The Estimation of Peripheral Vascular Resistance to Varying Rates of Flow in the Isolated Rat Hindquarter

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The relationship between flow and pressure was studied in the perfused hindquarters of the rat. The conclusion is drawn that peripheral resistance declines progressively with increasing intravascular pressure at various rates of flow, regardless of whether the vessels are relaxed or constricted.

In the intact animal and in man, variations in the peripheral resistance to flow, and hence in the arterial pressure, are produced by variation in the size of the arterioles. The relationship between flow and pressure is complicated in the intact animal by the fact that blood is not a homogeneous fluid. Its apparent viscosity varies, being greater in large than in small vessels.1

Hemodynamic studies on the relationship between flow and pressure in isolated organs have been reported by several authors. Whittaker and Winton,1 and Pappenheimer and Maes2 thought that the resistance to flow was unaltered by variations in pressure. More recently, Nichol and co-workers3 found the resistance to be almost independent of the pressure, as long as this was well above the critical closing pressure. Green and co-workers,4 however, suggested that a decrease in resistance occurred in response to increasing intravascular pressure.

Most of the studies on the relationship between flow and pressure were made by measurement of the venous outflow at various fixed pressures. This method has the disadvantage that the measured venous outflow may be less than the total flow through that part of the vascular bed in which the main resistance to flow occurs—namely, the arterioles—since some fluid may be lost as edema or through alternative venous channels. Furthermore, there is no data on the flow-pressure relationships at low constant rates of flow, although Nichol and colleagues and Green and colleagues studied the relationships at low pressures.

In the present study, perfusion of the pithed isolated rat hindquarter has been carried out at various constant known rates of flow and the resistance to flow has been measured. The results agree to some extent with those obtained by the majority of workers, but the interpretation of the results differs considerably.

Methods

(a) Perfusion Media. The perfusion medium used was a bicarbonate buffered Ringer's solution warmed to 39 C. which, after equilibration with oxygen and 5 per cent carbon dioxide, had a pH of 7.4. The solution described by Krebs and Hensleit5 contained 0.035 per cent KCl, 0.025 per cent CaCl2, 0.692 per cent NaCl, 0.029 per cent MgSO4, 0.016 per cent K2HPO4 and 0.21 per cent NaHCO3. By the addition of 6 per cent Dextran (m.w. 75,000) in some experiments, a homogeneous fluid of increased viscosity and without pharmacologic activity was obtained. Blood was not used, since its variations in viscosity are an additional complicating factor, and obscure interpretation of flow-pressure relationships.

(b) Perfusion Apparatus. The apparatus used was a modification of that described by Pastier and Smirk,6 the essential modification being the introduction of a variable speed synchronous electric motor to drive the rotary pump. By suitable adjustment, 13 different rates of flow could be used, each being measured before and after every series of experiments. The flow at any speed is independent of the peripheral resistance and remains constant. The resistance to flow was measured on a mercury manometer, corrected for the pressure drop across
the cannula and for the difference in height between the manometer and the cannula. Perfusion pressure was recorded on a kymograph, and was not measured until it had reached a constant level for each rate of flow.

c) The Rat Hindquarters Preparation. Albino Wistar rats, 250 to 350 Gm. in weight, were anesthetised with an intraperitoneal injection of 20 mg. of sodium pentobarbital. The abdomen was opened and the cut edges clamped with large artery forceps. The iliolunbar vessels and the testicular vessels were ligated and the pelvic colon divided between ligatures. A 0.5 mm. bore polythene cannula was introduced into the abdominal aorta after proximal ligation, just distal to the origin of the renal arteries. The inferior vena cava was divided at the same level. The animal was then bisected transversely above the level of the cannula and the hindquarters preparation pithed. A tight wire ligature was placed around the cut end of the trunk in order to prevent loss of perfusion fluid from the divided vessels.

RESULTS

(a) Flow-Pressure Relations in a Capillary Glass Tube. The accuracy of the apparatus was tested by the perfusion of a glass tube of capillary bore with Ringer's solution and with Dextran in Ringer's solution. In both cases perfusion pressure was directly proportional to flow so that, when pressure was plotted against flow for each perfusion medium, straight lines passing through the origin were obtained.

(b) Flow-Pressure Relations in the Rat Hindquarter without Vasomotor Constriction. Flow-pressure studies were carried out on 10 preparations using Ringer's solution. There was little variation in pressure at each rate of flow from one preparation to the next, and all flow-pressure curves were very similar. It will be seen from figure 1 that at the lower rates of flow the pressure rapidly increases until it has reached
approximately 30 mm. Hg. At this point an apparently linear relationship develops, which, when extrapolated backwards, intercepts the pressure axis at a little over 20 mm. Hg. Perfusion with Dextran Ringer was carried out in a further ten preparations and, although the rises in pressure at lower rates of flow were greater, the curve again assumed a linear appearance at much the same pressure level as with Ringer. Whereas the flow-pressure curves for Dextran Ringer and Ringer consist, as would be expected, of two diverging straight lines when rigid tubes are perfused, the two lines obtained by perfusion of the rat hindquarters preparations with these media were almost parallel.

When the pressure is plotted against the resistance in P.R.U., as in figure 2, it is apparent that at low rates of flow the resistance is high, and that the resistance falls as the flow increases. The fall in resistance is rapid at first, but it continues to fall more slowly but progressively over the whole range of observations.

(c) Flow-Pressure Relations in the Rat Hindquarter When the Vessels are Constricted. Flow-pressure studies in the hindquarter of the rat were carried out in a further 15 preparations, using Neosynephrine hydrochloride, S-methyl isothiourea and barium chloride to produce tone. The constricting agent to be studied was introduced into the perfusion fluid before passage through the pump. The flow-pressure relations measured (which are shown in fig. 3) again agree in general with those obtained by other workers, an apparently linear relationship appearing after an initial curved rise at low rates of flow. The height of the interception of the pressure axis was increased, and the greater the constriction produced, the higher was the level of interception. The slope of the curve became steeper but, as was the case with the unconstricted vessels, when the flow was doubled the pressure was not proportionally raised. It may be assumed, therefore, that even when a considerable constriction such as that shown in figure 3 has occurred, the resistance falls progressively with increasing intravascular pressure, although at higher pressures the fall occurs more slowly. This is shown in figure 4. It will be noted that, although the proportional fall in pressure and hence the fall in resistance is smaller when the vessels are constricted, nevertheless the actual difference between the observed pressure and
that which would have been recorded without reduction of resistance is considerably greater at the higher than at the lower pressures. Hence variations in pressure caused by variations in flow increase in degree as the tone of the vessels increases.

**Discussion**

The flow-pressure studies carried out by the constant flow method have given results which agree with the reports of similar studies by other workers using a constant pressure method. It is clear, however, that a linear flow-pressure relationship does not imply an unchanging resistance to flow unless the line intersects the pressure axis at its origin. The flow-pressure relationship recorded indicates that the resistance to flow falls as the intravascular pressure rises. The fall of resistance is rapid at low pressures, but even over the linear portion of the flow-pressure curve the resistance continues to fall, although the rate at which it does so is greatly reduced. The addition of vasoconstrictor substances to the perfusion medium, although reducing the fall in resistance, does not abolish it.

There is no conclusive evidence to indicate whether the fall in peripheral resistance is the result of the opening of previously closed vascular channels with increase in flow, or whether it is the result of dilatation of the arterioles as a result of intravascular pressure. Nichol and co-workers made direct observations of the arterioles of the frog at varying pressures and found that they became unstable below a critical pressure, which varied with the state of tone. This observation might account for the rapid fall in resistance which occurs at the beginning of the curve, but does not seem to apply to the continued slow decrease in resistance which occurs at higher rates of flow. They were unable to detect by direct observation any further dilatation of arterioles in response to increased pressures, but this is not conclusive evidence in itself, since an increase of internal radius of a vessel from 20 μ to 21 μ would produce a fall in resistance of about 20 per cent. The flow-pressure graphs which they show are very similar to those obtained in the present study, yet in graphs derived from the flow-pressure studies in which resistance is plotted against flow, the resistance is shown to be unchanged at higher pressures. If the resistance remained the same at pressures higher than the critical closing pressure, the part of the curve at higher pressure would consist of a straight line directed towards the origin. This is not shown either in flow pressure curves in the present study, or in those obtained by Nichol and colleagues. Further, it is difficult to suppose that vessels which possess sufficient inherent elastic tension to close when the pressure within them falls below a certain critical level, are yet sufficiently rigid to withstand very considerable intravascular pressures without any dilatation.

It seems very likely that the initial rapid fall in resistance at low rates of flow is due to the opening of vascular channels which were previously closed, but that the slower fall in resistance which occurs at higher rates of flow in the linear portion of the flow-pressure curve is due to dilatation of the vascular bed, in response to increasing intravascular pressures.

The results obtained in this study support the conception of a critical closing pressure put forward by Burton, and it is clear that this pressure increases with the degree of tone in the vessels. Burton suggests that the presence of a critical closing pressure may be a factor in the production of renal ischemia in shock states when the arterial pressure falls, since in these circumstances a high tone and a low arterial pressure may cause the vessels to behave in an unstable fashion. This conception could account for the fact that evidence of cardiac or renal ischemia is rarely found after the use of hypotensive agents in man, since when vascular tone is reduced by these agents a much lower pressure may be tolerated before instability occurs.

The demonstration that increasing intravascular pressure produces dilatation of vessels, and hence reduction of the peripheral resistance, would support the view of Restall and Smirk that the postural fall in arterial pressure observed after vagal blockade with hexamethonium salts or sympathectomy may be due in part to the hydrostatic dilatation.
tion of the arterioles in the legs, due to the raised intravascular pressure which occurs in these vessels on standing.

SUMMARY AND CONCLUSIONS

The isolated pithed rat hindquarters preparation has been perfused with Ringer's solution and with 6 per cent Dextran in Ringer's solution at various rates of flow. The relationship between flow and pressure has been studied and compared with that occurring in rigid tubes. The peripheral resistance falls progressively with increasing intravascular pressure at various rates of flow, whether the vessels are constricted by various agents or whether they are unconstricted.

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