Analog Computer Analysis of Flow Characteristics and Volume of the Pulmonary Vascular Bed

By Daniel Parrish, B.S., Daniel T. Hayden, Ph.D., Wayne Garrett, M.D., and Rex L. Hupp, M.D.

Radioisotope dilution data were obtained from the pulmonary artery and pulmonary vein of catheterized dogs and an analysis for pulmonary transfer characteristics was performed with an electronic analog computer. The analog for these studies consisted of a cascade of linear delay units arranged so that both transport delay and dispersion could be independently varied. This technic makes it possible to characterize the pulmonary vascular bed without making any assumptions as to its nature. The results indicate that the dominant response of the lung is not that of a single mixing pool as suggested by Newman and others, but rather is more analogous to a laminar flow system.

In addition it has been shown that an exponential extrapolation of the downslopes of the indicator dilution curves to calculate pulmonary blood volume results in a measurable error.

This investigation was undertaken in order to describe the hemodynamic effect of the pulmonary vascular bed on a pulse of tracer substance passing through it. One of the most general assumptions that can be made concerning a fluid flow system is that the system behaves as a single mixing pool, where mixing is instantaneous and complete and the ratio of flow-rate to volume is a constant. This concept has the virtue of being easily treated mathematically and, from the distortion suffered by a known input function, the volume and turn-over rate of the pool can be calculated. While this is valid in many cases (at least to a first approximation) there exist fluid-flow systems which cannot be treated in this manner—for example, laminar flow through a pipe. In this case an input function will suffer a pure delay which is dependent on average fluid velocity and pipe length as well as a dispersion which is a function of diffusion, fluid viscosity and pipe diameter.

In a recent publication, Hayden, Garrett, and Jordan described analysis by means of an electronic analog computer of indicator-dilution curves obtained from the cardio-pulmonary circulation of dogs and the inadequacy of representing pulmonary hemodynamics by a single mixing pool was pointed out. Newman and co-workers have developed an analytic method for estimating the amount of blood in the pulmonary vasculature which also treats the lung as a single mixing pool. Shadle, Moore and Billig using Newman's method, have calculated pulmonary blood volumes in dogs and their results are of the same order of magnitude as those obtained by computer analysis where the lung analog is a single mixing pool. These volumes were shown to be much smaller than those calculated from the cardiac output and mean transit time between pulmonary artery and left atrium by the Stewart-Hamilton method. In the analog computer treatment, this discrepancy results from the fact that while the single mixing pool (or simple combinations of mixing pools) can produce a dispersion similar to the lung, it cannot produce the transit time delay observed between pulmonary artery and left atrium.

These observations, coupled with a consideration of pulmonary anatomy, suggest that the mixing pool assumption is open to
question, and indicate the need to determine the kind of modification suffered by an indicator-pulse as it traverses the pulmonary vascular bed in order to more accurately characterize the hemodynamic effect of the lung.

**METHODS**

Mongrel dogs, 10 to 26 Kg., were anesthetized with sodium pentobarbital (approximately 30 mg./Kg. administered i.v.) and heparinized (approximately 5 mg./Kg.). Following left thoracotomy, polyethylene sampling catheters were inserted in the pulmonary artery via the right ventricle and into one of the pulmonary veins via the left atrial appendage. The animals respiratory function was maintained with a positive pressure breathing device using air.

Generally two successive injections into a jugular vein were performed on each animal. For the first injection approximately 2 μC./Kg. of I\(^{131}\) human serum albumin were carefully measured into a 1 ml. syringe fitted with a 21 gauge needle. The radioactivity of syringe and needle was counted before injection by means of a suitably shielded sodium iodide scintillation crystal connected to a scaler. The radioactivity remaining in the syringe and needle after injection was counted and the difference between the two readings used as a measurement of I\(^{131}\) (HSA) injected. Since the radioactivity of the blood was substantially raised after the first experiment, the amount of isotope injected for the second experiment was doubled in order to achieve a good "signal-to-background ratio." Injection of I\(^{131}\) was always made in less than 1 sec.

After injection, samples of blood were withdrawn simultaneously at 1 sec. intervals by means of a double automatic pipetting machine\(^*\) adjusted to deliver 0.5 ml. into a sample vial each second. The response time of the instrument was experimentally determined to be 1.5 sec. Usually some 60 consecutive samples were withdrawn through each sampling catheter,\(^\dagger\) followed by equilibrium samples taken at 3, 5 and 10 min. intervals after injection. The automatic pipetting machine and catheters were calibrated so that the first samples collected in the first vials corresponded to a sample in the blood stream at the sampling catheter tip 1 sec. after injection. Since approximately 100 ml. of blood were withdrawn during sampling, original blood volume was usually restored between injections by transfusing either whole blood or a 6 per cent dextran solution in isotonic sodium chloride.

The collected samples were counted individually in a well-type scintillation counter and their activities plotted against time. Figure 1 shows a representative set of activity-time curves for both the pulmonary artery and a pulmonary vein.

**DATA ANALYSIS**

An arbitrary input function to any fluid flow system will be modified in a manner characteristic of the physical properties of the system. Thus, the nature of the system can be determined by a consideration of the difference between an input function to the system and the output function from the system. However, since it is difficult to analytically describe these functions when obtained experimentally from pulmonary artery and pulmonary vein, direct comparisons cannot be made. Electronic analog computer techniques make it possible to duplicate the observed pulmonary input function modification, thus assuring that the characteristic physical properties of the pulmonary bed are accurately reflected in the analog.

It is then possible to pulse the analog with a simplified input function, i.e., a step input, and observe the response of the system to this step input. The Duhamel superposition theorem\(^6\) states that the effect of a system on any arbitrary input function will be identical with its effect on a unit step input. This unit step response has been termed "admittance" by von Karman and Biot\(^7\) and is uniquely characteristic of the system under consideration.

Paynter\(^8\) points out that this admittance function, \(A(t)\), can be considered as an operator, which when applied to the input, \(I(t)\), generates the output, \(O(t)\). The relationship between \(I(t)\), \(O(t)\) and \(A(t)\) is expressed numerically by the superposition theorem,

\[
O(t) = \sum A_{i,t} I_i
\]

where \(O\), \(A\) and \(I\) represent the instantaneous values of output, admittance and input, respectively. In the expansion of this equation, for every integer value of \(t\), \(k\) assumes the values 1 to \(t\):

\[
O_1 = A_1 \cdot I_1 \\
O_2 = A_2 \cdot I_1 + A_1 \cdot I_2 \\
O_t = A_t \cdot I_1 + A_{t-1} \cdot I_2 + \ldots + A_1 \cdot I_t
\]

From the foregoing equations it is possible to derive expressions for \(A_1, A_2, \ldots, A_n\), and numerically calculate the admittance function for any physical system, if the input and output functions are known.
Figure 2 shows theoretical admittance functions for a step-input applied to a mixing pool and a linear transport system. The admittance function of a mixing pool begins to rise at zero time and continues exponentially to unit input. The slope of this exponential is a unique characteristic of the volume and turnover rate of the mixing pool. The admittance function of a linear transport system shows a characteristic delay, $T_d$, and associated with it a rise time, $T_r$.

Paynter\(^7\) has applied the concept of admittances to a flood control problem involving the dynamic routing of water flow through drainage basins, and has used these equations for the analytic calculation of admittances, knowing both input and output functions. However, he points out that in practice the calculations become unstable and suggests the use of electronic analog equipment for the determination of admittances. We have confirmed his statements concerning difficulties of the analytic approach by applying these equations to our data.

The electronic analog computer used in these studies* consists of a collection of integrator, coefficient and summing modules, as well as special display and control circuitry. It is a repetitive machine operating with a 50 msec compute period with provisions for displaying 5 simultaneous outputs on an oscilloscope. These integrators, coefficients and summers can be interconnected to form systems of mixing pools with appropriate feedback and forward flow characteristics. In addition, the computer has 30 "uncommitted" operational amplifiers which have been used in this investigation to construct the pulmonary analog.

Since the primary objective was to characterize the pulmonary vascular bed by determining its effect upon an experimentally observed input function, an electronic analog was devised, capable of simulating mixing pool and/or laminar flow characteristics. Such a general analog is diagrammed in figure 3, where $D$ are individual R-C networks whose admittance functions show a delay of 0.8 sec. and rise time of 0.88 sec. $C$ are coefficients continuously variable from 0 to 1, and $A$ is a summing module. The ability of this analog to approximate mixing pool and/or laminar flow characteristics is demonstrated in figure 4, where the extremes of response to a step input are plotted. It will be noted that pure delay, as shown by these admittance functions, can be made to vary from zero to 7 sec. The slopes of the admittance functions, as well as their shapes, can also be varied widely.

ANALOG COMPUTER ANALYSIS OF PULMONARY CIRCULATION

I I I I I

TIME, SECONDS

0 sec. (or 2-sec step input)

Fig. 5 Middle. Response of pulmonary analog to a 2 sec. step input with the calculation for mean pulmonary transit time.

Fig. 6 Bottom. Typical pulmonary admittance functions.

time determined by taking the moment of the resulting response curve and subtracting from it one second, which is the moment of the 2-sec. step input (fig. 5). The product of the computer-calculated mean pulmonary transit time and the cardiac output is taken as the pulmonary blood volume. Mean pulmonary transit time and pulmonary blood volume by the Stewart-Hamilton method were also calculated in each experiment. Details of these calculations are already well documented.

RESULTS AND DISCUSSION

A comparison between pulmonary transit times calculated by the Hamilton method and from the computer analysis is shown in table 1. The average pulmonary transit time for 31 experiments, calculated by the Hamilton method, is 5.6 sec., as compared with 4.5 sec. for the computer-calculated transit time. Similarly, the average Hamilton-calculated pulmonary blood volume for these experiments is 14.8 per cent of the total blood volume, whereas the average computer-calculated pulmonary blood volume is 11.7 per cent of the total blood volume. This compares favorably with Plummer's now-classic 1904 experiment in which, after simultaneous ligation of pulmonary artery and pulmonary veins, he weighed the amounts of blood in the lungs and found an average pulmonary blood volume equal to 10 per cent of the total blood volume.

This significant discrepancy between the two methods arises because of the fact that the Hamilton method requires the exponential extrapolation of the descending slopes of pulmonary artery and pulmonary vein curves. In the case of the pulmonary artery curve this extrapolation is probably valid because the pulmonary artery curve closely reflects the mixing characteristic of the right ventricle. However, an exponential extrapolation of the pulmonary vein function arbitrarily assigns a mixing pool characteristic to the pulmonary vascular bed. This mixing pool delay, added to the inherent delay in the data, results in a longer mean pulmonary transit time. In the computer analysis only real data (including recirculation) are used for both input and output functions. An exponential extrapolation of the pulmonary artery curve is made only for the purpose of calculating the cardiac output. This extrapolation is justified on the basis of the
mixing pool characteristic of the right ventricle.

Figure 6 represents typical variations in pulmonary admittance functions. These show the characteristic transport delay and rise time associated with laminar flow. The magnitude of delay is the time required for a particle of fluid to travel from injection site to sampling site and is equal to linear velocity divided by the distance travelled. As related to our method of analysis, this transport delay is the principal characteristic of laminar flow. From theoretical considerations it has been established by Lamb that a parabolic velocity gradient exists in a viscous fluid flowing through a pipe under conditions of laminar flow. If this were the only effect, the admittance functions would rise parabolically from zero to unity input. However, it is apparent that diffusion as well as local turbulence in the larger vessels will produce deviations from the shape of the ideal admittance function. These considerations apply to flow through a single pipe, but if the lung is considered as a multitude of parallel channels, each with a char-

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**Table 1.—Comparison of Hamilton and Computer Calculated Pulmonary Blood Volumes**

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<tr>
<th>Expt. no.</th>
<th>Dog wt. (Kg.)</th>
<th>Total blood vol. (ml.)</th>
<th>Cardiac output (ml/sec.)</th>
<th>Pul. transit time (sec.)</th>
<th>Pul. blood vol. (ml.)</th>
<th>% Total blood vol.</th>
<th>Pul. transit time (sec.)</th>
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Av.  
Standard error of the mean  
5.6  
15  
4.5  
172  
11.7  
0.6
characteristic length and velocity of flow, then the observed pulmonary admittance function is a composite curve reflecting the average length and velocity of flow through the pulmonary bed.

It will be observed that the shape of these admittance functions varies from an almost perfectly symmetric sigmoid (fig. 6B) to one of pronounced asymmetry with a definite break in the curve as it approaches unity input (fig. 6F). This abrupt change of slope suggests that some effect other than the transfer characteristic of the lung may be present. A possibility which has been considered is that of feedback from the aorta to the pulmonary vasculature via the bronchial arteries.

In order to investigate the way in which such feedback might affect the admittance function an hypothetical lung-left heart analog was programmed on the computer and varying amounts of left heart output were fed back from the aorta into various parts of the pulmonary vasculature. It was observed that a feedback greater than 5 per cent of the cardiac output was required in order to produce a significant break in the slope of the lung admittance function. However, Brunner and Schmidt have measured right bronchial flow in anesthetized dogs with a bubble flowmeter and estimated maximum intrapulmonary flow to be less than 1.25 per cent of the cardiac output. Williams has measured bronchial flow after ligation of the left lower lobe pulmonary artery (a procedure designed to increase bronchial flow) and reported a maximum flow 2 to 4 hours after ligation of 9 ml./min. These magnitudes of bronchial flow, produced under experimental conditions similar to those of this investigation, would appear to be too small to produce the asymmetric admittance functions of figure 6. Coronary flow can also be rejected because the major return through this system is to the right atrium. These admittance functions reflect only the fluid flow characteristics between the sampling sites and the effect of coronary return would be present in both the pulmonary artery and pulmonary vein curves. Thus, it is reasonable to assume that these asymmetric admittance functions are truly representative of pulmonary flow characteristics under the experimental conditions obtaining.

It must be pointed out that the significance of the shape of these admittance functions is at present not clearly understood. However, additional experimentation under conditions known to effect pulmonary hemodynamics may be helpful in evaluating these curves. They occurred in approximately 20 per cent of the 31 experiments but their inclusion in table 1 does not effect the value for average pulmonary blood volume.

SUMMARY

Thirty-one sets of activity-time curves have been obtained by catheterization and simultaneous sampling from the pulmonary artery and pulmonary vein of dogs. A universal analog was designed capable of simulating linear transport delays coupled with completely arbitrary rise time characteristics.

With the pulmonary artery curve as an input the analog was adjusted to duplicate the observed pulmonary vein curve after which the transfer characteristics of the analog were determined by pulsing it with a unit step input. The results indicate that the response of the lung to an arbitrary input function is analogous to that of a laminar flow system with a characteristic delay and rise time.

In 31 experiments, the average computer calculation pulmonary transit time was 4.5 sec. and the average pulmonary blood volume was 11.7 per cent of the total blood volume. It has been shown that the application of Hamilton's method for calculation of volume of a laminar flow system with recirculation results in a measurable error.

SUMMARY IN INTERLINGUA

Trenta-uno gruppos de curvas de activitate-tempore esseva obtenite per catheterismo con prension simultanee de specimens ab le
arteria pulmonar e le vena pulmonar de canes. Esseva construite un analogo universal, capace a simular retardos de transporto linear accopulate con completamente arbitrari characteristicas de ascendita de tempore.

Con le curva del arteria pulmonar como input, le analogo esseva adjustate a dupliear le observate curva del vena pulmonar. Postea le characteristicas de transferimento del analogo esseva determinate per pulsar lo con un input graduate in unitate. Le resultatos indica que le responsa del pulmon a un function de input arbitrari es analoge a illo de un systema de fluxo laminar con un characteristica retardo e tempore de ascendita.

In trenta-un experimentos, le valor medie del tempore de transito pulmonar seconde le calculation del computator esseva 4,5 secundas, e le valor medie del volume de sanguine pulmonar esseva 11,7 pro cento del volume total de sanguine. Il ha essite mostrate que le application del methodo de Hamilton pro le calculation de volumines de systemas de fluxo laminar con recirculation resulta in un error de mesurabile magnitude.

REFERENCES
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