The Relation of a Venous-Arteriolar Reflex to Transmural Pressure and Resistance in Small and Large Systemic Vessels

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Data are presented which indicate that, even in pressure ranges well above critical closing pressures, transmural pressure is an important factor in determining systemic vascular resistance but that a mechanism is present which actively limits these pressure changes in resistance when transmural pressure is varied on the venous side.

Transmural pressure, the absolute level of intraluminal over extraluminal pressure, is one factor controlling vessel radius and thereby flow resistance in vascular beds. This factor appears to be of major importance in determining total pulmonary flow resistance. Previous resistance studies have not, however, clearly defined its role in the systemic circuit. In partial explanation may be cited the failure to employ methods permitting known changes in transmural pressure while maintaining other important resistance determining factors (viscosity, nervous activity, concentrations of humoral and metabolic substances) constant. Thus, variation of inflow pressure to alter transmural pressure also changes the gradient along the length of the bed. This results in variation of flow rate as well as transmural pressure. A varying flow rate introduces the possibility of changes in apparent viscosity as well as active changes in radius due to varying metabolite concentrations. The use of homogenous non colloidal perfusion fluids obviates viscosity changes but permits both passive and active variations in vessel radius due to changes in extraluminal pressure and metabolite concentrations respectively. The addition of colloid prevents changes in extraluminal pressure but suffers from the same criticism regarding metabolite concentrations. Changes due to varying nervous activity and concentrations of humoral substances have not offered difficulty because the former can be easily controlled and the latter easily recognized. A further criticism of previous studies concerns the measurement of only total resistance across a vascular bed. Such a procedure ignores the possibility that various vessel segments may respond differently to changes in transmural pressure.

The following study, concerning the effect of changes in transmural pressure upon the geometric component of resistance in the systemic circuit, was designed so that transmural pressure could be varied with the factors of viscosity, nervous activity and metabolite and humoral concentrations maintained relatively constant or controlled. Furthermore, methods were employed which permitted separate resistance measurements in the arteries, small vessels and veins, as well as total resistance across the bed.

**Methods**

Mongrel dogs were anesthetized with sodium pentobarbital and placed on their sides. The brachial artery was exposed high in the lowermost foreleg. A dorsal foot vein and a ventral foot artery, each about 1 mm. in diameter, were dissected free. After completely heparinizing the animal, a variable flow pump was interposed in the brachial artery. Retrograde catheterization of a subcutaneous small paw vein and a foot pad small artery (both 0.2 to 0.5 mm. in diameter) was carried out according to methods previously described.1 A 20 gage needle was inserted in the cephalic vein at the level of the elbow. Pressures were measured in the brachial artery just.

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distal to the pump, in the cephalic vein and in the small vessels utilizing 0-75 cm. Hg resistance wire pressure transducers (Statham strain gages).

The study included two phases. The first phase comprised a study of the effect of elevation of arterial, small vessel and venous transmural pressures on small and large vessel radius. To accomplish this, brachial artery flow was maintained constant at 77 cc./min. while a tourniquet was progressively tightened around the leg above all sites of cannulation. Change in cephalic vein pressure from its control value was used as a guide to the degree of obstruction produced. Cephalic vein pressure was elevated in increments of 5 mm. Hg until the total elevation equalled 25 mm. Hg. The various vessel pressures were measured at each 5 mm. Hg increment in cephalic vein pressure after permitting a few seconds to elapse to obviate the complicating effect of transients. The series of measurements were completed within a five minute period to prevent edema formation. The tourniquet was then released and the entire transverse diameter of the leg just above the level of the elbow was infiltrated with procaine to block all the nerves to the leg. The experiment was then repeated.

The second phase of the study comprised an investigation of the effect of elevation of arterial transmural pressure alone upon small and large vessel resistances. To accomplish this, flow was progressively elevated with the pump from an initial value of 56 to a final value of 133 cc./min. Pressures in various vessels were measured at each 20 cc. increment in flow after waiting a few seconds for transient changes to vanish. Not more than five minutes elapsed from the first to the last measurement. Flow was returned to its initial value, the nerves blocked as above and the experiment repeated.

The initial and final pressure gradients from brachial artery to cephalic vein, brachial artery to small artery, small artery to small vein and small vein to cephalic vein were calculated. In the first experiment, where flow was maintained constant throughout, the average change in gradient was subjected to statistical analysis. With flow constant, the direction of the change in the pressure gradient between any two points of measurement could be interpreted as the direction of change in the geometric component of resistance for the intervening vascular segment. Resistance values at initial and final conditions were calculated for each vascular segment in both experiments. Resistance was taken to be the ratio of pressure gradient to flow and expressed as mm. Hg/cc./min. The average change in resistance was subjected to a statistical test to determine whether the change from zero change was significant. Total resistance refers to the resistance to flow between the points of measurement of pressure in the brachial artery and cephalic vein. Arterial resistance refers to the resistance between brachial artery and foot pad small artery, small vessel resistance to that between small artery and small vein and venous resistance to that between small vein and cephalic vein.

RESULTS

The effect of gradual venous obstruction upon average vascular pressure in 10 dog forelegs with constant brachial artery blood flow is presented in figure 1. The average initial and final pressure gradients are also presented. It will be noted that an elevation of cephalic vein pressure of 25 mm. Hg was associated with elevations of brachial artery, small artery and small vein pressures which were equal to, greater than and less than cephalic vein pressure elevation respectively. While the total gradient did not change (mean, \(-0.9 \pm 3.4\) mm. Hg) there was a decrease in arterial \((-11.7 \pm 3.8\) mm. Hg, \(P < 0.05\)) and venous \((-5.5 \pm 1.5\) mm. Hg, \(P < 0.01\)) gradients and an elevation of small vessel \((+15.5 \pm 4.0\) mm. Hg, \(P < 0.01\)) gradient from initial to final conditions. The vascular system of the dog foreleg does not, therefore, respond to transmural
pressure changes as predicted for a simple passive elastic system. Over the ranges studied, elevation of distending pressure did not decrease the total geometric component of resistance. Though the arteries and veins dilated, this dilatation was completely compensated for by constriction in the small vessel segment.

Figure 2 presents the effect of gradual venous obstruction upon average vascular pressures and pressure gradients in seven animals following procaine nerve block. The vessels now respond as predicted for a simple passive elastic system. Elevation of cephalic vein pressure by 25 mm. Hg was associated with a lesser elevation of pressure in all other vessels. Total gradient decreased from initial to final conditions (−13.3 ± 2.4 mm. Hg, P < 0.01). This decrease in total resistance occurred even though arterial and small vessel pressures failed to reach the same high levels observed prior to nerve block. These differences after procaine nerve block are entirely explained by a failure of the small vessel segment to constrict, as evidenced by an absence of rise in small vessel gradient (−3.9 ± 3.3 mm. Hg). The absence of a statistically significant decrease in arterial gradient (−4.3 ± 2.3 mm. Hg) after procaine is also explained by an absence of small vessel constriction. This resulted in a smaller pressure rise in the arteries after procaine than before procaine. The distending effect on their walls, therefore, was less.

Figure 3 summarizes the effect of elevation of distending pressure by venous obstruction on calculated total, arterial, small vessel and venous resistances before and after total nerve block. Total resistance remained surprisingly constant over the entire range of transmural pressure elevation in the unprocainized leg. It decreased by 13 per cent from initial to final conditions after nerve block even though the average of the pressure elevations in the various vessel segments (fig. 2) was less than 25 mm. Hg. The progressive rise in calculated

![Figure 2](image1.png)

**Fig. 2.** Effect of gradual venous obstruction upon vascular pressures and pressure gradients with flow rate constant at 77 cc./min. both before and after infiltration of all the nerves with procaine at the level of the elbow. Average of seven experiments after procaine block. The pressure gradient from brachial artery to cephalic vein after procaine was 106.3 before obstruction and 99.2 mm. Hg at maximum obstruction.

![Figure 3](image2.png)

**Fig. 3.** Effect of elevation of distending pressure by venous obstruction upon average calculated total and segmental resistances before and after procaine nerve block.
resistance in the small vessel segment of the unprocainized leg can only indicate an increase in the geometric component of resistance in this segment, since flow rate was constant. The constriction may have been even greater than indicated by the calculations since apparent blood viscosity probably decreased as constriction progressed because of increased flow velocities. The fact that total cross sectional area of the small vessels decreased in spite of the distending effect of a rising transmural pressure establishes the active nature of the resistance change. Since the veins and arteries passively dilated, the net effect of this small vessel constriction is to maintain total resistance essentially unchanged. The absence of this effect after nerve block indicates that it is based upon a nervous mechanism the pathways of which likely extend beyond the leg.

Figure 4 presents the effect of flow variations upon average small and large vessel pressures. Of particular interest is the absence of a large elevation in venous pressures (cephalic vein +1.5 ± 0.5 mm. Hg, P < 0.05; small vein +2.6 ± 0.7 mm. Hg, P < 0.01) when flow was raised from 56 to 133 cc./min. The elevations in arterial pressure (small artery +32.0 ± 3.6 mm. Hg, P < 0.01; brachial artery +72 ± 2.4 mm. Hg, P < 0.01) were, on the other hand, very large. The changes were not greatly different following nerve block. Elevation of flow rate, then, provides a method for preferentially increasing pressure in arteries while leaving venous pressure relatively constant.

Interpretation of deviations of calculated resistance in the presence of a changing flow rate is complicated by two new variables. In the first experiment, change in resistance could be attributed to either transmural pressure or nervous activity. In the present experiment, consideration must also be given to the factors of apparent viscosity and metabolite concentrations. The problem may be obviated by comparing the resistance changes which occur in the procainized and non-procainized preparations in response to equivalent changes in the viscosity, metabolic and transmural pressure factors. A different resistance response in the two preparations would indicate the presence of active changes in the geometric component of resistance based upon a nervous mechanism. Figure 5 presents the pressure flow curves of the various vessel segments before and after nerve block obtained from a typical experiment. Two points are to be especially noted. The curves are essentially linear over the ranges studied and the slopes of the curves obtained from a given segment are not greatly different before and after procaine nerve block. The mean values and standard deviations of the slopes of the pressure flow curves of the venous, small vessel, arterial and total vascular segments before procaine were 36.8 ± 51.6, 3.5 ± 1.9, 1.9 ± 0.4 and 1.1 ± 0.1 respectively. After procaine block they were 37.7 ± 22.6, 3.8 ± 1.4, 1.9 ± 0.4 and 1.1 ± 0.2 respectively. Therefore, resistance changes based upon nervous mechanisms were not demonstrated in the present experiment. In the first experiment, change of arterial, small vessel and venous pressures evoked reflex changes in small vessel resistance. The present preferential elevation of arterial pressure did not. Hence, the small vessel constriction observed in the first experiment was not elicited from the arteries. By inference then the receptors responsible for the
observed active change in small vessel caliber most likely lie in the veins.

The direction of calculated resistance changes with increasing flow rates are shown in figure 6. Total calculated resistance decreased significantly from initial to final condition (mean, $-0.45 \pm 0.07 \text{ mm Hg} / \text{cc./min.}, P < 0.01$). This decrease is likely the result of decreases in both the viscous and geometric components of resistance. Affecting the radius are two opposing forces. The arteries and possibly the small vessels and veins are passively dilated by elevation of transmural pressure at high rates of flow. The veins and possibly the venous end of the capillary tend to be actively constricted by the local actions of an elevated $pO_2$, decreased $pCO_2$ and decreased $[H^+]$ subsequent to increasing rates of flow. The viscous component is decreased at high flow rates. The summated effect of these three factors produces the changes in calculated total and segmental resistance to flow depicted in figure 6.

The experiments do not permit a precise quantitative analysis of the relative contributions of transmural pressure, viscosity and metabolite concentration change to the deviations in calculated resistance observed in the various vessel segments of the flow variable leg. However, examination of figures 2, 3, 4 and 6 shows that calculated small vessel resistance decreased more in the procainized flow variable than in the procainized flow constant leg for a given elevation of mean small vessel pressure over comparable ranges. Some of this difference may be due to a decrease in the apparent viscosity of blood as the flow velocity was gradually elevated. A definite fraction cannot be established, however, because the decrease in the geometric component of small vessel resistance in the procainized flow constant leg may have been greater than the calculations indicate since increased vessel diameter is associated with decreased flow velocity and, hence, secondary increases in the viscous component of resistance. Furthermore, in the flow variable leg, the passive distending effect of the increase in transmural pressure is opposed by metabolic factors tending to produce active constriction.

It was anticipated that more precise information would be afforded by a similar comparison in the arterial segment, where metabolic factors need not be considered. In this segment, large differences in the resistance change for a given pressure elevation were not observed between the flow constant and flow variable legs, either with the nerves intact or blocked. This differ-
ence between the arterial and small vessel segment is in accord with the view that the role of anomalous viscosity in determining flow resistance is more important in small than in large vessels.

**DISCUSSION**

The experiments reported show that elevation of systemic venous pressure to levels frequently observed under a variety of normal and abnormal circumstances elicits reflex small vessel constriction. The mechanism maintains an unchanged total resistance despite passive changes in arterial and venous geometry attributable to changes in transmural pressure. The study does not indicate which small vessels constrict in response to venous distention. Arterioles, capillaries and venules are included in the small vessel segment of these experiments. The observed constriction may have been in any one or all of these vessels. Anatomical and physiological knowledge of the vascular system as well as teleological reasoning, however, most likely places the variable resistance at the arteriolar level.

A venous-small vessel or venous-arteriolar reflex may serve the organism under a variety of circumstances. It may serve to maintain flow constant through vascular beds during changes in position relative to the heart. In the absence of such a mechanism the predicted effect upon flow through an extremity placed below heart level is an increase. The elevated flow would result from lowering of total vascular resistance across the bed due to simple mechanical distention proportional to an increment in transmural pressure equal to the hydrostatic head from heart to limb. The presence of a pressure sensitive venous-small vessel reflex would prevent elevation of flow as well as part of the expected blood pooling. Such a mechanism may also be operative in preventing the predicted decrease in flow when an extremity is raised above heart level. The partial collapse of vessels resulting from a decrease in transmural pressure may be appreciably prevented by active small vessel dilatation. The mechanism may also serve a useful purpose during changes of whole body posture. The peripheral vasoconstriction with subsequent maintenance of a normal systemic arterial pressure which occurs upon transition from a recumbent to an upright position, may be partially mediated by the mechanism under consideration. Certain pathologic conditions characterized by venous hypertension may also be usefully served by the mechanism. The absence of such a mechanism in congestive heart failure would most likely permit a decrease in vascular resistance resulting in elevated flow rates for a given pressure drop, a fall in systemic arterial pressure should the heart not deliver the additional flow and an increment in small vessel blood volume. If the compensatory small vessel constriction occurred at the arteriolar level, not only would the above events be prevented but elevation of capillary pressure and edema rate formation might also be minimized subsequent to a decrease in flow rate for a given pressure gradient. The latter statement may also be applicable in conditions characterized by venous obstruction.

Unbeknown to the authors at the time of the study, the presence of a venous-small vessel reflex has been suggested previously. Girling showed that raised, and stationary, venous pressure in the hind limb of the rabbit initiated a venous motor reflex resulting in elevation of critical closing pressure. Gaskell and Burton showed that apparent blood flow of the human toe, as measured by plethysmography, decreased as the leg was lowered below heart level. This response was attributed to a “veno-vasomotor” reflex which represented a constriction of arterioles, or capillaries, of a vascular bed elicited by distention of the walls of the local veins. They felt that this reflex supplemented the central buffer reflexes in controlling the blood flow in changes of posture of individual limbs of the body and might possibly account for arterial spasm in phlebitis. These observations are in accord with those of the present study. However, since the response was present even following sympathectomy they expressed the belief that this reflex was local in origin. The latter statement is difficult to harmonize with the present study. That the reflex may be mediated by a nervous system other than the sympathetic or that some of the procaine was carried distally to inactivate a purely local reflex are possibilities to be considered. In an extension of the veno-vasomotor reflex...
study, Yamada, and Burton demonstrated that reduction of human finger tissue pressure caused a decrease in apparent blood flow. They interpreted this as additional evidence that distention of the venous bed elicits constriction of local arterioles and that the receptors in the veins respond to stretch of the wall rather than to absolute pressure in the vessel.

Though other systemic vascular beds have not been critically studied in regard to the presence of a venous-arteriolar reflex, the observations of Selkurt suggest that such a mechanism may be present in the dog's splanchnic bed. There does not appear to be such a mechanism in the pulmonary circulation. Elevations of both pulmonary venous pressure with near constant flow rates and elevation of pulmonary arterial pressure with increasing flow rates produce decreases in total pulmonary vascular flow resistance. Such behavior is similar to that observed for the nerve blocked systemic circulation in the present study. Thus the intact pulmonary and the nerve blocked systemic circuits exhibit behavior predicted for a simple passive elastic system whereas the intact systemic circuit displays no such behavior. These observations again emphasize the fact that nervous and humoral factors are more completely determining of flow resistance in the systemic system than in the pulmonary system.

The study also provides information of interest concerning blood flow in veins. The data presented show that from 6 to 9 per cent, on the average, of the resistance to flow around the entire leg vascular system occurs between veins of 0.2-0.5 mm. bore and those of 5-10 mm. diameter, the higher percentage being associated with the lower rates of flow. The low average value for venous resistance is further emphasized by the fact that an average increment in venous gradient of only 1.8 mm. Hg was associated with an elevation of venous flow rate from 56 to 133 cc./min. The fraction that venous resistance contributes to total resistance, however, varied from 2 to 20 per cent in different anesthetized animals. Some of this variation may be dependent upon the inability to catheterize precisely the same size small vein in every animal. However, we have previously reported that small vein pressures are sometimes spontaneously variable with time in a given vein of an unanesthetized animal. The changes were as large as 25 mm. Hg. The occurrence of spontaneous cyclic changes in small vein pressure without concomitant fluctuations in cephalic vein pressure strongly suggested that the small vein system is subject to active venomotion through nervous and/or humoral mechanisms. Positive proof for this was lacking, however, because flow rates could not be measured under local anesthesia. General anesthesia under pentobarbital abolished the cyclic changes in small vein pressure. The present finding of minimal changes in small vein pressure when flow was varied over wide ranges greatly strengthens the conclusion that the mentioned spontaneous variations in pressure were truly on the basis of active changes in venous caliber and, therefore, resistance. Thus the bore of these small veins may play a significant role in determining the pooling and the flow of blood. Also, by influencing capillary pressure the small vein pressure will have a controlling effect upon water and salt distribution between blood and the tissue spaces.

The low levels of small artery pressure recorded in these experiments suggest either that arteries of 0.2 mm. and larger offer a greater flow resistance than hitherto recognized or that the methods employed really record the pressure in arteries of much smaller diameter. The latter is likely the case since the catheter used occluded the artery it was in and the pressure measured was then that in distal collateral vessels. The absence of collaterals until the vessel became near arteriolar diameter would explain the level of pressures recorded.

Conclusions

Observations have been made upon small and large vessel resistance in the foreleg of the pentobarbital anesthetized dog in relation to changes in transmural pressure.

Elevation of pressure in the veins, small vessels and arteries by venous obstruction with flow rate constant was associated with no change in total resistance, decreased arterial and venous resistances but elevated small vessel resistance. When all of the nerves were blocked high in the leg with procaine, total resistance decreased and the small vessels
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failed to constrict. The inference is that passive changes in the geometric component of resistance effected by variations in transmural pressure by venous obstruction are accompanied by directionally opposite active changes in small vessel resistance and that the latter changes are mediated over nervous pathways which are likely not local in distribution.

Elevation of arterial pressure only by increasing flow rate with a perfusion pump failed to elicit reflex constriction of small vessels. Hence, the constriction observed when pressure was elevated in all of the vessels by venous obstruction likely originated in the veins. The value to the organism of a pressure and/or distention sensitive venous-arteriolar reflex is discussed.

The observation of minimal changes in small vein pressure when flow was varied widely indicates that the previously reported spontaneous fluctuations in the small vein pressures of unanesthetized dogs is on the basis of active venoemotion.

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SUMMARIO IN INTERLINGUA

In le gamba de fronte de canes anesthesiate a pentobarbital, observationes esseva facite in re le resistentia de parve e grande vasos in relation con alterationes del pression transparietal.

Le elevation del pression effectuate per obstruction venose in venas, parve vasos, e arterias esseva associate, in tanto que le fluxo esseva constante, con nulle alteration del resistentia total, sed con reduction del resistentias arterial e venose e augmento del resistentia del parve vasos. Quando al alto del gamba omne nervos esseva blocate per procaina, le resistentia total se diminuve e le parve vasos non se constrinvea. Es a inferer que alterationes passive in le geometric componente del resistentia, le quales es effectuate per variationes del pression transparietal in consequentia de obstruction venose, es accompaniante per active alterationes de direction opposite in le resistentia del parve vasos e que iste alterationes es mediate per vias nervous que es probablemente de distribution non local.

Le elevation de solmente le pression arterial, resultante del augmento de fluxo que eseva effectuate per un pumps perfusional, non evoceva un constriction reflexe del parve vasos. Ergo, le constriction observe quando le pression in omne vasos esseva elevate per obstruction venose habeva probablemente su origine in le venas. Nos discute le valor que inhere pro le organismo in un reflexo venose-arteriolar sensible a pression e/o distension.

Le observation de minime alterationes del pression in le parve venas quando le fluxo essevo subjecte a grande variationes indica que venoemotion active es le base del previoentemente reportate fluctuationes spontane in le pressiones de parve venas in canes non anestesiate.

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