Influence of Anomalous Blood Viscosity on Resistance to Flow in the Dog's Hind Limb

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Observations were made on an isolated hind leg preparation of dogs, perfused with blood and various homogeneous perfusates. A wide range of intravascular pressures were used while a constant arteriovenous pressure gradient was maintained. It was found that parallel increases in arterial and venous pressures result in a reduction in resistance to blood flow. A similar change in resistance is observed when more homogeneous perfusates are employed. Therefore, under the conditions of these experiments, the reduction in resistance with elevation of intravascular pressure must be ascribed principally to passive distention of the vascular bed.

In a previous study, it was demonstrated that parallel increases of arterial and venous pressures in an isolated hind leg result in a reduction of the calculated resistance to blood flow. The initiating factor responsible was concluded to be passive distention of the vascular bed. It was recognized, however, that vascular distention may then induce secondary changes in resistance due to the anomalous viscous behavior of blood (the apparent viscosity of all suspensions, including blood, varies with tube dimensions and velocity of flow). Therefore, it was not possible to assess the relative contributions of vascular distensibility and of anomalous viscosity to the overall modification of the computed resistance. An attempt has been made in the present study to evaluate these factors by comparing the changes in resistance observed over a wide range of intravascular pressures during perfusion with blood and with more homogeneous perfusates, such as plasma and isotonic solutions of sodium chloride, dextran,* and human hemoglobin.

Methods

Eleven experiments were performed on mongrel dogs anesthetized with sodium pentobarbital, 30 mg./Kg. body weight. In each animal, a femoral artery and vein were exposed in the proximal half of the thigh, and all branches above the saphenous vessels were divided between double ligatures. Cephalic circulation was then precluded by placing a wire tourniquet about all of the tissues of the upper thigh except for the femoral vessels. Heparin was then administered, and T-cannulas were placed in the femoral artery and vein.

In figure 1, a diagram is presented depicting the perfusion apparatus which was employed in each experiment. By means of this device, it is possible to perfuse the isolated limb continuously and automatically at any desired arterial and venous pressure levels with metered quantities of arterial blood or of homogeneous perfusates. While the apparatus is not in operation, clamps $C_1$ and $C_2$ occlude the side arms of the T-cannulas in the femoral artery, $F_A$, and femoral vein, $F_V$. During artificial perfusion, clamps $C_1$ and $C_2$ are released. Reservoirs $R_1$ and $R_2$ are connected in parallel, and communicate alternately with the femoral artery. $R_3$ is weighed continuously by means of an optically recording balance, $OB$, which has been described previously.

By opening solenoid valve $S_1$ and closing $S_1$, reservoir $R_1$ may be filled either with blood from a peripheral artery, $PA$, or with a homogeneous perfusate from $R_4$, by releasing either $C_3$ or $C_4$. When $R_3$ is nearly filled, the light beam from the optical

* The dextran used in this study was Plavolex, a sterile solution, 6 per cent w/v, which was generously contributed by Wyeth Laboratories, Inc.

† Heparin was supplied through the courtesy of Dr. W. R. Kirtley, The Lilly Research Laboratories.
balance strikes a photoelectric cell. This actuates a relay which causes all of the odd-numbered solenoid valves to open, and all of the even-numbered valves to close. This permits air pressure from the output of an arterial pressure regulator, AR, to be exerted upon the surface of the liquid in R. This forces the liquid in R through valve S, through the polyethylene coil, which is immersed in a temperature control bath, and past the bubble trap, BT, to the cannula in the femoral artery.

During artificial perfusion of the leg from reservoir R, R is being filled with blood or homogeneous perfusate. During this phase of the cycle, S is closed to permit venting of this chamber. Meanwhile, the quantity of liquid in R is progressively diminishing. The rate of loss of liquid from R is equal to arterial inflow, and is recorded on a photokymograph during the last half of this phase. As soon as R is almost empty, another photoelectric cell is energized by the light beam from the balance, and the cycle is again reversed. Now, all the odd-numbered solenoids are closed and the even-numbered ones opened, permitting R to perfuse the leg, and R to refill with blood or perfusate.

The operation of the venous side of this perfusion apparatus is similar to that of the arterial side, and the venous solenoid valves are also controlled by the volume of liquid in R. Thus, since all the odd-numbered valves are open during perfusion from R, the venous outflow from the leg drains into reservoir R. The pressure in this chamber is established by the output of a venous pressure regulator, VR. As R becomes empty, the cycle is automatically reversed, and R receives the venous outflow from the leg, which is now being perfused by R. During this phase, the venous blood which had accumulated in R during the preceding half-cycle is returned to the animal via a peripheral vein (PV).

The actual arterial and venous pressures existing at the side arms of the cannula are recorded by means of optical manometers (MA and MV). Low resistance cannulas are employed, such that only 1 mm. Hg pressure drop occurs/100 ml./min. blood flow. The desired arterial and venous pressures are obtained by means of a simple pressure regulating device. The essential components of this apparatus are illustrated in figure 2. The inputs to the arterial and venous pressure regulators (APR and VR) communicate with mercury manometers (MM) which are arranged in parallel with the optical manometers (MA and MV) in figure 1. The mercury in each manometer serves as one input lead to a relay (RA or RV) in each of the control circuits. The second input lead is a wire suspended at any desired distance above the zero reference level of the manometer system. The relays in turn operate solenoid valves (SAR and SAV) in such a manner that when the mercury contacts a wire, the appropriate valve interrupts the supply of compressed air (AS) to the corresponding air reservoir (AR or VR). These air reservoirs, each furnished with a needle escape valve, constitute the outputs of the arterial and venous pressure regulators (APR and VR). As the pressure in the reservoir subsequently declines, contact is broken in the manometer, and air pressure is again applied to the reservoir. In this manner, the arterial and venous pressures are made to oscillate within 2 to 3 mm. Hg of the desired pressures. The arterial and venous pressures may be varied independently, or may be altered simultaneously by equivalent amounts by means of a rack and pinion arrangement. This apparatus makes it possible, therefore, to establish and maintain any desired pressures at the level of the femoral vessels, despite the variations in pressure gradients between blood reservoirs and T-cannulas which occur whenever the flow rate changes.

The temperature of the experimental limb is regulated to ±1 C. and recorded at 1 min. intervals throughout each experiment by means of a needle
thermocouple inserted into the deep muscles of the thigh. This actuates a Micromax temperature recorder with circuit controlling contacts. Within the limits imposed by an independent thermostat, these contacts regulate the temperature of the water bath surrounding most of the tubing and all of the reservoirs except Ri, which is suspended from the optical balance.

RESULTS

The results of a representative experiment are illustrated in figure 3, where flow, Q, in ml./min., is plotted against venous pressure, $P_v$, in mm. Hg. The lower curve depicts the data obtained during perfusion with blood; the upper, during perfusion with isotonic saline. The regression lines were computed by the method of least squares. A logarithmic scale is employed along the ordinate to facilitate comparison of relative changes.

The lowest solid circle represents the first Q measured; an arterial pressure, $P_A$, of 103 mm. Hg and $P_v$ of -1 mm. Hg were arbitrarily employed. At approximately 1 min. intervals, $P_A$ and $P_v$ were elevated in a stepwise fashion, in such a manner that a constant arteriovenous pressure gradient, $P_A - P_v$, was maintained throughout. The solid circles represent the flows obtained as pressures were progressively elevated, while the open circles portray Q as $P_A$ and $P_v$ were progressively returned toward the original levels. Under these conditions, $P_A - P_v = 105.5 \pm 1.5$ mm. Hg (mean ± range). Despite this constant gradient, there is a distinct tendency for Q to vary directly and appreciably with the intravascular pressure.

After these data had been collected, the perfusion apparatus was cleared of blood, and isotonic saline was circulated through the leg. The pressure-flow data under these conditions are illustrated by the upper curve, where the solid squares represent Q measured while $P_A$ and $P_v$ were progressively elevated, and the open squares while pressures were being returned to their original levels. Under these conditions, values were recorded at about 30 sec. intervals, and $P_A - P_v = 87 \pm 5$ mm. Hg throughout. It is evident from the figure that, for any given value of $P_v$, Q for saline was more than twice as great as Q for blood, despite the lower value of $P_A - P_v$. Furthermore, it is apparent that Q for saline is also positively correlated with $P_v$. The relative changes are similar in magnitude to those for blood, since the slopes of the regression lines, plotted semilogarithmically, are not appreciably different.

In approximately one fifth of the studies with homogeneous perfusates, a definite tendency toward progressive vasodilatation was manifest. Figure 4 illustrates a typical example. The lower curve portrays the changes in Q as intravascular pressures were varied during perfusion with blood. The arrows indicate the sequence with which these observations were made. $P_A - P_v = 110.5 \pm 1.5$ mm. Hg over the entire range of pressures employed. It is apparent that Q varies directly with $P_v$, despite the constant value of $P_A - P_v$. Subsequent perfusion with saline is depicted by the upper series of curves, during which $P_A - P_v = 105 \pm 3$ mm. Hg. During the first series
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FIG. 4. The relationships between venous pressure, $P_V$, in mm. Hg, and flow, $Q$, in ml./min., during perfusion with blood (open circles) and normal saline (solid circles) in an experiment in which progressive vasodilatation was manifest during saline perfusion. Of pressure elevations, a considerable increase in $Q$ was recorded. With subsequent diminution of pressures, $Q$ also declined, but the values observed were appreciably greater than those obtained with rising pressures. A second stepwise augmentation of pressures elicited a change in $Q$ which paralleled that observed during the first pressure increase. Finally, reduction of pressures again resulted in a diminution of $Q$, but the descending values again exceeded those of the preceding ascending series. Thus, a definite tendency toward progressive vasodilatation was manifest during this perfusion. A similar tendency was observed in 2 other cases during saline perfusion, and in 1 of the 3 experiments in which dextran was employed. In each case, however, the development of progressive dilatation could not mask the tendency for increased intravascular pressures to augment $Q$.

In the experiment depicted in figure 4, the relative changes in resistance during saline perfusion were somewhat greater than with blood, although the development of progressive vasodilatation renders precise quantification impossible. In other experiments, the influence of intravascular pressures upon $Q$ was somewhat more pronounced during perfusion with blood than with saline. In most cases, however, the situation illustrated by figure 3 was representative; that is, no appreciable difference could be detected. In figure 5, the composite results are presented for 7 experiments in which blood and isotonic saline were perfused in turn over a range of intravascular pressures, and in which the complication of progressive vasodilatation was absent or negligible. To render the results with the two perfusates comparable, the flows for blood (closed circles) and for saline (open circles) for each experiment are expressed in terms of per cent of the initial flow with each perfusate. It is evident that a significant positive correlation obtains, both for blood ($r = 0.806; p < 0.001$) and for saline ($r = 0.407; p = 0.02$). The regression line for blood (continuous line) is $Q = 94.1 + 0.798 P_V$; that for saline (interrupted line), $Q = 106.9 + 0.540 P_V$. The difference between the regression coefficients for blood and saline was not significant ($p = 0.3$).

FIG. 5. The relationships between venous pressure, $P_V$, in mm. Hg, and percentage increase in flow, $Q/Q_i$, in 7 experiments during perfusion with arterial blood (solid circles) and normal saline (open circles). The unbroken oblique line is the regression line for blood; the dotted line, for saline.
Similar results also were observed in three experiments with dextran solutions, four with hemoglobin solutions, and one with plasma. The regression line for the composite data is $Q = 102.6 + 0.440 P_v$. The regression coefficient is not appreciably different from that for saline ($p > 0.5$). Thus it may be concluded that variations in intravascular pressure influence flow in a similar manner when the hind limb of the dog is perfused with arterial blood and with various more homogeneous perfusates.

**DISCUSSION**

It has been demonstrated previously that, when the hind leg of the dog is perfused with blood over a range of intravascular pressures while $P_a - P_v$ is maintained constant, the resistance to flow diminishes appreciably as the intravascular pressure is elevated. The blood perfusion data in the present study confirm these findings. If the vascular bed were rigid, $Q$ would be independent of absolute pressures as long as $P_a - P_v$ remained constant, despite the known anomalous rheologic properties of blood. It may be deduced, therefore, that the initiating factor responsible for the observed positive correlation between intravascular pressures and $Q$ must be an alteration in vascular dimensions. Once the change in tube dimensions has occurred, an appropriate change in resistance will result, and this will be reflected by a modification of the rate of flow. These two factors, namely, tube dimensions and rate of flow, may then in turn exert a secondary, but conceivably potent, influence upon the apparent viscosity of the blood, and, therefore, upon the overall resistance to flow. It has been demonstrated in physical models that, over a critical range, increased velocity of flow may evince a considerable reduction in the apparent viscosity of blood. It has also been shown that the apparent viscosity of blood is augmented as tube diameter is increased. Although data are not available concerning the viscous behavior of blood in tubes with diameters as small as those of the arterioles, the slopes of the curves relating apparent viscosity to tube diameter become progressively more steep as diameter diminishes. Extrapolation of such curves indicates that small variations in tube dimensions would result in appreciable changes in apparent viscosity.

In the present study, however, no significant difference could be detected between the relative changes in resistance resulting from changes in intravascular pressures during perfusion with blood and with more homogeneous perfusates. It must be concluded, therefore, that the observed variations in resistance are attributable almost exclusively to modifications of vascular dimensions. Since the rheologic properties of blood are potentially capable of contributing to the overall change in resistance, it is essential to account for the absence of any significant influence in this study. Increased intravascular pressure, for example, produces vascular distention, which would, in turn, tend to increase apparent viscosity. Vascular distention, in addition, would result in acceleration of blood flow, which would tend to reduce the apparent viscosity. Hence, the changes in vascular dimensions and velocity of flow which result from any given alteration of intravascular pressure would have opposing effects upon the apparent viscosity of the blood being perfused. If these effects were approximately equal in magnitude, the resultant absence of any detectable influence would be explained.

As an example, the data in figure 5 indicate that blood flow would increase 25 per cent when intravascular pressure is raised by about 30 mm. Hg. If such an alteration in flow were accomplished entirely by a passive distention of small blood vessels, it may be estimated that an average increase in tube diameter of 6 per cent had been produced. Furthermore, an increase in $Q$ of 25 per cent occurring in a hydraulic system in which tube diameter had increased 6 per cent would imply that the mean linear velocity of flow had increased by an average of 11 per cent. At present, it is impossible to predict the precise effect upon the apparent viscosity of blood which would result from such alterations in tube dimensions and linear velocity in those blood vessels which offer the principal resistance to blood flow. Unfortunately, insufficient data is available concerning
the rheologic behavior of blood in tubes with dimensions equivalent to those of the arterioles. It is apparent, however, that those changes in viscosity which would result from a 6 per cent change in diameter would be counteracted or reversed by the concomitant 11 per cent increase in linear velocity. This probably accounts for the failure to detect any significant effects which could be ascribed to anomalous viscosity in the present study.

It must be recognized, however, that other relationships between apparent viscosity and resistance to flow might obtain under different circumstances. For example, it has been demonstrated by Whittaker and Winton that, in a maximally dilated vascular bed, the apparent viscosity of blood diminished appreciably as $P_A$ is augmented. This finding has recently been confirmed. Therefore, in a maximally dilated vascular bed, the anomalous rheologic properties of blood do contribute significantly to net changes in resistance. It is probable that, under these conditions, the high-resistance vessels behave more like rigid tubes. Changes in vascular dimensions would be minimal, and thus would not tend to counteract the influence of increased linear velocity of flow. It is apparent, therefore, that the role of anomalous viscosity in contributing to changes in peripheral resistance is, to a large extent, dependent upon the prevailing conditions.

**Summary**

The isolated hind leg of the dog was perfused with blood and with various homogeneous perfusates (saline, dextran, hemoglobin, and plasma) over a wide range of intravascular pressures, while a constant arteriovenous pressure gradient was maintained. For any given combination of arterial and venous pressures, the actual flows were usually about three times greater with homogeneous perfusates than with blood. In both cases, however, the rate of flow increased appreciably as intravascular pressures were elevated. Furthermore, no appreciable difference was detectable between the relative changes observed with blood and with the artificial perfusates. It was concluded, therefore, that vascular distensibility is the principal factor responsible for the positive correlation between intravascular pressure and flow when the arteriovenous gradient is held constant. The anomalous rheologic properties of blood exert only a negligible net influence under the conditions of these experiments.

**References**


History of the Tetralogy of Fallot

In medicine as in war the services of unknown soldiers are often forgotten. It was a revelation to the present writer, and perhaps to others, that the description of this congenital malformation “includes some of the most famous names in medicine, and yet its own designation perpetuates the memory of a physician who has little other claim to fame.”

The complex malformation consisting of pulmonary stenosis, ventricular septal defect, dextro position of the aorta and right ventricular hypertrophy was first described by the Danish anatomist Neils Stenson (1673); hence in Denmark the malformation is called Steno-Fallot’s tetralogy. A century or more later the Dutch anatomist Edward Sandiford, described another case. In 1814, John Farre, of London, cited references to fifteen described cases. In 1839, James Hope described the main diagnostic signs in his textbook on cardiology, but there is no proof that he made a bedside diagnosis substantiated by subsequent necropsy. By 1856 Thomas Peacock had amplified Hope’s observations and recorded the physical signs of 64 cases. In 1888 Arthur Fallot described the malformation in two patients cyanosed since birth, made the correct diagnosis in a third, and wrote his famous paper. Thus we honor not the discoverer, but the person who succeeded for the first time in giving currency to previous observations.

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