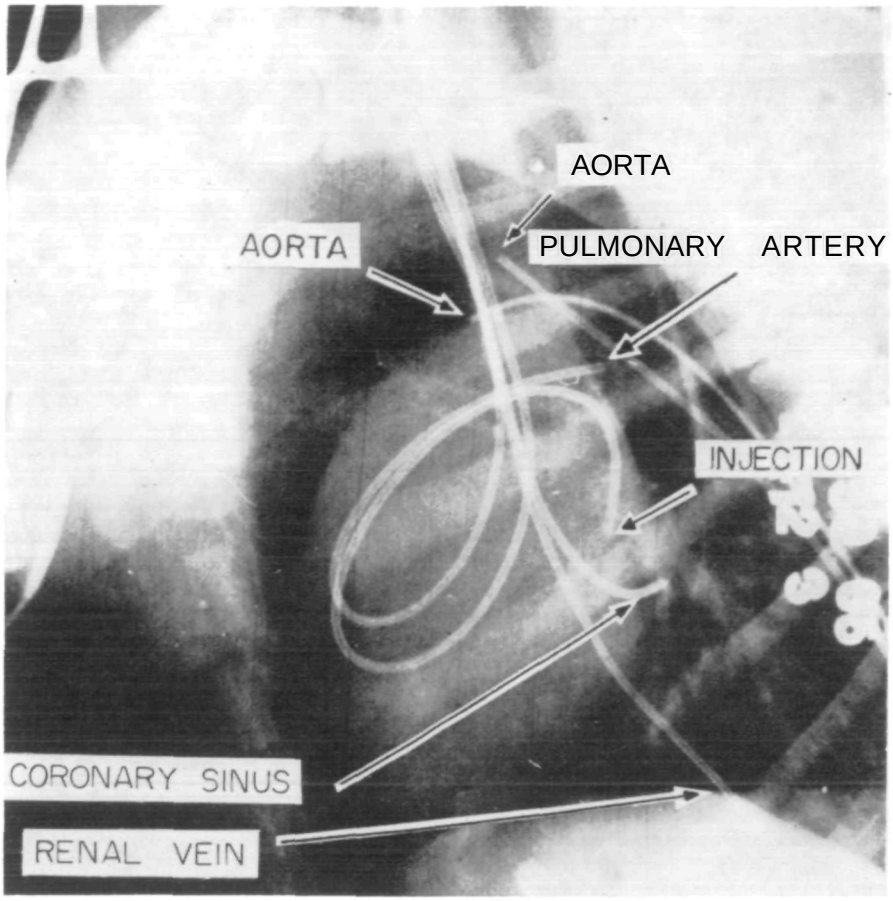

FIGURE 4

X-ray showing location of catheters. The tip of the pulmonary artery sampling catheter is upstream to the injection catheter. The tip of the more proximal (downstream) "aorta" catheter is used for drug infusion into the ascending aorta and the more distal "aorta" catheter is for "upstream" sampling. The tips of the "downstream" sampling catheters are located in the pulmonary artery, coronary sinus and renal vein (tip not shown). Catheters were inserted via percutaneous puncture of peripheral vessels and their tips positioned without recourse to thoracotomy.

vein (Fig. 6), is superimposed upon the computer output curve and the two are displayed as circles and x's respectively. The dotted line is the transfer function relating the upstream curve to the downstream curve and represents the distribution of transit times through the designated circulation. All curves are scaled so that their maximum values coincide. The accuracy of the transfer function may be estimated from the value of the correlation coefficient relating the recorded and computed output curves. It is to be noted that the first portion of the transfer functions of the coronary and renal circulations resemble lagged normal distributions as predicted by Nicholes, Warner and Wood, but the tail portions contain damped oscillations (5). The nature of these oscillations has been discussed.

The aortic or input curve, the recorded mixed systemic venous output or pulmonary artery curve, the pulmonary artery transfer function, and the mixed venous pulmonary artery curve computed by convolving the transfer function with the aortic curve are shown in Figure 7. This transfer function, which describes the total systemic circulation, contains one main peak and a long, diffuse tail that is characterized by several smaller

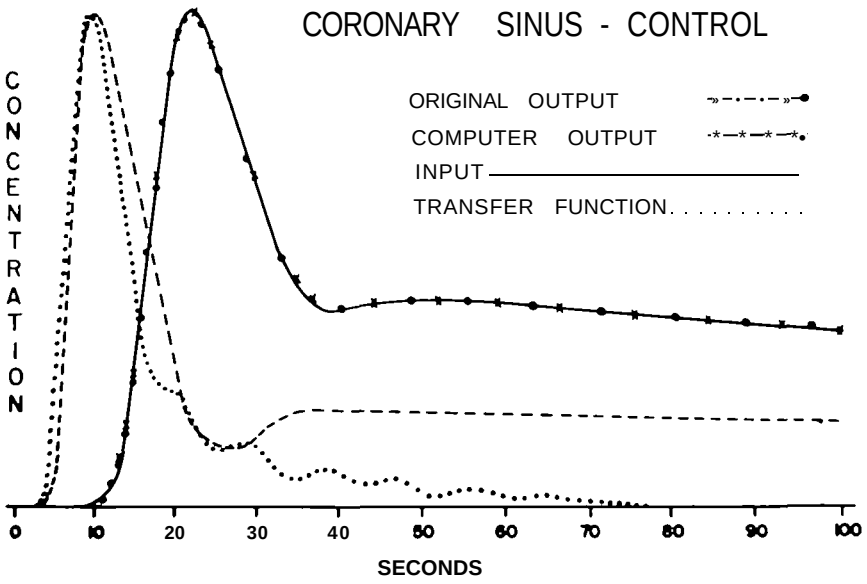

FIGURE 5

Comparisons of input (upstream) dilution curve to the coronary circulation recorded from the ascending aorta, the computer transfer function of the coronary circulation (dotted line) and the recorded (circles) and computed (crosses) output (downstream) curves from the coronary sinus. All curves are scaled to their maximum values, lndocyanine green (5 mg) was injected into the pulmonary artery at time zero (pentobarbital anesthesia, dog weight 19.1 kg). Recorded and computed output curve correlation is 0.9996.

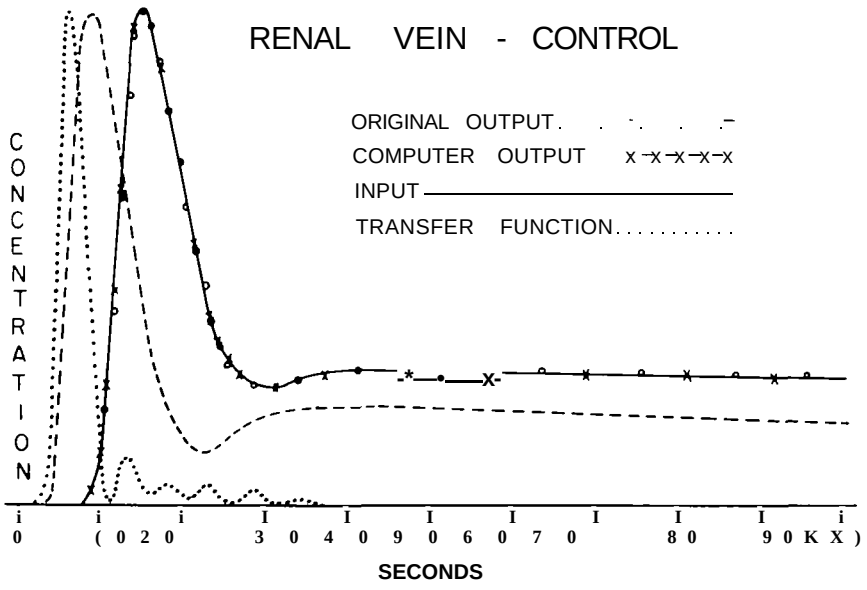

FIGURE 6

Comparisons of input (upstream) dilution curve to the renal circulation recorded from the ascending aorta (dashed line), the computer transfer function of the renal circulation (dotted line) and the recorded (circles) and computed (crosses) output (downstream) curve from the renal vein. lndocyanine green (5 mg) was injected into the pulmonary artery at time zero. The dog was under pentobarbital anesthesia and weighed 19.1 kg. Recorded and computed output ourve correlation is 03989.

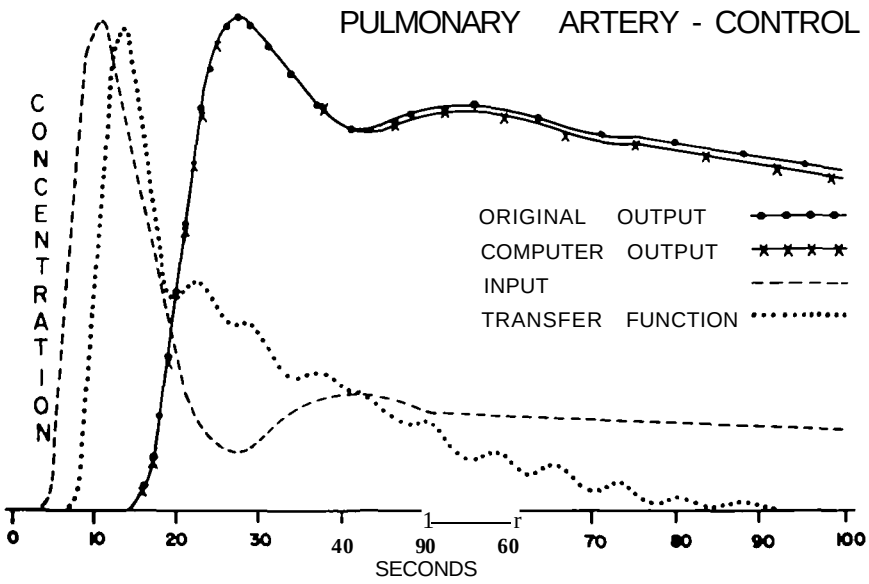

FIGURE 7

Comparisons of input (upstream) dilution curve to the total circulation recorded from the ascending aorta (dashed line), the computer transfer function of the total circulation (dotted line) and the recorded (circles) and computed (crosses) output, i.e. the mixed systemic venous (downstream) curve from the pulmonary artery. Indocyanine green (5 mg) was injected into a distal pulmonary artery at time zero. The dog was under pentobarbUal anesthesia and weighed 19.1 kg. Recorded and computed output curve correlation is 0.9993.

peaks or bumps. It is not possible to distinguish which, if any, of these bumps represent the effects of dye traversing specific pathways in the systemic circulation.

The curves shown in Figure 8 are transfer functions obtained from 1 dog during the control state and during infusion of the three indicated drugs. These transfer functions represent the distribution of transit times between the upstream recording site (aortic arch) and three downstream recording sites as shown in the figure. Since the pulmonary artery curve contains the distribution of transit times through all of the organs of the systemic circulation, the coronary sinus and the renal vein curves must contribute to this. Each of the states induced by drug infusion affects the pulmonary artery curve in a different way and permits some conclusions as to the effect of these agents on the circulation. The variation around the mean transit time in each of these systems is mainly due to two factors: the variation in velocity of flow as a function of position in the cross section of a given vessel, and the variability in path lengths and flow velocities in the vascular pathways through the organ. It is not possible by the present technique to assess the relative importance of each of these mechanisms.

With the animal in the control state (see Fig. 8), mean transit time through the renal circulation is considerably shorter than through the coronary (t_{ren}«i = 6.5 sec; tcoruutiT= 13.7 sec) and the variation about the renal mean transit time is much smaller. Enough overlap exists between the renal and coronary distribution curves, however, to result in a single peak in the pulmonary artery curve. Notice that in the control state the pulmonary artery curve is very broad with transit times for some of the dye as long as 75 sec. It is possible that very slow pathways may have transit times that are even longer than this and therefore would not have been detected by the experimental method because sampling was not continued beyond 3 min.

Intra-aorta infusion of angiotensin resulted

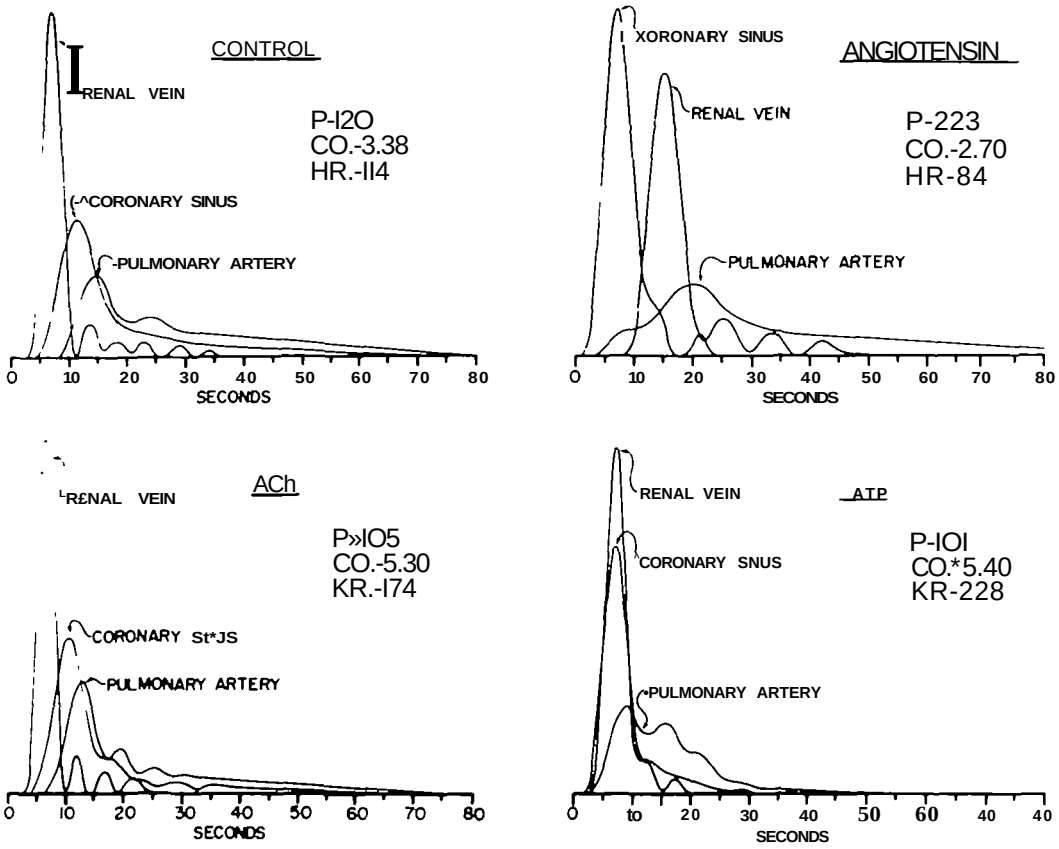

FIGURE 8

Comparison of transfer functions of coronary, renal and total systemic circulations (pulmonary artery) during the infusion of various drugs into the ascending aorta. Each transfer function curve is normalized to unit area. P indicates the mean aortic pressure in millimeters of mercury; CO., the cardiac output in liters per minute, and H.R., the heart rate in beats per minute. The average rates of infusion of the drugs used were: angiotensin 2, 1.87 ng/min; acetylcholine (ACh), 0.75 mg/min; and adenosine triphosphate (ATP), 1.23 mg/min. All correlations between recorded and computed downstream curves are ^0.9983.

in a definite time separation of the coronary sinus and renal vein distribution curves. The mean transit time through the renal system was more than doubled ($t_{.mml}$ = 15.7 sec), while the mean coronary sinus transit time was shortened (*fmonur*. = 6.6 sec). The effect of this separation on the distribution of transit times through the whole circulation is clearly shown by the double hump on the rising limb of the pulmonary artery curve. It should not be inferred, however, that the initial hump is composed solely of coronary circulation, even though the coronary circulation may contribute most to it. The increased velocity of flow through the coronary sinus is probably due to the marked rise in mean aortic pressure which occurred, while the prolongation of mean transit times through the renal pathways can be explained by renal vasoconstriction resulting from the direct effects of the drug.

Acetylcholine (ACh) produced a vasodilatation with a fall in arterial pressure and a marked rise in cardiac output. Heart rate increased in this case, probably in response to the decreased arterial pressure. Since the heart rate did increase, it means that the effects of ACh on the heart were minimal, even though the drug was infused in the ascending aorta. Renal transit time was approximately

the same as in the control state ({,,;;,,! = 6 sec) because ACh apparently had little effect on the renal vascular smooth muscle. Coronary transit time decreased slightly (tcoronary=—12.1 sec) while cardiac output increased due to a marked fall in peripheral resistance. In general, the time relationship between renal and coronary distribution patterns did not change enough to alter the first peak of the pulmonary artery curve.

Intra-aortic infusion of adenosine triphosphate (ATP), on the other hand, did have a selective effect on the coronary circulation (fcoromy = 7.1 sec; t^ai = 6.9 sec) even though mean pressure fell and cardiac output rose in much the same way as it did with acetylcholine infusion. The gross effects of this drug seemed to be especially marked on those vascular beds through which transit times were originally the longest. This is apparent from the fact that the pulmonary artery transfer function has almost completely lost its "tail."

Discussion

The validity of the transfer-function approach is dependent upon the assumption that the system being described is linear and stationary (8). The linearity of the system has been tested by injecting varying doses of indicator and finding that the recorded curves differ only in the area under the curve since this is proportional to the dose of indicator injected (9). Stationarity can only be evaluated in terms of the repeatability of the measurements and the extent to which the transfer functions, calculated in the frequency-domain, can be used to retrieve the original downstream curves from the upstream curves. Any obvious changes in the state of the animal during the recording of the dye curves result in clear cut discrepancies in the transfer function which are often not apparent in the input and output curves themselves.

The Fourier series approach to the calculation of the transfer function assumes a periodic function. This is obtained in the case of the dye curve data by stopping the sampling of dye after 2 or 3 min and then mathematically treating the curve as though it repeated itself indefinitely. The end of sampling, however, results in a discontinuity in the recorded curve which introduces artifact into the frequency-domain representation. A special method, based upon an iteration approach, was used for handling this effect.

The oscillations found in the tails of the renal and coronary transfer functions under certain physiological states can be attributed to the fact that the number of harmonic terms present in the upstream (aortic) curve was inadequate to describe the transfer function of the renal and coronary circulations under these conditions. This problem can possibly be alleviated by making the dye injections into the left ventricle rather than the pulmonary artery. Since this will eliminate the dispersion of dye particles which occurs during passage through the lungs, the aortic curve will contain higher frequency components.

Examination of Figures 5, 6 and 7 shows an apparent discrepancy between shortest transit time as calculated by the transfer function and the difference between time of first appearance of dye at upstream and downstream sites. Figure 9 shows input and output curves generated by an analog computer and the corresponding transfer function. Note that the same apparent discrepancy in appearance time exists as in the calculations made from the biological data. The digital computer programs will recover this known transfer function accurately from the simulated upstream and downstream curves (correlation .9997). Thus, it can be seen that estimates of shortest transit time between sites in the circulation cannot be reliably made from observing the differences in time of first dye appearance recorded at the dye curves

Noise in the recording system introduces a source of potential error in the method. The most bothersome noise is that due to variations in concentration recorded on the venous side of the circulation, probably due to inadequate cross-sectional mixing at the point of sampling plus differential effects of the respiratory cycle on the rate of drainage of venous blood from

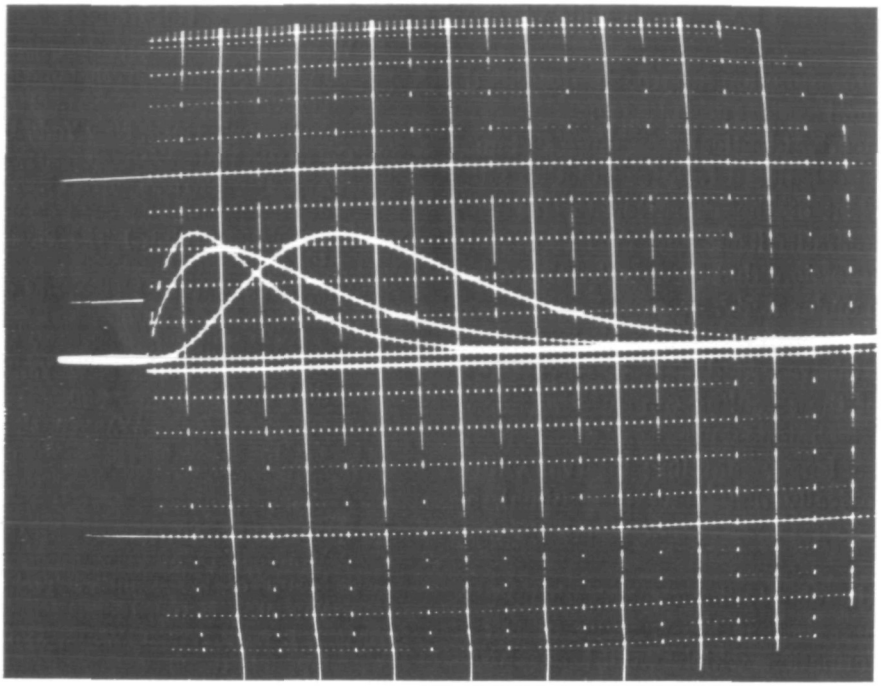

FIGURE 9

An *analog computer simulation of input curve (first appearing curve), transfer function (second appearing curve) and resulting output curve (last appearing curve) shows that the appearance time of the transfer function is much shorter than the apparent difference in appearance times of input and output curves.*

different circulatory beds containing different concentrations of the indicator. In a site such as the inferior vena cava, accurate sampling (representative of mean concentration across the vessel) with a catheter becomes impossible due to movement of the catheter tip into various flow streams which contain differing dye concentrations and which may vary in relation to one another due to effects of the cardiac and respiratory cycles (10). The roentgen videodensitometer offers a potential solution to this problem since it can provide a measurement of average cross-sectional dye concentration (approaching the ideal flow averaged dye concentration) (11). Variations in the state of the blood (i.e., P_{CO_2}, pH, etc.) with respect to the respiratory cycle also produce noise which tends to create spurious drifts in the recording apparatus. In some experiments, the animal was hyperventilated prior to injection of dye and its respirations were arrested during the recording of the curves. In other animals, rapid, shallow ventilation was maintained during the recording since this minimized the respiratory effects. The latter procedure was the most effective.

The durations of the sampling times for each set of curves were generally between 2 and 3 min. With the present sampling techniques this involved withdrawing approximately 30 ml of blood from each of the sites, which undoubtedly affected the physiologic state of the animal. Although it would have been desirable to sample for a longer period of time, this was not feasible because of the amount of blood loss involved and the slow drift that occurs in the recording instruments. Undoubtedly, in the control state some dye particles are circulating over such slow pathways (e.g., bone marrow) that they do not pass the downstream recording site during the recording period. This loss of dye particles would result in a computed aorta to pul-

monary artery mean transit time which is too short.

The transfer function approach described here has several distinct advantages:

First, if nearly identical sampling systems are used, the calculated transfer function will be independent of the characteristics of the sampling apparatus itself and thus represent only the dispersion that occurs in the vascular system under study.

Second, the transfer function that is computed from the recorded data is correct for the length of the sampling time used. Therefore, when techniques are available which will permit a longer sampling interval without physiologically disturbing the animal, a more complete transfer function may be obtained.

Third, and probably the greatest advantage of the method, is that the transfer function contains information which would not normally be seen in the recorded downstream dye curve due to the presence of recirculating dye and to catheter-withdrawal distortion. This is apparent from the curves presented in this paper.

By the use of the mathematical model of Nicholes, Warner and Wood, one can theoretically calculate the portion of the cardiac output perfusing each organ of the body from the time course of concentration of dye in the aorta and pulmonary artery (5). The present study was undertaken to develop a technique for obtaining the transfer functions required by that model. However, the practical limitation of obtaining a true representation of the time course of indicator concentration in vessels where marked streamlining occurs, such as the inferior vena cava, still exists.

References

1. WOOD, E. H. (ED.): Symposium on Use of Indicator-Dilution Techniques in the Study of the Circulation. American Heart Association Monograph, No. 4, New York, 1962.
2. COULAM, C. M., WARNER, H. R., WOOD, E. H., AND BASSINCTHWAICHTE, J. B.: Distribution of Transit Times Through Coronary and Renal Circulation, (abstr.) The Physiologist 8: 141, 1965.
3. LEE, Y. Y.: Statistical Theory of Communication. New York, John Wiley and Sons, 1961, p. 5.
4. SCHWARTZ, M.: Information Transmission, Modulation and Noise. New York, McGraw-Hill Book Co., 1959, pp. 34-80.
5. NICHOLES, K. R. K., WARNER, H. R., AND WOOD, E. H.: Study of Dispersion of an Indicator in the Circulation. Ann. N. Y. Acad. Sci. **115:** 721, 1964.
6. Rossi, H. H., POWERS, S. H., AND DWORK, B.: Measurement of Flow in Straight Tubes by Means of the Dilution Technique. Am. J. Physiol. **173:** 103, 1958.
7. FOX, I. J., SuTTERER, W. F., AND WOOD, E. H.: Dynamic Response Characteristics of Systems for Continuous Recording of Concentration Changes in a Flowing Liquid. J. Appl. Physiol. **11:** 390, 1957.
8. BASSINCTHWAICHTE, J. B., ACKEHMAN, F. H., AND ESSEX, H. E.: Mathematical Linearity of the Dog's Arterial System, (abstr.) Federation Proc. 14: 338, 1956.
9. BIRKHEAD, N. C, Fox, I. J., AND WOOD, E. H.: Effect of Doubling and Quadrupling Indicator Dose on Dilution Curves (abstr.). The Physiologist 1: 11, 1957.
10. WOOD, E. H., BOWERS, D., SHEPHERD, J. T., AND Fox, I. J.: Oxygen Content of Mixed Venous Blood in Man During Various Phases of the Respiratory and Cardiac Cycles in Relation to Possible Errors in Measurement of Cardiac Output by Conventional Application of the Fick Method. J. Appl. Physiol. 7: 621, 1955.
11. WOOD, E. H., STURM, R. E., AND SANDERS, J. J.: Data Processing in Cardiovascular Physiology with Particular Reference to Roentgen Videodensitometry. Mayo Clinic Proc. 39: 849, November, 1964.