Hemodynamics of Intestinal Circulation

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The pressure-flow relationship was studied in isolated denervated intestinal loops of the dog in a range of pressure varying from 0 to 210 mm. Hg. The relationship was curvilinear, convex to the pressure axis. Flow started at a minimal pressure of 16 mm. Hg, then increased more rapidly than pressure up to 210 mm. Hg. Critical closure, passive expansion of vessels with rising intraluminal pressure, and anomalous viscosity of blood appeared to be the important factors influencing vascular resistance and flow in the present studies.

RECENT studies of the role of the mesenteric circulation in hemorrhagic shock have emphasized the need for a better understanding of the basic hemodynamic characteristics of this vascular bed. In these studies there was an absence of, or minimal increase in, the calculated mesenteric vascular resistance upon bleeding. Another manifestation difficult to explain was the overshooting of flow which accompanied restoration of blood volume after prolonged hemorrhagic hypotension. It appeared important, therefore, to provide further information concerning the response of the intestinal circulation to a wide range of arterial perfusion pressures. This would establish a base line relationship to aid in evaluation and quantitation of vasomotor changes. The purpose of the present investigation, therefore, was to make a pressure-flow (P:F) study of an isolated intestinal loop of the dog.

METHODS

A loop of the terminal ileum, averaging 230 Gm. in weight, was exteriorized under pentobarbital anesthesia through a flank incision and isolated from the rest of the intestine by severing all mesenteric connections. Only the arterial and venous supply was left intact. Denervation was completed in the process of preparing the artery and vein for cannulation. The lumen of the intestine was kept continuous by insertion of suitable glass cannulas, as shown in the diagram. After adequate heparinization the intestinal artery was supplied with blood via an external Tygon tubing circuit originating from the carotid artery. There was minimal interruption (less than 1 min.) of the blood supply during the cannulation procedure. Flow was usually measured with an optical rotameter in series with this circuit. Provision was made for the inclusion of a pump into the circuit, shown in the upper left of the figure. Air chambers minimized the pulsatile effect of the pump on the arterial pressure. Through the use of the pump or by compressing the tubing to various degrees with a clamp, a wide range of perfusion pressures could be attained. Usually, the intestinal vein was cannulated and blood returned to a reservoir which emptied into the jugular vein. Optical manometers registered arterial and venous pressures. In some experiments a second rotameter was connected into the venous circuit for simultaneous measurement of inflow and outflow. Alternatively, outflow was measured by diverting the flow briefly into a graduated cylinder and timing the period of outflow. Another variation in the procedure was that the intestinal vein was not cannulated, and emptied as normally into the portal vein while arterial inflow was measured. When this was done, venous pressure was measured.
through a small branch of the portal vein near the point of entry of the intestinal vein.

After cannulation the loop was either returned into the abdomen to keep it warm and moist, or left lying on the animal's flank, covered with saline moistened gauze and kept warm with a lamp. It was established in a series of preliminary experiments that the minimal time interval after changing perfusion pressure needed for flow equilibrium approximated 30 sec. Therefore, in the P:F experiments to be described, the minimal equilibration period was 30 sec. In experiments designed to establish the normal P:F relationship, readings were typically taken at 30 sec, 1, 2, and 4 min., starting at the mean arterial pressure and either increasing or decreasing pressure in sequential steps. Data used in the construction of the curves of figure 2 were selected from a larger group of experiments using two criteria for stability of flow: (a) agreement of the 30 sec. and 4 min. flow readings at a given perfusion pressure; (b) reasonable agreement of the P:F curves obtained by increasing and decreasing arterial perfusion pressure (or vice versa) in the same animal.

RESULTS

Average flow and pressure readings in the 30 sec. to 4 min. interval from 18 dogs are plotted in figure 2. In the curve at the left depicting the P:F relationship, vertical lines indicate the standard error of the mean of each group. The line is drawn as the best fit of points and relates flow in ml./min./100 gm. of intestinal weight to the A-V perfusion pressure. The curve appears to be nonlinear with flow beginning at an average of 16 mm. Hg, which is taken to be the point of "critical closure" of the intestinal vessels. Flow then increases progressively more rapidly than pressure up to 240 mm. Hg.

The curve in the right of the figure, relating intestinal vascular resistance to perfusion pressure for the same data, is also nonlinear, rising steeply to the left as the vessels approach critical closure, but continuously decreasing to the right throughout the range of perfusion pressure studied, which does not conform with Poiseuille's law.

To obtain further insight into the factors contributing to the relationship of flow to pressure, a fluid with viscosity virtually independent of shear, dextran (Plavolex), was used as the perfusion medium. This was warmed to body temperature when used and equilibrated with 95 per cent O₂ and 5 per cent CO₂ at atmospheric pressure, then perfused from a reservoir. The intestinal vasculature was flushed free of blood with dextran before flow measurements were begun. The adequacy of oxygenation of the intestinal tissue with dextran as used here should be considered. In other experiments done in this laboratory by Dr. Paul C. Johnson, oxygen consumption for similar in-
flow readings taken at 30 sec. after changing pressure were recorded in these experiments.

A representative experiment is shown in figure 3. The lower curve depicts the control P : F curve in this animal, one with unusually high hematocrit value (60.5 per cent). The upper curve, sigmoid in character, shows the best fit for all values obtained in two successive determinations in the same animal, done by decreasing pressure in successive decrements from starting pressures between 150 to 180 mm. Hg, and then returning to approximately the same starting point.

The reasonable correspondence of the values argue for the stability of the system, and permits employment of the mean curves for assessment of certain physical factors which operate to modify the P : F curve. These are brought out by comparing the relationship of vascular resistance to the A-V pressure gradient for blood and dextran, as shown in figure 4. The upper curve is that for blood, the lower for dextran. Taking the viscosity (\( \mu \)) of dextran to be constant and assuming L (length of vessels) to remain constant, or nearly so, supported by the observations of Fenn, the following proportionality can be set up relating the experimental effective radius (\( r_2 \)) to the starting effective radius (\( r_1 \)), derived from the fundamental equation \( I = \frac{P}{R} \).

\[
\frac{I_1}{I} = \frac{P_1(r_2)}{P(r_1)} \quad \text{or} \quad \frac{I_2}{I_1} = \frac{P_2/r_2}{P_1/r_1}
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This proportionality is shown to the right of figure 4, where \( P_1 \) and \( I_1 \) are the starting pressure (180 mm. Hg) and flow (165 ml./min./100 Gm.) respectively, and \( P_2 \) and \( I_2 \) the experimental changes in flow, using a dextran solution for perfusion.

The dashed curve then shows the change of effective radius related to the A-V pressure gradient. The ratio of the experimental to the starting value is shown in the scale to the right. The curve shows three phases. Below 20 mm. Hg, \( r_2 \) decreases rapidly, approaching critical closure. From 20 mm. to ca 100-110 mm., \( r_2 \) increases. The constancy of the ratio \( r_2/r_1 \) above ca 100 mm. Hg suggests that the limit of passive expansion of the vessels with rising intraluminal pressure has been reached, or, alternatively, that all vascular channels are being perfused, or both.

The relationship of vascular resistance to perfusion pressure, which does not conform with Poiseuille's law, emphasizes that studies involving neurogenic or humoral modifications of intestinal resistance should be based on comparisons of experimental flow changes with the flow obtained at the same pressure in a control P : F curve. An example of such application pertains to the infusion of a dilator substance, ATP (adenosine-5-triphosphate, disodium 3 H : O, crystalline Sigma from muscle) into the intestinal artery at the rate of 1.12 mg./min. (fig. 5). In the upper part of the figure the P : F relationship obtained during ATP infusion is compared to the control curve. Below, the flows are compared as a ratio of the experimental/control at corresponding pressures. Flow with ATP infusion remained at an average of 36 per cent above control until a pressure of less than 48 mm. Hg was reached, and the flow rate was 10 ml./min./100 Gm. Although ATP con-
continued to be infused, at the lower flow rates the hyperemia was not maintained, for reasons not known.

Other substances found to produce hyperemia in the denervated intestinal loop preparation were adenylic acid, adenosine, and substance P, a polypeptide which has been isolated from the intestine and brain.

The converse response, increase in vascular resistance, is illustrated in figure 6, in which norepinephrine (Levophed) was continuously infused at the rate of 14 µg/min. into the intestinal artery. Flow was reduced to an average of 45 per cent of the control (dashed curve). At pressures and flows lower than those shown in the dashed curve, complete closure of the vascular circuits and cessation of flow were commonly noted. Other substances studied which showed constrictor properties were epinephrine and serotonin.

Results relating flow to pressure differing from the trend of the experiments summarized in figure 2 were obtained in some of the experiments. Two representative experiments appear in figure 7. In experiment A, as pressure was progressively increased with the pump, the P:F curve was not typically convex to the pressure axis, but developed a progressive concavity as the result of increase in vascular resistance at the higher pressures, an effect which persisted for a minimum of 2½ min. after restoration of pressure to the initial value. This effect varying in degree was noted in a total of 4 experiments.

Another effect was observed during pressure decrement, and is illustrated in experiment B done in another animal. Here, between 120 and 100 mm. Hg, the curve turned up from its expected trend, so that a curve concave to the pressure axis and flows in excess of those usually observed were obtained at the lower pressures. Critical closure occurred at 5 mm. Hg. These manifestations of hyperemia persisted for 4 min. after restoration of pressure to ca 132 mm. Hg. Similar results were noted in 4 other experiments.

DISCUSSION

Despite seemingly different vascular architecture, the P:F relationship found in the canine small intestine is quite similar to that found in some of the experiments of Green et al. and to those of Levy and Share in the hind limb of the dog. The latter workers...
found that the relationship became more linear in maximally dilated preparations. The intestinal curves also resemble those found by Edwards in the pulmonary vascular circuit of the dog, the latter in the much smaller range of pressure typical of the pulmonary artery circuit. Furthermore, the intestinal P:F curve resembles the relationship found in the perfusion studies of the isolated rat liver portal system by Brauer et al, although the latter results tended to have a more sigmoid character, similar to the present experiments in which the intestine was perfused with dextran. Experiments done in the canine liver by Riecker showed a greater variability, complicated by changes in vascular resistance during the P:F analysis, thus making it difficult to characterize the relationship. A P:F analysis was made for the superior mesenteric artery circuit in the dog by Tropold. The relationship appeared quite linear in the range studied (up to 150 mm. Hg), but was not controlled from the standpoint of extrinsic (neurogenic) influences, nor possible collateral blood flow influences.

It is generally conceded that departure from linearity of P:F curves, regardless of the organ studied, makes it necessary to measure experimental vascular resistance changes in relation to a control P:F curve. Some of the more important factors modifying the relationship appear to be embodied in the present intestinal flow studies. Cessation of flow at some pressure higher than 0, and here found to occur at an average A-V difference of 16 mm. Hg, has been variously interpreted, but more recently the concept of critical closure, as outlined by Burton, has gained popularity.

A second factor concerned is the probability that the effective radius of the vessels varies with the intraluminal pressure. This appears to operate from minimal pressures up to 100 to 110 mm. Hg in the present studies. Above this, it may be, as Levy has proposed, that further distensibility of the (arteriolar) wall is limited by a basketwork of connective tissue. Another possible explanation is that previously dormant capillary circuits may be opened incident to an increase in perfusion pressure.

A third factor concerns the apparent viscosity of blood. Its anomalous nature has been amply established by a number of studies (see refs. 7 and 12) which have shown that the apparent viscosity is dependent upon the internal diameter of the tube and upon the mean velocity of flow. Thus the apparent viscosity diminishes as the radius of the tube decreases, while the apparent viscosity increases when mean velocity falls below a certain critical level.

Based upon the evidence of the dextran experiments, which showed approximately constant vascular resistance above ca 100 mm. Hg, it is our belief that the continued decrease in vascular resistance above 100 mm. Hg is the result of the anomalous viscosity of blood caused by increasing flow through small vessels. It is noted in figure 2 that an inflection occurs in the curve of vascular resistance at 105 mm. Hg, coinciding approximately with the pressure found to cause maximal expansion of vessels in the dextran experiments.

The change in vascular resistance in the range from 105 to 240 mm. is from 7.5 to 6.0 PRU, a decrease of 20 per cent. For purposes of comparison it is interesting to note that the data of Levy and Share obtained in the denervated hind limb preparation showed that a change in relative viscosity of the blood from 1.0 to 0.8 corresponded to a decrease in red blood cell concentration from 45 to 20 per cent. If it can be assumed that the only factor contributing to the change in resistances in the higher pressure range is the decrease in
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viscosity of the blood, an approximation of the change in functional hematocrit is thus made available. This carries the further assumption that hemodynamics are sufficiently similar in the intestine to the hind limb to permit comparison, an assumption supported by the similarity of the P:F curves.

In summary, critical closure, passive expansion of vessels, and anomalous viscosity of blood appear to be the important factors influencing vascular resistance and flow at the lower perfusion pressures. In the middle range of pressure the latter two are operative and, finally, at the higher pressures, anomalous viscosity appears to be the chief factor contributing to the continued decrement in vascular resistance.

The relationship of flow to pressure observed in certain experiments such as illustrated in figure 7 merits further consideration because of their physiologic interest. Results such as typified by experiment A, contrary to expectation, appear to show a reduction in vessel caliber and/or number of vascular channels perfused as perfusion pressure is increased. With pressure reduction, results such as exemplified by experiment B suggest an increase in vessel caliber and/or opening of new vascular circuits or shunts. Reactive hyperemia resulting from reduced blood flow may be the basis for the type of response noted in B, but difficulties are encountered in evoking a metabolic basis for the effects noted in A.

It is assumed, based on earlier experiments, that sufficient time has been allowed between the change in pressure and measurement of flow so that hysteresis phenomena are not involved. Possibly, intrinsic reflex mechanisms may be activated by changes in arterial pressure which then lead to compensation in flow by changes in vessel caliber. A third possibility is that A-V shunts or additional vascular circuits may open at low perfusion pressure and close at high pressure, thus modulating total flow through the intestinal bed.

In conclusion, no explanation can be offered for the difference in vascular reactivity in preparations such as discussed in the preceding paragraph and the more usual pattern illustrated in figure 2. Major emphasis has been placed in the present report on the seemingly "less reactive" (and hence more stable) preparations because of the probability that these would more accurately portray the influence of physical factors on intestinal blood flow, thus achieving the major purpose of the present undertaking.

SUMMARY

The pressure-flow relationship was studied in a denervated isolated loop of ileum of the dog in an A-V perfusion pressure range of 0 to 240 mm. Hg. The zero flow intercept on the pressure axis was at 16 mm. Hg, and flow increased somewhat more rapidly than pressure throughout the range observed, resulting in a curve somewhat convex toward the pressure axis. Flow averaged 21 ml./min./100 Gm. of intestine at 120 mm. Hg and increased to 57 ml./min./100 Gm. at 240 mm. Hg.

The curve relating vascular resistance to A-V perfusion pressure showed three phases:
a steep rise at the lower pressures while approaching cessation of flow; a more moderate decrement up to 105 mm. Hg; and a continued gradual decrease to 240 mm. Hg, the upper limit of pressure studied. Critical closure of vessels, passive expansion of vessels with increase in intraluminal pressure, and anomalous viscosity of blood appear to be the important factors influencing vascular resistance and flow in the intestine. All three operate at lower perfusion pressures; in the middle range the last two are operative, and, finally, it is believed that anomalous viscosity of the blood appears to be the chief factor contributing to the continued decrement in vascular resistance at high perfusion pressure.

The nonlinearity of the curve of vascular resistance related to pressure emphasizes that experimental changes in resistance be evaluated against a control P:F curve, so that flow in the experimental state be compared with flow during the control state at the same perfusion pressure. Examples using ATP as a dilator substance and norepinephrine as a constrictor substance are presented to illustrate this principle.

Finally, examples of atypical responses of intestinal flow to increase and decrease in perfusion pressure are presented and possible mechanisms discussed.

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