LEVERETT, Jr., Sidney Duncan. THE CORRELATION OF PRESSURE AND FLOW IN THE ARTERIAL SYSTEM OF INTACT, ANESTHETIZED DOGS AND ITS CHANGES UNDER THE EFFECT OF VASOMOTOR ACTIVITY.

The Ohio State University, Ph.D., 1960
Physiology

University Microfilms, Inc., Ann Arbor, Michigan
THE CORRELATION OF PRESSURE AND FLOW IN THE ARTERIAL SYSTEM OF INTACT, ANESTHETIZED DOGS AND ITS CHANGES UNDER THE EFFECT OF VASOMOTOR ACTIVITY

Dissertation

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

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The Ohio State University
1960

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ACKNOWLEDGEMENT

The author wishes to express his appreciation to Dr. Heinz Pieper for his many hours of patient collaboration, advice, and suggestions during the entire course of this dissertation. His technical ability and willingness to manufacture necessary items for the successful conclusion of an experiment went far above the normal role of an advisor.

In addition I should like to thank Dr. Fred A. Hitchcock who served as my advisor for the master's degree and who assisted and encouraged me during my tour of duty at Wright Field, Ohio in attempting to set up a program which would enable me to continue my academic progress towards a Doctor of Philosophy degree.

Finally, I should like to extend my appreciation to all personnel of the Air Force Institute of Technology, Wright-Patterson Air Force Base, Ohio, without whose help this tour of duty at Ohio State University would not have been possible.
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INTRODUCTION

A. A Review of the Problem

The problem of relating pressure to flow in the circulatory system has intrigued investigators for many years. The first relationship of pressure and flow was given by Poiseulle in 1841 (1). His law is restricted to laminar flow of a homogeneous fluid through rigid tubes.

\[ i = K (P_1 - P_2) = \frac{\pi r^4}{8 \eta l} \cdot P_1 - P_2 \]

Later Hagenbach (2) recognized that the empirical coefficient of Poiseulle's law is a measure of the viscosity. He also found that the law is valid only within limits inasmuch as turbulence will increase the effective resistance. In elastic tubes one can expect that both the radius \( r \), and the length \( l \), of the tube will undergo changes if the perfusion pressure \( P_1 \) is altered. Changes of the radius will be of more significance because \( r \) is in the fourth power. For this reason it is not surprising that although Poiseulle's Law represents a linear relationship of pressure, flow, and resistance, whenever pressure/flow studies on the cardiovascular system have been done in the past a nonlinear relationship has been found.

The mathematical formulation of the underlying function has been attempted by Green et al (3) Wezler and Sinn (4) Folkow (5) and Lamport (6). Green established his equation on the basis of experimental studies on isolated vascular beds. Wezler and Sinn tried
to solve the problem by an expansion of Poiseuille's Law. Their complicated equation for the resistance to flow in an elastic tubing system tries to account for all factors which could possibly have mechanical influences on the resistance. In particular they directed their attention to the possible effect of turbulence, the effect of the viscosity of the blood, and to the effect of the elasticity of the vascular wall. They concluded that the occurrence of turbulence should change the proportionality between pressure and flow in such a way that the curve becomes concave to the pressure axis. When all other conditions are maintained stable, the resistance to turbulent flow is greater than to laminar flow. Since a curve concave to the pressure axis was never observed, they ruled out turbulence as one of the factors causing the disproportionality between pressure and flow.

In dealing with the viscosity of the blood, they were concerned primarily with the dynamic changes of the viscosity. Rothlin (7) could show that the viscosity decreases by 7.3 per cent when pressure increases from 40 to 200 mm Hg, while Müller (8) found a decrease of the viscosity by 3.7 per cent when the rate of flow was increased five-fold. From this Wezler and Sinn concluded that the dynamic changes could be neglected in comparison with the effect of the elasticity of the vascular wall on the pressure/flow relationship.

In their equation they took into account that both radius and length of the elastic tube are functions of pressure, $P$, and also that factors like the opposing tissue pressure surrounding the elastic blood vessel have to be considered.
It may be mentioned that the non-linearity of the elasticity coefficient of the vascular wall and its considerable difference for different parts of the vascular bed have been shown Kafka (9) and King and Lawton (10) and must complicate the mathematical formulation of the effect of the perfusion pressure on radius and length of the tube. Nevertheless, Wezler (11) gave the interpretation of a good many experimentally obtained pressure/flow curves and attempted to analyze the individual contribution of the different terms of his equation.

Both Green and Wezler and Sinn tried to express changes of the vasomotor tone quantitatively as changes of certain terms of their equation. The validity of their separate equations for the total arterial system has never been shown. Changes of the vasomotor tone of the total arterial system are generally expressed as changes of the total peripheral resistance, thereby relating mean aortic pressure to cardiac output. It is shown in Figure 1 that single simultaneous determinations of pressure and flow, in order to arrive at a resistance to flow value, may be insufficient for the complete understanding of the changes of vasomotor tone. In this example a first determination of pressure and flow may have shown the values, \( P = 100 \times 10^3 \text{ dynes/cm}^2 \), \( F = 20 \text{ cm}^3/\text{sec} \), indicated by A, resulting in a resistance \( R = 5000 \text{ dyne-sec/cm}^5 \). A second determination obtained at a higher blood or perfusion pressure may have resulted in the values \( P = 150 \times 10^3 \text{ dynes/cm}^2 \), \( F = 30 \text{ cm}^3/\text{sec} \), leading to the point B and a calculated resistance of \( R = 5000 \text{ dyne-sec/cm}^5 \). This indicated that in the time
period between the two determinations no apparent change of resistance took place although the pressure changed. From this one is inclined to conclude that vasomotor tone did not change. Assuming the possibility to determine stepwise the pressure/flow relationship at constant vasomotor tone under the conditions which existed at A, one would arrive on the grounds as discussed above at a non-linear relationship as indicated by the curved line. This means that elevation of pressure $P$ up to $150 \times 10^3$ dynes/cm$^2$ alone without a simultaneous change in vasomotor tone should lead to a flow value of only $24.5$ cm$^3$/sec must have resulted from a change of vasomotor tone.

The above procedure whereby the calculated resistance is obviously very limited in evaluating the amount of vasomotor activity has been applied to a great extent in the past for this particular purpose. As the example shows, the knowledge of the pressure/flow relationship for the total arterial system for the condition of a given vasomotor tone seems to be necessary.

The purpose of this paper is to describe how such pressure/flow relationships for the total arterial system can be established. It will be further discussed how this relationship can then be applied to obtain a better understanding of changes in vasomotor tone following the principle as discussed in Figure 1.

Pressure/flow relationships for the total arterial system, but more often for isolated parts thereof, have been investigated in several ways in the past. They showed considerable disagreement about the shape of the curves and about the effect of a change in vasomotor
tone thereon. However, in none of the experiments in the past was the constancy of the vasomotor tone assured during the time period needed for the stepwise determination of the pressure/flow relationship. In principle, three different methods have been used.
Figure 1. A hypothetical peripheral resistance curve and its interpretation in terms of vasomotor activity.
Figure 1

Increase of flow rate as a result of a change of peripheral resistance attributable to change of vascular tone between A and B.
B. Perfusion Experiments on Isolated Organs or Isolated Vascular Beds

In 1933 Whittaker and Winton (12) indirectly approached the problem in their perfusion experiments on dog's isolated hind limbs. The primary purpose was to show a change in the pressure/flow relationship as a result of altering the apparent viscosity of the perfusing medium. The point that became evident was that both pressure/flow plots (using defibrinated blood and Ringer's solution) were straight-line relationships. This finding seemed to indicate that the linear relationship as expressed in Poiseuille's Law was valid for the cardiovascular system. This has been both confirmed or contradicted in many subsequent investigations. It should be pointed out that the perfusion in their experiment took place with the vessels maximally dilated by adding 0.1 per cent chloral hydrate solution to the perfusing medium and by denervating the vascular area involved. Also a perfusion time of two to three hours ahead of the actual experiment was required in order to obtain a stable situation and reproducible results. Later Pappenheimer and Maes (13), using isolated hind limbs of dogs with intact nervous connection, found a linear relationship between pressure and flow. However, increased vasoconstriction in the vascular bed caused by adding epinephrine to the defibrinated blood produced a curved relationship in the lower pressure ranges which became a straight line at higher pressures. When the straight line portion was extrapolated back to zero flow, it intercepted the axis at pressures from 10-80 mm Hg. Green (3), using isolated hind limbs of dogs with intact nervous connections, found a parabolic relationship convex to the pressure axis during the control runs and
also during periods of heightened vasomotor activity. Vasomotor activity was changed either spontaneously or in response to hemorrhage. In a log-log graphical presentation of his data, he found in six out of 15 experiments a straight line and from this he derived the mathematical relationship:

\[ F = \left( \frac{P}{C} \right)^n \]

\( F = \text{Flow} \)
\( P = \text{Perfusing Pressure} \)
\( C = \text{Constant} \)
\( N = \text{An Exponent} > 1 \)

Using this he believed that a change in the numerical value of the exponent and the constant of the equation when compared with the control values was a quantitative measure of the effect of increased vasomotor activity on peripheral resistance. It should be pointed out that in all of his perfusion experiments a period of at least twenty minutes was required to collect a series of pressure/flow points, with the pressure head maintained at each level for 5-20 seconds. An argument used by Green to support the parabolic nature of his curves was a report by Fleisch in 1919 in which he showed a parabolic relationship between pressure and flow while perfusing fresh, surviving rabbit kidneys (14). Fleisch's experiments on isolated frog's hind limbs, however, resulted in a linear relationship which changed to a parabolic plot after adding epinephrine to the perfusion fluid.

Doyle (15), using isolated hind limbs of rats, measured flow while perfusing with Ringer's and Dextran solutions. His pressure/
flow plots followed a parabolic curve, again convex to the pressure axis. Levy and Share (16) also showed a parabolic plot in a perfusion experiment on dog's hind limbs. Ocher (17) obtained a parabolic plot when perfusing the coronary system in a heart-lung preparation, using a donor dog to supply directly the perfusing blood. In contrast Selkurt (18) and Ritter (19) obtained a pressure/flow curve of the intact kidney of a dog concave to the pressure axis.

In a series of innervated, perfused rabbit's ears Wezler (11) reports curves convex to the pressure axis in all instances. These include periods of raised and lowered tonus in the vascular bed. Depressed tonus was produced by heat radiation on the ear while simultaneously obtaining a pressure/flow relationship. Perfusion of isolated, denervated dogs' lungs by Wezler and Sinn (4) yielded the same type curve. Based on a theoretical analysis of an expansion of factors involved in Poiseuille's law, Wezler derived a "flow law for dilatable tubes." Simplifying the equation by a series of assumptions, he arrived at an expression equal to Green's for describing flow in elastic tubes. Wezler tested his flow law against curves obtained from experiments such as those described above and found that it in fact characterized the pressure/flow relationship. He agreed with Green that it was proved that the elasticity of the blood vessels was the decisive reason for the disproportionality of flow intensity and pressure in the circulation.

Thus, to the present date there seems to be no definite conclusion about the shape of the pressure/flow curve; however, the
majority of investigators working with the isolated perfusion experiment reported a parabolic curve convex to the pressure axis. Changing the viscosity of the perfusing medium did not show any effect on the shape of the curve. The only time the curve deviated from the parabolic plot was during complete denervation and maximum dilation. In these instances it approached a linear relationship.

C. Experiments on Whole Animal Preparations

Levy et al (20) was capable of varying the mean arterial pressure level of dogs between 40-100 mm Hg. The pressure was maintained at each level for 10 minutes, during which time a direct Fick cardiac output determination was performed. Since cardiac output had to be equal to total arterial outflow, pressure/flow curves could be obtained. With an intact nervous system these plots resembled a parabola convex to the pressure axis. When the carotid sinus and aortic baroreceptors were eliminated and bilateral vagotomy performed, the plot became linear. These results are in agreement with both the isolated, innervated perfusion experiments of Green and the isolated denervated perfusion experiments of Whittaker and Winton.

Read et al (21) obtained parabolic curves only in dogs with high vasomotor activity while the control curves and those following pithing were linear.

Guyton et al (22) also found curves convex to the pressure axis as did Flacke et al (23) both using separate methods for measuring flow and for changing perfusion pressure. However, neither Guyton
nor Flacke found a linear relation between pressure and flow in any experimental situation.

Folkow (5) using pithed cats, obtained a pressure flow curve concave to the pressure abscissa and stated that this was a regular finding in all of his experiments.

D. Use of Intact Animals to Measure Volume Flow During Diastole

In 1896 Hurthle stated that "the fall in pressure in the arteries in diastole is only dependent on the rate of flow from the arteries into the veins. Therefore, the velocity of fall of pressure is a direct measure of the resistance opposed to this flow (24)."

Three years later Frank (25) introduced his "Windkessel Theory" and gave the mathematical formulation to Hurthle's statement. Frank felt that the flow from the arterial reservoir during diastole could be more easily described mathematically than that occurring during systole. While the pressure changes in the arterial system during systole are determined by the difference between inflow and outflow, the diastolic decline of pressure is caused by the outflow alone.

In 1953 Wetterer and Pieper (26) developed a method primarily to determine the distensibility of the arterial reservoir in an intact, anesthetized animal. The method utilized a sinusoidal pump which rhythmically changed the content of the arterial reservoir, thus causing a slow oscillation of the arterial pressure. This concept was extended to enable them to calculate the outflow of the arterial reservoir during diastole (27) and was used to determine
experimentally a pressure/flow relationship in intact dogs. Although their curves were presented as linear functions, the relatively large scatter of their values does not permit definite conclusions as to the true shape of the curve. The above procedure of Wetterer and Pieper has now been improved, and its experimental application is the basis of the following attempts to better describe the pressure/flow relationship in intact, anesthetized animals. Furthermore, it will be shown in what way changes of the vasomotor tone, for example, under the influence of drugs, become effective with respect to this pressure/flow relationship.
A. General Approach

The theoretical approach for determining volume flow per unit of time during diastole is based on Wetterer and Pieper's work in 1953 and on an original analysis of the coefficient of elasticity of the arterial system by O. Frank in 1899 (25). According to Frank the elasticity coefficient of the total arterial reservoir can be expressed thus:

\[ E' = \frac{dP}{dV} \approx \frac{\Delta P}{\Delta V} \]

\[ E' = \text{Coefficient of elasticity of the arterial reservoir} \]

\[ \Delta P = \text{Change in pressure per unit change in volume in the arterial reservoir} \]

The total peripheral runoff during diastole is:

\[ i_R = \text{Average flow rate in the total arterial system during diastole} \]

\[ i_R = \frac{-\Delta V}{\Delta t} \]

\[ -\Delta V = \text{Change in volume of the total arterial system during diastole} \]

\[ \Delta t = \text{Time in seconds for diastole} \]

In (2) the sign is negative because the contents of the arterial system are decreasing in size as a result of the diastolic runoff. If \( \Delta P \) is the decline of the arterial pressure during diastole then:

\[ F = \frac{\Delta P}{\Delta t} \]

\[ F = \text{is a measure of the slope of this decline with respect to time. At this point an approximation must be made if} \]
Equation (3) should hold true. Although the decay of pressure in the arterial system occurs exponentially, for the normal duration of diastole the portion of the exponential curve can be considered to be straight (28). For this reason excessively long durations of diastole leading to markedly curved pressure slopes, i.e., during extreme bradycardia, cannot be used for the evaluation. Expressing $\Delta t$ by conversion of Equation (2)

\begin{equation}
\Delta t = \frac{-\Delta V}{i_R}
\end{equation}

and substituting this value in Equation (3) one obtains:

\begin{equation}
\zeta = \frac{\Delta P}{-\Delta V}
\end{equation}

\begin{equation}
\zeta = \frac{\Delta P}{-\Delta V}
\end{equation}

which can be written as:

\begin{equation}
\zeta = -E \cdot i_R
\end{equation}

on the grounds of Equation (1).

Similar to Wetterer and Pieper a sinusoidal pump is attached to the arterial system of intact, anesthetized dogs. This adds to or depletes from the total volume of the arterial reservoir in a rhythmical manner, causing a corresponding oscillation of the mean arterial pressure. Superimposed on these slow rhythmical oscillations are the arterial pulses (Figure 2). A linear recording of the piston movement of the pump permits the calculation of the volume displacement
Figure 2. Photographic reproduction of an experimental record indicating the pump cycle, arterial pressure, right atrial pressure, and the stroke output tracing. Time lines are at 0.1 second interval.
of the pump for every period during the cycle. From this the flow rate, $i$, of the pump can be computed for every moment. During the input phase of the pump when $i$ is positive, the diastolic decrease of arterial contents will be smaller by the diastolic input from the pump resulting in a smaller pressure decline, $\Delta P$. On the same grounds the diastolic pressure decline will be larger during the withdrawal phase of the pump when $i$ is negative. This effect of the pump can be visually noted by comparing the slopes of the diastolic pressure during the input and output phases of the pump operation. Thus, Equation (6) can be rewritten:

(7) $\Sigma = -E'(i_i - i)$ with the pump either adding to or withdrawing from the arterial reservoir.

It is now only necessary to select arterial pressure pulses with the same mean diastolic pressure during the input and output phase of the pump operation. These are referred to as pulse A and pulse B, Figures 2 and 3. When selecting pairs of pulses, the mean diastolic pressures of A and B are not allowed to deviate more than 2 per cent. It can then be assumed that the elasticity coefficient, $E'$, as well as the peripheral resistance and, therefore, the peripheral runoff, $i_R$, are equal for the diastoles in both A and B. Equation (7) can then be rewritten as:

(8a) $\Sigma_A = -E'(i_R - i_A)$

(8b) $\Sigma_B = -E'(i_R - i_B)$

or, solving both equations for $-E'$
\[ (9a) \quad E' = \frac{\xi_A}{i_R - i_A} \]

\[ (9b) \quad E' = \frac{\xi_B}{i_R - i_B} \]

then combining (9a) and (9b)

\[ (10) \quad \frac{\xi_B}{i_R - i_B} = \frac{\xi_A}{i_R - i_A} \]

From this \( i_R \) can be calculated as:

\[ (11) \quad i_R = \frac{\xi_A i_B - \xi_B i_A}{\xi_A - \xi_B} \]

In short, while Equation (7) still contained two unknowns, \( E' \) and \( i_R \), the final calculation is made possible by establishing a matching pair of pulses and thus eliminating \( E' \). All other quantities in Equation (11) can be determined from the recording. \( i_R \) then represents the calculated flow at the particular mean diastolic pressure. By selecting other pairs of pulses at different mean diastolic pressure levels, a flow relationship for the different pressures can be established, resulting in a curve which relates pressure and flow for a given vasomotor tonus in the intact animal.

B. Animal Preparation and Instrumentation

Thirty-nine mongrel male and female dogs varying in weight from 11.6 to 29.9 Kgm were used as the experimental animals. All were anesthetized with 30 mgm/Kgm pentobarbital sodium (Nembutal*)
administered intravenously with maintenance dosages given as needed. Arterial pressure was transduced through a miniature, catheter-tipped manometer described by Wetterer (29), Wetterer and Pieper (30) and Gauer and Gienapp (31). This manometer was threaded through a femoral artery to a point in the descending aorta where the reflected pulse waves on the diastolic pressure decline were eliminated and a straight line decay was observed. This nodal point is usually in the region of the proximal thoracic aorta (28). A cathode ray oscilloscope with a long persistency tube was utilized to aid visually in the proper placement of the arterial manometer (Electronic Tube Corp., Philadelphia, Pa., Model K-11R). A similar miniature manometer mounted to a double-lumen catheter (U.S. Catheter Instrument Co., Glens Falls, N.Y.) was placed in the right atrium via the external jugular vein. This pressure tracing was used in the subsequent record analysis to avoid pulses occurring during a respiratory cycle. The other lumen of the catheter was utilized for intravenous injection of various drugs.

The sinusoidal pump was modified from a Zero-Max, 1/3 horsepower, a-c motor (Zero-Max Company, Minneapolis, Minn.). The drive shaft of the motor was attached to a calibrated crank sidepiece upon which a sliding arm was connected. This sliding arm in turn was coupled to the piston rod. Movement of the sliding arm along the calibrated crank sidepiece increased or decreased the volume displacement of the pump up to a maximum of 82 cm³. The piston carried two sets of O-rings, separated from each other by 10 cm. This formed a dead space into
which light oil was filled in order to lubricate the O-rings for free movement and also to insure better sealing of the piston and to avoid the entrance of air. The cylinder contained physiological saline at the beginning of an experiment which became mixed with blood after pumping began. In all cases the dogs were heparinized (5 mgm/Kgm) in order to preclude alteration of the pump action by clotting (Heparin sodium, 10 mgm/cc, Upjohn Co., Kalamazoo, Mich.). Both volume displacement and frequency of the pump could be varied continuously. In our experiments the frequency ranged from 0.13 to 0.26 cps and the volume displacement used according to the size of the dog varied from 28.0 to 79.4 cm³. The pump was attached to the dog via a blunt-tipped polyethylene catheter (usually a PE-360, outside diameter 4.82 mm., Clay-Adams Co., Inc., New York, N.Y.) introduced through the femoral artery and passed well into the abdominal aorta. The diameter of the catheter had to be varied sometimes according to the size of the femoral artery. In several experiments a simultaneous dye dilution cardiac output determination was performed. The dye was injected into the aforementioned double lumen catheter. Whenever this was done during the infusion of vasoactive drugs, a simultaneous infusion of vaso-active drugs could be administered through another catheter introduced into the femoral vein. A catheter-type flowmeter described by Pieper (32) was introduced into the left common carotid artery and passed into the ascending aorta. This flowmeter, which was used in parallel studies of the dynamics of the heart, delivered a beat by beat recording of cardiac output. It became valuable for the detection of irregularities of the performance of the heart as, for example, pulsus alternans.
In this respect it was superior to the arterial pressure curve.

The piston displacement was transduced through a linear differential transformer, the iron core of which was suspended on proximal and distal springs which in turn were attached on one side to the piston and on the other side to the mounting of the transformer coils. The purpose of the springs was to reduce the displacement of the iron core with respect to the transformer windings while the piston was traveling its full way.

All of the signals were fed into individual carrier amplifiers as described by Wetterer and Pieper (30) and then into Hathaway galvanometers and photographically recorded on a Hathaway oscillograph recorder, Type S-14 E.

C. Analytical Procedure

In analyzing the arterial pressure, matching pairs of pulses at equal mean diastolic pressure (+ 2 per cent) were selected. Pulses that occurred simultaneously with an inspiration were not used for the calculation. A respiratory effort was indicated on the right atrial pressure trace by a fall in pressure. In some few cases, particularly under the influence of Levophed, irregularities of the heart rate during a pump cycle occurred. Such changes in heart rate were interpreted as changes in vasomotor tone during operation of the pump and the recordings were, therefore, discarded. Time lines at 0.1 second intervals were photographically impressed. The paper speed of the Hathaway recorder was approximately 114 mm/sec and was confirmed.
for each record.

All arterial pressures were converted to $10^3$ dynes/cm$^2$ and flow values were presented as cm$^3$/sec. In calibrating the catheter-tip manometers used for transducing aortic and right atrial pressures, a warm zero was recorded immediately after the sensing tip was withdrawn from the blood vessel. This warm zero point was then used as the basis for establishing the calibration scale for the manometers.

$i_A$ and $i_B$ can be calculated from the recording of the piston movement of the pump. This recording was calibrated at the end of each experiment. For this purpose the pump was attached to a graduated cylinder and the volume displacement during a pump cycle could be measured.

The final Equation (11) was used in calculating $i_R$, previously defined as the average flow rate from the total arterial reservoir during diastole. Each part of the equation was determined separately from the record analysis and was calculated as described in Figure 3.

Pressures in $10^3$ dynes/cm$^2$

$$\xi_A = - \frac{\Delta P}{\Delta t} = \frac{P_2 - P_1}{\Delta t} = \frac{201 - 220}{.28} = - 67.8 \times 10^3 \text{ dynes/cm}^2 \text{ sec.}$$

$$\xi_B = - \frac{\Delta P}{\Delta t} = \frac{P_2 - P_1}{\Delta t} = \frac{183 - 235}{.27} = - 192.5 \times 10^3 \text{ dynes/cm}^2 \text{ sec.}$$

1 mm. piston displacement corresponds to 0.775 cm$^3$.

$$i_A = \frac{\Delta l_A \cdot 0.775}{\Delta t_A} = \frac{(5.5)(0.775)}{(.28)} = + 15.22 \text{ cm}^3/\text{sec.}$$
Figure 3. Tracings of Pulse A and B in Figure 2 indicating the analysis procedure for determining diastolic outflow. The mean diastolic pressure in Pulse A is $210.5 \times 10^3$ dynes/cm$^2$ and in Pulse B, $209 \times 10^3$ dynes/cm$^2$. 
\[-i_B = \frac{\Delta I_B}{\Delta t_B} \cdot 0.775 \quad \frac{(5.0)}{(0.775)} = -14.35 \text{ cm}^3/\text{sec.}\]

\[i_R = \frac{\xi_A i_B - \xi_X i_A}{\xi_A - \xi_B} = \frac{(-67.8)(-14.35) - (-192.5)(-15.22)}{(-67.8) - (-192.5)}\]

\[i_R = \frac{3902}{124.7} = 31.3 \text{ cm}^3/\text{sec.}\]

In some cases \(P_2\) may be greater than \(P_1\). This occurs only during the input phase of the pump when the volume as injected by the pump, \(i_A\), exceeds the diastolic outflow, \(i_R\). The sign of \(\xi_A\) then becomes positive.

It was desirable to have a mean diastolic pressure fluctuation of from \(40-50 \times 10^3\) dynes/cm\(^2\) in order to obtain a peripheral resistance curve for a greater pressure range. In some cases this was not achieved; however, a small portion of the peripheral resistance curve could always be determined.

The effect of vasoactive drugs on the pressure/flow ratio was investigated. Levophed\textsuperscript{*} bitartrate (Winthrop Laboratories, New York, N.Y.) and Adrenalin\textsuperscript{*} chloride (Parke-Davis & Co., Detroit, Mich.) were infused at the rate of 10-20 gamma per minute with a Harvard constant infusion pump. In each case a test recording before the infusion of the drug was taken. When, during the infusion of either drug, the arterial pressure stabilized at a new level of vasomotor tone, the pump was placed in operation for the experimental procedure and a recording was taken. It may be noted that each recording of a pump cycle was immediately preceded by a short recording showing the
situation without operation of the pump.

The procedure for the dye dilution cardiac output determination was similar to that of Hamilton, et al (33). BSP* (Bromosulphalein, Hynson, Wescott & Dunning, Inc., Baltimore, Md., 50 mgm/cc) was used. Two cm$^3$ were injected rapidly into the right atrial catheter, previously filled with physiological saline. This catheter had a dead space of approximately 0.7 cm$^3$. A T connection within the catheter which connected the pump with the abdominal aorta was used for collecting the arterial blood. Samples were taken at the rate of one per second. Immediately after the collection period the sampling catheter was closed and the pump was started.

D. Experimental Protocol

The outline listed below generally defines the sequential procedure in the over-all experiment. However, this varied between individual experiments and deviations from this pattern will be noted in RESULTS.

1. All catheters and manometers were surgically placed and tested for proper operation.

2. A control run in which the pump was placed in operation was performed. Usually five complete pump cycles were recorded for each procedure. In a number of our experiments, several control runs with different pump frequencies were recorded.

3. Bilateral common carotid occlusion was performed. Occlusion was held for at least 30 seconds before the pump was started, at which
time the arterial pressure had stabilized at its new level.

4. Epinephrine was infused at the rate of 10-20 gamma per minute for a variable period of time. The pump was started after arterial pressure had stabilized at the new level while the perfusion was continued.

5. Similarly to 4, Levophed* was infused at the rate of 10-20 gamma per minute and several pump cycles were recorded.

6. A post-experimental control was taken. In two experiments the dog was given an additional 120 mgm of Nembutal* before the recording in order to further depress any vasomotor response. In those experiments during which several dye dilution determinations were performed, this post-experimental control run represented the condition after hemorrhage. The amount of blood lost due to the sampling was estimated from the total number of samples and generally was in the range of 200-250 cm$^3$. 
RESULTS

The recordings of nine animals were selected for evaluation. The choice was determined by the fact that these experiments were without the interference of any undesired technical or physiological occurrences. Some of these occurrences, for instance, were rapid oscillations on the pressure recordings due to turbulence in the aorta during the input phase of the pump. Among the interferences of physiological origin, irregularities of the performance of the heart were predominant. While arrhythmias could be detected easily, irregularities of the pulsus alternans type are sometimes so obscure that they are scarcely reflected in the arterial pressure curve, although they could be easily detected in the aortic flow tracing. Theoretically, differences in systolic filling should not affect the calculation of diastolic outflow. However, whenever such pulsus alternans was present, the recording was not evaluated since it was felt that in this case the integrity of the circulatory system may have been compromised.

It became helpful for the evaluation of the stability of the vasomotor tone during a recording to plot pulse by pulse the pre-systolic pressure against the systolic peak pressure of each pump cycle. As shown by Pieper (34) this plot results in a linear relationship with little scatter. The only deviation from this plot occurs normally during the respiratory cycle where the peak systolic pressure is higher. It was assumed that the degree of scatter of this relationship was a measure of the stability of the vasomotor tone, little
scatter indicating good stability and vice versa. Thus, only recordings indicating a stable situation have been evaluated.

In all experiments one or several control runs were performed immediately following the preparatory surgical procedures. In these controls the pump rate and/or the volume displacement were often varied from one recording to the other. See Tables 1-9. It may be mentioned here that variations of pump frequency or volume displacement do not have any effect on the calculated flow values provided the animal's vasomotor tone does not change in between recordings. Twenty-one control pressure/flow curves could be calculated. Any experimentally produced variation is in reference to the individual animal's control curve. In all cases the control curves followed an exponential curve convex to the pressure axis. See Figures 4-12.

Eleven bilateral carotid occlusions were performed and again the shape of the curve resembled an exponential relationship between pressure and flow with the curve convex to the pressure axis. In all instances the carotid occlusion curve shifted to the right of the control curve, indicating an increase in peripheral resistance.

The pressure/flow relationships could also be determined for five recordings taken during the infusion of epinephrine. See Figures 4, 6, 8, 10, and 12. Thereby, the stimulating effect of epinephrine on respiration leading particularly to an increase in the rate made it more difficult to find pulses of equal mean diastolic pressure which were completely unaffected by the influence of respiration. This may in part explain that in some of our experiments a larger scatter of
the calculated values can be noticed. However, there seems to be little
doubt that these plots also follow an exponential curve as can be seen
particularly in Figures 4, 6, and 8. There was no consistency con-
cerning the location of the epinephrine curve with respect to the
controls. While in the experiments represented by Figures 4 and 10,
the peripheral resistance is lowered as compared to the control,
Figures 6 and 12 show a marked shift to the right indicating increased
peripheral resistance. In Figure 8 no appreciable change in peripheral
resistance occurred although the heart rate and arterial pressure
varied widely when compared with the control situation. No definite
statement about the effect of epinephrine can be made. The inconsist-
ency may be only a consequence of totally different control situations
in different animals.

Six pressure/flow relationships could be calculated for the total
arterial system under the effect of Levophed\* infusion. The above
remarks concerning the effect of epinephrine on respiration also apply
to Levophed\*. Again, the calculated curves are exponential. Whenever,
during an experiment, the epinephrine curve and the Levophed\*curve
could be established in succession, considerable differences in the
effect of the two drugs become apparent. See Figures 4, 8, and 12.
Although the number of experiments is too small to arrive at definite
conclusions, it is surprising to see that, with respect to the control
curve, in Figures 4 and 8 Levophed\*raised the resistance while epineph-
phrine had a lowering effect and in Figure 12 the situation is just the
reverse.
In two experiments a post-experimental control was performed immediately after an additional amount of Nembutal was injected intravenously. Both curves shifted to the left of the control curve indicating a fall in total peripheral resistance. See Figures 9 and 10.

Eight dye dilution cardiac output determinations were performed. The arterial pressure was recorded during the sampling period. From this, the average mean pulse pressure during this period could be determined. Each dye dilution determination was immediately followed by operation of the pump, from which recording the usual pressure/flow curve could be calculated. In Figures 9 and 10 the flow values as calculated from the dye dilution determinations, if plotted against their respective mean arterial pressures, are in extremely close agreement with our pressure/flow curves. It can be noted that these flow values are always within the upper range of the curve. This can be explained by the fact that the pump is generally halted after operation at the end of its injection phase, thus leaving all the blood within the animal between runs. The subsequent pressure oscillation during the next run can, therefore, take place only within a range below the preceding mean arterial pressure.

It was desirable to derive a mathematical function for all pressure/flow curves which, in its basic form, could be applied to all pressure/flow curves as calculated from our experiments. This function should serve two purposes: first, the calculation of intermediate values within the range of our experimental observations and
secondly, the determination of the differential quotient for any point of this portion of the curve. It was first attempted to find a mathematical expression similar to the one given by Green or Wezler and Sinn. Since a log-log plot of our curves always resulted in a curved line, Green's equation could not be applied. The theoretical basis for a pressure/flow law seems to be still missing and, therefore, any mathematical formulation which fits the curves is acceptable. In our experiments it was most convenient to derive an exponential function. For the function for each of our experimental curves, see Tables 1-9. The general form of the equation is:

\[ F = a e^{bP} + C, \text{ where } a = \frac{1}{d} \]

This exponential function was obtained by transforming preliminary curve as estimated on the basis of our experimental pressure/flow values into a logarithmic curve. This curve, then, delivered in turn the logarithmic equation which is also given in the Tables. It is of the general form:

\[ \log (F-C) = mP - n \]

Comparison of (12) with (13) shows that:

\[ m = b \cdot \log e \]

or

\[ b = \frac{m}{\log e} \]

and
(16) \[ n = \log d \]

Thus, all values of (12) can be calculated.
LEGEND FOR FIGURES 4 - 13

F = Diastolic Flow
Pd = Mean Diastolic Pressure
Rtp = Total Peripheral Resistance
★ = Control
☆ = Carotid Occlusion
□ = Epinephrine
○ = Levophed
● = Levophed
★ = Post-run Control
★ = Dye Dilution Cardiac Output Determination

LEGEND FOR TABLES 1 - 9

C = Control
CO = Carotid Occlusion
E = Epinephrine
L = Levophed
PC = Post-run Control
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate</th>
<th>Arterial Pressure</th>
<th>Pump Freq.</th>
<th>Pump Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>( \text{Log (F-2.5) = 0.0138P -1.051} )</td>
<td>( F = 0.089e^{+2.5} )</td>
<td>158</td>
<td>193/158</td>
<td>0.23</td>
<td>28</td>
</tr>
<tr>
<td>C₂</td>
<td>( \text{Log (F-3.95) = 0.029P -3.93} )</td>
<td>( F = 1.175 \times 10^{-4}e^{+3.95} )</td>
<td>150</td>
<td>215/170</td>
<td>0.22</td>
<td>28</td>
</tr>
<tr>
<td>C₃</td>
<td>( \text{Log (F-20) = 0.0174P -2.045} )</td>
<td>( F = 9.02 \times 10^{-3}e^{+20} )</td>
<td>150</td>
<td>239/171</td>
<td>0.22</td>
<td>28</td>
</tr>
<tr>
<td>C₀</td>
<td>( \text{Log (F-3.85) = 0.0127P -1.585} )</td>
<td>( F = 0.026e^{+3.85} )</td>
<td>120</td>
<td>247/190</td>
<td>0.21</td>
<td>28</td>
</tr>
<tr>
<td>L₁</td>
<td>( \text{Log (F-3.85) = 0.0127P -1.585} )</td>
<td>( F = 0.026e^{+3.85} )</td>
<td>135</td>
<td>226/188</td>
<td>0.19</td>
<td>28</td>
</tr>
</tbody>
</table>

*See Figure 4*
Figure 5

The graph shows the relationship between $F$ (in cm$^3$/sec) and $P_d$ (in $10^3$ dynes/cm$^2$) or $10^3$ dynes/cm$^2$. The data points are plotted and connected with a smooth curve, indicating a nonlinear relationship.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate Beats/Min.</th>
<th>Arterial Pressure</th>
<th>Pump Freq. Cycles/Sec.</th>
<th>Volume Cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>( \log(F-57) = 0.0173P -2.07 )</td>
<td>( F = 8.52 \cdot 10^{-3}e^{0.0398P} +57 )</td>
<td>210</td>
<td>223/170</td>
<td>0.25</td>
<td>59</td>
</tr>
<tr>
<td>C₂</td>
<td>( \log(F-57) = 0.0173P -2.07 )</td>
<td>( F = 8.52 \cdot 10^{-3}e^{0.0398P} +57 )</td>
<td>195</td>
<td>223/170</td>
<td>0.26</td>
<td>59</td>
</tr>
<tr>
<td>C₃</td>
<td>( \log(F-57) = 0.0173P -2.07 )</td>
<td>( F = 8.52 \cdot 10^{-3}e^{0.0398P} +57 )</td>
<td>195</td>
<td>223/170</td>
<td>0.18</td>
<td>59</td>
</tr>
<tr>
<td>C₄</td>
<td>( \log(F-57) = 0.0173P -2.07 )</td>
<td>( F = 8.52 \cdot 10^{-3}e^{0.0398P} +57 )</td>
<td>180</td>
<td>223/170</td>
<td>0.16</td>
<td>59</td>
</tr>
<tr>
<td>L</td>
<td>( \log(F-10) = 0.008P -0.02 )</td>
<td>( F = 0.955e^{0.0184P} +10 )</td>
<td>150</td>
<td>284/201</td>
<td>0.21</td>
<td>59</td>
</tr>
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*See Figure 5*
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate Beats/Min.</th>
<th>Arterial Pressure</th>
<th>Pump Freq. Cycles/Sec.</th>
<th>Pump Volume cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>( \log (F-16) = 0.00684P - 0.023 ) ( F = 0.95e^{+16} )</td>
<td>( 0.0158P )</td>
<td>170</td>
<td>179/145</td>
<td>0.22</td>
<td>57</td>
</tr>
<tr>
<td>C₂</td>
<td>( \log (F-16) = 0.00684P - 0.023 ) ( F = 0.95e^{+16} )</td>
<td>( 0.0158P )</td>
<td>160</td>
<td>193/158</td>
<td>0.24</td>
<td>38</td>
</tr>
<tr>
<td>C₃</td>
<td>( \log (F-16) = 0.00684P - 0.023 ) ( F = 0.95e^{+16} )</td>
<td>( 0.0158P )</td>
<td>150</td>
<td>187/150</td>
<td>0.26</td>
<td>37</td>
</tr>
<tr>
<td>C₄</td>
<td>( \log (F-16) = 0.00684P - 0.023 ) ( F = 0.95e^{+16} )</td>
<td>( 0.0158P )</td>
<td>150</td>
<td>206/161</td>
<td>0.21</td>
<td>37</td>
</tr>
<tr>
<td>C₀</td>
<td>( \log (F-14) = 0.0158P - 1.752 ) ( F = 0.0177e^{+14} )</td>
<td>( 0.0364P )</td>
<td>150</td>
<td>236/187</td>
<td>0.26</td>
<td>38</td>
</tr>
<tr>
<td>E</td>
<td>( \log (F-9) = 0.0206P - 2.975 ) ( F = 1.06 \cdot 10^{-3}e^{+9} )</td>
<td>( 0.0474P )</td>
<td>100</td>
<td>230/180</td>
<td>0.23</td>
<td>40</td>
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*See Figure 6
<table>
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<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate Beats/Min.</th>
<th>Arterial Pressure</th>
<th>Pump Freq. Cycles/Sec.</th>
<th>Pump Volume Cm³</th>
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</thead>
<tbody>
<tr>
<td>C</td>
<td>( \log (F-50.95) = 0.0435P - 7.245 )</td>
<td>( F = 5.68 \times 10^{-6}e^{0.1P} + 50.95 )</td>
<td>240</td>
<td>229/185</td>
<td>0.24</td>
<td>54</td>
</tr>
<tr>
<td>( \text{CO}_1 )</td>
<td>( \log (F-46.8) = 0.0392P - 8.32 )</td>
<td>( F = 4.78 \times 10^{-7}e^{0.09P} + 46.8 )</td>
<td>210</td>
<td>271/215</td>
<td>0.19</td>
<td>52</td>
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<tr>
<td>( \text{CO}_2 )</td>
<td></td>
<td></td>
<td>210</td>
<td>266/213</td>
<td>0.23</td>
<td>52</td>
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*See Figure 7*
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<th>Heart Rate Beats/Min.</th>
<th>Arterial Pressure</th>
<th>Pump Freq. Cycles/Sec.</th>
<th>Pump Volume cm³</th>
</tr>
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<tbody>
<tr>
<td>C₁</td>
<td>Log (F-48) = 0.0165P -1.292</td>
<td>F = 0.051 • e 0.038P +48</td>
<td>210</td>
<td>249/205</td>
<td>0.16</td>
<td>79.4</td>
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<tr>
<td>C₂</td>
<td>Log (F-16) = 0.007P -0.134</td>
<td>F = 0.654 • e 0.0161P +16</td>
<td>210</td>
<td>289/240</td>
<td>0.16</td>
<td>77</td>
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<tr>
<td>C₀₁</td>
<td>Log (F-16) = 0.007P -0.134</td>
<td>F = 0.654 • e 0.0161P +16</td>
<td>210</td>
<td>289/240</td>
<td>0.16</td>
<td>77</td>
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<tr>
<td>C₀₂</td>
<td>Log (F-16) = 0.007P -0.134</td>
<td>F = 0.654 • e 0.0161P +16</td>
<td>210</td>
<td>289/240</td>
<td>0.16</td>
<td>77</td>
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<tr>
<td>E</td>
<td>Log (F-47) = 0.025P -3.928</td>
<td>F = 1.18 • 10⁻³e 0.577P +47</td>
<td>188</td>
<td>200/165</td>
<td>0.16</td>
<td>76</td>
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<tr>
<td>L</td>
<td>Log (F-24.5) = 0.0241P -3.532</td>
<td>F = 2.94 • 10⁻³e 0.0562P +24.5</td>
<td>180</td>
<td>200/171</td>
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<td>74.4</td>
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*See Figure 8*
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<th>Arterial Pressure</th>
<th>Pump Freq.</th>
<th>Pump Volume</th>
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</thead>
<tbody>
<tr>
<td>C</td>
<td>$\log (F-31) = 0.0254P - 4.02$</td>
<td>$F = 9.55 \times 10^{-5} e^{0.0586P} + 31$</td>
<td>135</td>
<td>233/181</td>
<td>0.17</td>
<td>60</td>
</tr>
<tr>
<td>CO</td>
<td>$\log (F-18) = 0.0134P - 2.77$</td>
<td>$F = 1.68 \times 10^{-3} e^{0.0423P} + 18$</td>
<td>150</td>
<td>262/211</td>
<td>0.23</td>
<td>57</td>
</tr>
<tr>
<td>L</td>
<td>$\log (F-25.6) = 0.0307P - 4.31$</td>
<td>$F = 4.91 \times 10^{-5} e^{0.0708P} + 25.6$</td>
<td>135</td>
<td>232/176</td>
<td>0.23</td>
<td>60</td>
</tr>
<tr>
<td>PC</td>
<td>$\log (F-24.7) = 0.0307P - 3.68$</td>
<td>$F = 2.09 \times 10^{-4} e^{0.0708P} + 24.7$</td>
<td>120</td>
<td>194/147</td>
<td>0.23</td>
<td>60</td>
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</table>

*See Figure 9*
<table>
<thead>
<tr>
<th>Procedure</th>
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<th>Exponential Equation</th>
<th>Heart Rate</th>
<th>Arterial Pressure</th>
<th>Pump Freq.</th>
<th>Pump Volume</th>
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</thead>
<tbody>
<tr>
<td>C</td>
<td>Log (F-27.7) = 0.0353P - 4.38</td>
<td>F = 4.17 \cdot 10^{-5}e^{+27.7}</td>
<td>135</td>
<td>186/145</td>
<td>0.22</td>
<td>61</td>
</tr>
<tr>
<td>CO</td>
<td>Log (F-17) = 0.0068P + 0.035</td>
<td>F = 1.216 \cdot e^{+17}</td>
<td>150</td>
<td>240/186</td>
<td>0.22</td>
<td>60</td>
</tr>
<tr>
<td>E</td>
<td>Log (F-18.3) = 0.016P - 0.84</td>
<td>F = 0.1445e^{+18.3}</td>
<td>135</td>
<td>198/138</td>
<td>0.22</td>
<td>57</td>
</tr>
<tr>
<td>FC</td>
<td>Log (F-17.5) = 0.0199P - 1.265</td>
<td>F = 5.43 \cdot 10^{-2}e^{+17.5}</td>
<td>127</td>
<td>161/117</td>
<td>0.22</td>
<td>60</td>
</tr>
</tbody>
</table>

*See Figure 10
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate</th>
<th>Arterial Pressure</th>
<th>Pump Freq.</th>
<th>Pump Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_1$</td>
<td>$\log (F - 40.6) = 0.0333P - 4.6$</td>
<td>$F = 2.51 \times 10^{-5}e^{0.077P}$</td>
<td>180</td>
<td>217/163</td>
<td>0.19</td>
<td>78</td>
</tr>
<tr>
<td>$c_2$</td>
<td>$\log (F - 45.5) = 0.0482P - 9.765$</td>
<td>$F = 1.72 \times 10^{-8}e^{0.011P}$</td>
<td>180</td>
<td>194/154</td>
<td>0.22</td>
<td>78</td>
</tr>
<tr>
<td>$c_3$</td>
<td></td>
<td></td>
<td>165</td>
<td>203/157</td>
<td>0.24</td>
<td>78</td>
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*See Figure 11*
### TABLE 9*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Log Equation</th>
<th>Exponential Equation</th>
<th>Heart Rate Beats/Min.</th>
<th>Arterial Pressure</th>
<th>Pump Freq. Cycles/Sec.</th>
<th>Pump Volume Cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>Log ( (F-43.9) = 0.073P -12.56 )</td>
<td>( F = 2.76 \times 10^{-11} e^{43.9} )</td>
<td>140</td>
<td>219/164</td>
<td>0.13</td>
<td>60</td>
</tr>
<tr>
<td>C₂</td>
<td></td>
<td></td>
<td>140</td>
<td>200/161</td>
<td>0.17</td>
<td>60</td>
</tr>
<tr>
<td>C₃</td>
<td></td>
<td></td>
<td>140</td>
<td>211/167</td>
<td>0.14</td>
<td>60</td>
</tr>
<tr>
<td>C₀</td>
<td>Log ( (F-44.5) = 0.073P -16.5 )</td>
<td>( F = 3.16 \times 10^{-15} e^{44.5} )</td>
<td>160</td>
<td>284/215</td>
<td>0.16</td>
<td>60</td>
</tr>
<tr>
<td>E</td>
<td>Log ( (F-43.4) = 0.034P -6.235 )</td>
<td>( F = 5.82 \times 10^{-5} e^{43.4} )</td>
<td>150</td>
<td>233/171</td>
<td>0.17</td>
<td>60</td>
</tr>
<tr>
<td>L</td>
<td>Log ( (F-47) = 0.0475P -7.49 )</td>
<td>( F = 3.24 \times 10^{-6} e^{47} )</td>
<td>140</td>
<td>244/185</td>
<td>0.19</td>
<td>60</td>
</tr>
</tbody>
</table>

*See Figure 12
A. Constancy of Vasomotor Tone

It is the basic assumption for the validity of our approach that the vasomotor tone during the operation of the pump remains unchanged. One might suspect that during the pressure oscillation caused by the pump nervous reflexes of the intact animal would respond and, with probably some phase shift, constantly operated to re-establish the original pressure level. However, experimental evidence of our own and of other authors indicates that this is not so. We can observe that in all our experiments the heart rate remains unchanged during the pressure oscillation. Furthermore, the mean arterial pressure which existed immediately before operation of the pump is always re-established within less than one second after the pump is turned off, provided the pump is halted in the same position it was in originally. It may also be mentioned that the right atrial pressure, even when measured with high sensitivity, does not show any fluctuations other than those caused by respiration during the oscillation of the mean arterial pressure. Similar observations have been made by Berglund (35) and Sarnoff and Berglund (36) who altered the aortic pressure by some other means. Our observations indicate that the frequency with which the pump is operated is of importance. One has to assume that the pressure receptors do not respond to cyclic changes in arterial pressure if these changes occur fast enough. While the duration of our own pump cycle is of the order of four seconds, Guyton et al (37) could demonstrate that pressure oscillations faster than twenty seconds
per cycle were ineffective on the baroreceptors. Identical observations have been made by Scher (38) who connected the isolated pressure sensitive sections of the carotid arteries to a sinusoidal pump and studied the response of the total arterial system to local pressure changes on the carotid sinuses. He could clearly demonstrate that local pressure oscillations faster than ten seconds per cycle remained ineffective on the arterial blood pressure of the anesthetized animal. Along this line are our own observations made during bilateral common carotid occlusion which was routinely performed in each experiment. The interval between occlusion and a first rise in systemic arterial pressure was determined and was found to be never shorter than seven seconds. In this connection it is very interesting that prolonged duration of the pump cycle which was gradually established in several experiments, caused sudden changes in heart rate whenever it approached seven seconds or longer. We then believe that it is justified to assume that the pressure oscillations which served for the calculation of our pressure/flow relationship do not disturb the animal's vaso-motor tone. It may be pointed out that it was undesirable to operate the pump with a frequency greater than that used for two reasons. First, the pressure oscillation has to be slow relative to the propagation velocity of pressure in the arterial system so that this oscillation occurs in all parts of the arterial system simultaneously as it would occur in a lump system. This is essential since O. Frank's coefficient of elasticity, E', actually applies to a lump system. Secondly, it was necessary to have as many pulses as possible during
a pump cycle for the selection of matching pairs.

B. The Curve

All 29 curves presented in Figures 4-12 are calculated curves using the exponential equation of the basic form \( F = ae^{bp} + C \). It can be observed that the majority of our experimental values fit these curves very well. Wherever a larger scatter occurs, the reason can be found in the instability of the vasomotor tone or the influence of respiration. For instance, in establishing the control curve of Figure 6, four different control runs had to be used since a sufficient number of matching pairs of pulses could not be obtained otherwise. Comparison with Table 3 shows that heart rate as well as arterial pressure changed markedly from one control run to the other, indicating a shift of the vasomotor situation.

Although the exponential function used seems to show that at pressure zero where the first term equals \( a \), a finite flow through the arterial system of the magnitude of \( a + c \) exists, it is obvious that this cannot be so. For this reason the function cannot be applied below a certain pressure and should be applied possibly only within the range of our observations.

In several of our experiments we made the observation that below a certain pressure the calculated values suddenly scattered and the flow values were unexpectedly low. See, for example, the carotid occlusion curve in Figure 9. In the beginning we thought that the reason for this was that calculations at this low pressure level had
to be based on pairs of pulses located at the lower "pole" of the pressure oscillation where the pump changes from its withdrawing to its injection phase. These pairs of pulses show little difference in their diastolic slopes and this could affect the accuracy of the calculation procedure. However, this consideration applies equally to pairs of pulses at the upper "pole" of the pressure oscillation and yet there such scatter could never be observed. The above explanation was thus untenable. Instead the following hypothesis is presented incorporating the theory of the existence of a so-called critical closing pressure as first expressed by Burton (39). This theory has been experimentally found valid by Nicol et al (40). For the intact animal, Pieper and Wetterer (41) could demonstrate that in the vascular bed of the common carotid artery flow ceases at pressures between 50 to $150 \times 10^3$ dynes/cm$^2$, according to the experimental condition. It seems to us unlikely that at any time the critical closing pressure for the different parts of the vascular bed could be equal. If, during the pressure oscillation, the lower pressure happens to come within the range of the critical closing pressure of those branches with high critical closing pressure, their sudden closure will consequently result.

This is contrary to the classical view where with decreasing pressure the resistance increases continuously. Thereby the flow, although still proportional to pressure, becomes negligibly small. According to Nicol's experimental observations (40), at the point of critical closing pressure, the blood vessel closes abruptly due to the instability at this point and flow changes immediately from a
relatively high value to a zero value. For the remaining part of the arterial system, with lower critical closing pressure, the pressure/flow relationship must then be different and the original curve becomes discontinuous at this point. The above explanation makes it likely that below a certain pressure level, the pressure/flow relationship will be found to approach zero flow in an unpredictable and irregular manner. It may be emphasized that the pressure oscillation of our experimentally established pressure/flow relationship covers the certainly more interesting part of the physiological pressure range.

From the shape of many of our curves, one must conclude that with increasing pressure the peripheral resistance first rises toward a maximum and then decreases rapidly when pressure increases further. This is shown in Figure 13. Data for this example was extracted from the epinephrine curve of Figure 4.

It can be seen in Figures 9 and 10 by the flow values obtained with the dye dilution technique that the normal working point for every vasomotor condition is within the part of the curve where resistance decreases rapidly with rising pressure. It is suggested that this represents a safety mechanism which might protect the heart against high pressure peaks during possible fluctuations of cardiac output.

C. Physiological Significance of the Equation and its Constants

At the present it is not possible to attribute any physiological significance to the equation or to its individual constants. However, of interest is the differential quotient of our equation. The
Figure 13. Peripheral resistance versus mean diastolic pressure. The data was obtained from the epinephrine curve in Figure 4.
particular form of the equation is unimportant since any function which fits the experimental curve would naturally result in the same differential quotient. We see in the differential quotient a measure of the distensibility of those parts of the arterial system which control the peripheral resistance. It has been mentioned before that the dynamic changes of the effective viscosity are negligible. The disproportionality of pressure and flow can, therefore, be explained only as the effect of the distensibility of the elastic system. For this reason it is obvious that the increase of flow for a given pressure increase will be greater the more distensible the system. In other words the steepness with which the curve rises must be closely related to the distensibility of the arterial system. Our curves, therefore, not only show the change in peripheral resistance, but may also allow one to express the relative change of the distensibility of the arterial system; however, further experimental analysis will be necessary.

D. The Principle of the Evaluation of Changes in Vasomotor Activity

In order to illustrate the manner in which the pressure/flow relationships which we have observed may be used to evaluate changes in vasomotor tone, let us consider the data represented in Figure 9. In the initial condition, the peripheral outflow measured by the dye dilution technique was $43 \text{ cm}^3/\text{sec}$ at a pressure of $200 \times 10^3 \text{ dynes/cm}^2$. After Levophed* the cardiac output was found to be $52 \text{ cm}^3/\text{sec}$ while the pressure had fallen to $188 \times 10^3 \text{ dynes/cm}^2$. The calculated
resistance in the initial condition was 4550 dyne-sec/cm^5 and after Levophed*, this value fell to 3600 dyne-sec/cm^5. Thus Levophed* apparently produced a fall in the peripheral resistance of about 20 per cent.

Now we must inquire whether this fall in peripheral resistance is greater or less than that which would follow from the pressure change alone, as a consequence of passive changes in the vascular bed, independent of changes in vasomotor tone. The control curve, in which, as discussed previously, the pressure/flow relationship is established with the vasomotor tone constant permits us to evaluate this. From this curve, we find that the expected peripheral outflow of the animal at a pressure of 188 x 10^3 dynes/cm^2 in the pre-existing vasomotor circumstances, would have been 36 ml/sec. The corresponding resistance would have been 5230 dyne-sec/cm^5. Thus the pressure fall in and of itself would have been expected to increase the apparent resistance 680 dyne-sec/cm^5. The observed fall in the resistance should be compared not to the initially calculated resistance value, but to that value adjusted for the passive change which accompanies the pressure change. The fall due to vasomotor change can be described as the fall from the expected value of 5230 (with the correction made for the pressure induced change) to the found value of 3600. The magnitude of the fall is then closer to 30 per cent than the 20 per cent which would have been assumed if the pressure factor had been neglected.
It can be seen in the same Figure 9 that when the above comparison is applied to the control condition and the condition during carotid occlusion, an extreme extrapolation of the control curve in the direction of a higher pressure is required. It is questionable if such extrapolation is justified. The basic concept, however, should hold true in this case as well. While the apparent increase in peripheral resistance during carotid occlusion is only of the magnitude of 650 dyne-sec/cm², suggesting a mild change within the vasomotor apparatus, the curves indicate a much more extensive alteration of the physiological properties of the arterial system.

It has to be considered that other factors than those immediately affecting the vascular wall may have some part in shifting the curves when, for example, drugs are administered in the course of the experiment. Changes in hematocrit leading to changes in viscosity of the blood should affect the resistance to flow. Pirofsky (42) investigated the relationship between hematocrit and absolute viscosity in vivo. From this one can conclude that changes in hematocrit after the injection of epinephrine, which are of the magnitude of +2 per cent as observed by Parsons et al (43), cause little change in viscosity.

E. Control Curves

For the control curves, it can be assumed that certain relationships exist to the body weight or body surface area of the experimental animals. Another correlation to the age of the animals can be suspected. Conclusions of this type necessitate a large number of
experiments in order to allow statistical evaluation, and were not in
the scope of this dissertation.

F. Carotid Occlusion Curves

In all our experiments the curve obtained during bilateral
carotid occlusion shifted to the right, thereby indicating a rise in
peripheral resistance. One has to realize that in addition to the
possible vasomotor changes as a result of the carotid sinus reflex,
the peripheral resistance must increase because the total vascular bed
is now diminished. It is suggested that other experiments be performed
in which other parts of the vascular bed not containing any baroreceptors
are temporarily occluded for comparison.

G. Epinephrine Curves

As already mentioned in the RESULTS, the effect of epinephrine
showed two principal variations. While in Figures 4, 8, and 10 the
epinephrine curve was at the left of the control curve thus indicating
a lower resistance, it shifted to the right in Figures 6 and 12. A
comparison of the arterial pressure values in Tables 1, 5, and 7 shows
that whenever the resistance was lowered during the epinephrine
infusion the diastolic pressure values were below control. During the
experiments where the epinephrine raised the resistance, Tables 3 and
9, the diastolic pressure was above control. This tends to confirm
the position of the epinephrine curve with respect to the control
curve. The varying effect of epinephrine as demonstrated in our experi-
ments is in agreement with Ahlquist (44) and Green and Kepchar (45).
II. Levophed Curves

The same unpredictability of the effect of epinephrine seems to apply to the effect of Levophed®. While it lowered the peripheral resistance in Figures 9 and 12, an increase of the resistance could be observed in Figures 4, 5, and 8.

I. Post-Run Control Curves

It is remarkable that in both control runs taken after a mild hemorrhage and an additional injection of Nembutal®, the curves indicated a decrease of the peripheral resistance. This result was not only confirmed by the simultaneous dye dilution determination, but was also indicated in the diastolic pressure values in comparison with the control runs. See Tables 6 and 7.

J. Summary of Discussion

There seems to be no other method at present which would equally allow a determination of the pressure/flow relationship in the intact animal at constant vasomotor tone. The dye dilution determination does not allow one to establish flow values during artificial pressure oscillations. Furthermore, it determines the input into arterial system instead of its outflow. The reliability of cardiac output determinations, von Rechlinghausen, 1908 (46), Frank, 1920 (47) Bramwell and Hill, 1923 (48), Bazett et al., 1935 (49), Wezler and Boger, 1939 (50), Aperia, 1941 (51), and Hamilton and Remington, 1947 (52) based on calculations from data, like pulse pressure, pulse
wave velocity, the durations of the different periods of the cardiac cycle, etc., is doubtful. Besides, these methods again deal with the input into the arterial system. For this reason a comparison of our results with work done previously by other authors is difficult. It has already been pointed out in the INTRODUCTION that studies on isolated perfused parts of the cardiovascular system can hardly be done without accompanying changes of the vasomotor tone. Pressure/flow relationships, however, as obtained with unstable vasomotor tone are meaningless. Experiments on the intact animal as done by Levy et al (20), Flacke et al (23), Fries et al (53), and Guyton et al (22)—all were performed on open-chested animals and utilized some direct or indirect method for the determination of cardiac output. However, many authors, using either method discussed above, found curved pressure/flow relationships. It is hoped that the pressure/flow relationships presented in this dissertation will be a basis for further understanding of the dynamics of the peripheral vascular bed.
SUMMARY

Based on a method described by Wetterer and Pieper which was refined, a pressure/flow relationship for the total arterial system of the intact, anesthetized dog has been established. It was found that considerable change of the pressure/flow relationship in comparison with the control situation could be obtained under the effect of the carotid sinus reflex and of epinephrine and Levophed infusion. This indicates that these agents generally do not shift the operating point on the curve of the pressure/flow relationship, their influence rather changes the physical characteristic of the cardiovascular system completely. Of the changes that have been produced, only the carotid sinus reflex consistently resulted in a shift of the pressure/flow relationship toward a higher pressure. The effect of epinephrine or Levophed were variable in our experiments. Since it could be compared only to the control situation, certain standards for the control situation should be first established on a statistical basis in order to allow comparisons of the control situation from one animal to another.

Each pressure/flow relationship could be described by an exponential function within the pressure range of our experimental observations, the general form of which was \( F = ae^{bp} + C \). Although other mathematical formulation may serve equally well, equations which have been given previously in the literature of the type \( F = \left(\frac{p}{c}\right)^n \) do not describe the curve for the total arterial system.
It is suggested that the slope of our curve at the operating point may be a measure of the distensibility of the part of the arterial system which represents the so-called peripheral resistance. It should be emphasized that the method described here can be used in the intact animal and may be repeated during an experiment as often as desired. The method is, therefore, particularly valuable for further studies of the dynamics of the arterial system.

In two experiments where the simultaneous dye dilution determination could be employed in eight separate situations, good agreement between both methods could be observed.
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AUTOBIOGRAPHY

I, Sidney D. Leverett, Jr., was born in Houston, Texas, November 27, 1925. I attended secondary schools in Texas and Mississippi and graduated from Lamar Senior High School, Houston, Texas, in 1943. I served in the Army Air Corps until May 1946, at which time I enrolled in the A & M College of Texas, College Station, Texas, and received a B.S. degree in 1949. I was recalled into the U.S. Air Force during the Korean War and returned from an overseas assignment in 1953. I applied for and was accepted in the Air Force Institute of Technology's Graduate Training Program and attended Ohio State University from 1953-1955, from which I received a M.S. degree in physiology.

I was then assigned to the Aeromedical Laboratory, Wright-Patterson Air Force Base, Ohio, where I served as Chief of the Acceleration Section. In 1958 I was accepted for additional training in physiology under the Air Force Institute of Technology and returned to Ohio State University to complete the requirements for the degree Doctor of Philosophy.