Effect of Acute Elevation of Portal Venous Pressure on Mesenteric Blood Volume, Interstitial Fluid Volume and Hemodynamics

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Measurement of blood flow through the portal vein of the dog revealed a reduction of flow and an increase in vascular resistance of the mesenteric bed in proportion to the elevation of portal venous pressure. To obtain further information on this mechanism, studies were performed on segments of terminal ileum with continuous measurement of both weight and flow. These studies demonstrated that the increase of vascular resistance was not dependent upon extrinsic or adrenergic innervation, and did not appear to be secondary to interstitial fluid formation. It is suggested that the response in this bed is due to a local reflex or to a myogenic reaction of the resistance vessels to increased transmural pressure.

It has been recognized that changes in venous pressure may alter the resistance to blood flow, an increase in venous pressure causing an increase in resistance in certain organs, and a decrease in other organs. Since the venous drainage of the intestine passes through the liver, the blood volume and venous pressure of the former would be expected to be particularly dependent upon the vascular resistance of the liver, and in the dog subject, in addition, to the action of the hepatic vein sphincters. Since the intestine is thus in a particularly vulnerable position to be subject to variations in venous pressure, it was of special interest to examine the mechanisms of hemodynamic response of this vascular bed to changes in portal venous pressure.

In the present investigation, studies of the effects of portal venous pressure changes were carried out in such a manner that possible effects from the liver were avoided or minimized. This was done in two ways. In one, the liver was removed from the circulation during the time of acute studies on portal flow, hypoglycemia being prevented by continuous glucose infusion. Such a technic furnished a reasonably stable preparation from the standpoint of circulatory homeostasis for at least 2 hours. The other approach was to carry out studies on small segments of the intestine so that minimal impairment of flow to the liver resulted.

The investigation was divided into 2 phases. The first phase was concerned with the influence of increasing portal venous pressure on the hemodynamics of the entire mesenteric (intestinal) circulation. The results of this phase led to the second phase, the purpose of which was to attempt an assessment of the possible role of extrinsic nervous mechanisms in regulation of the resistance vessels of the intestinal bed with increased venous pressure.

METHODS

A. The technic for measuring portal flow in an ahepatic preparation has been described in detail elsewhere. In this preparation, the spleen is removed to avoid complications arising from volume changes and vascular resistance alterations in this organ. Studies were made on dogs anesthetized with 30 mg./Kg. sodium pentobarbital, given intravenously. After splenectomy, portal vein flow was measured after adequate heparinization with an optically recording rotameter connected in series with a splenic vein-external jugular shunt. Hepatic circulation was interrupted by ligation of the portal vein at its entry into the liver, the common hepatic artery and the gastroduodenal branch, to eliminate retrograde flow. A clamp on the external circuit adjusted the portal pressure...
to any desired level, beginning at a control level comparable to that noted initially in the portal vein while discharging into the liver. After the liver circulation had been cut off, glucose infusion at the rate of 150 mg./Kg./hour was begun. Portal venous pressure and carotid arterial pressure were continuously recorded with Gregg optical manometers calibrated with mercury and water manometers. In the present experiments, made on a total of 9 animals, after a control period averaging 22 min., portal venous pressure was raised by adjustment of the clamp so that it was increased approximately twofold in one group of animals, and approximately threefold in another group. Pressure was kept elevated for about 40 min., then released, with recovery observations continuing for about 20 min. Peripheral resistance was calculated as a P/F ratio, where $P = \text{arterial} - \text{venous press.}$ in mm. Hg and $F = \text{flow through}$ the portal vein in ml./min.

B. Further studies, comprised of 2 series of 5 experiments each, were performed on 9 dogs and employed a combination of the gravimetric method and flow measurements in segments of intestine. A segment of terminal ileum of 35 to 75 gm. was prepared for continuous measurement of weight by a technic previously described, and the vein draining the segment was cannulated for measurement of venous outflow and regulation of venous pressure. The venous circuit consisted of a Gregg manometer and a water manometer for measurement of venous pressure, a three-way stopcock for measurement of outflow by diversion into a graduated cylinder for 15 sec., and a polyethylene reservoir which returned blood to the animal by way of the jugular vein. Nonwettable silicone tubing was used for all connections, and all metal and glass surfaces were siliconized. Venous pressure was altered by a screw clamp placed between the manometer system and the three-way stopcock, zero pressure being taken at the level of the pedicle of the segment. Arterial pressure was recorded optically from a carotid artery. Mannuronate was used as the anticoagulant in these experiments.

To determine the effects of extrinsic nerve activity, the first group of 5 experiments studied the effects of venous pressure elevation before and after denervation of the segment. Denervation was accomplished by stripping the blood vessels and ligating and dividing all extravascular tissue. The vessels were then painted with 10 per cent procaine solution.

To assure complete removal of all constrictor adrenergic influences, in a second series of 5 experiments the preparations were denervated as before and treated with phenoxybenzamine before and treated with phenoxybenzamine to any desired level, beginning at a control level comparable to that noted initially in the portal vein while discharging into the liver. After the liver circulation had been cut off, glucose infusion at the rate of 150 mg./Kg./hour was begun. Portal venous pressure and carotid arterial pressure were continuously recorded with Gregg optical manometers calibrated with mercury and water manometers. In the present experiments, made on a total of 9 animals, after a control period averaging 22 min., portal venous pressure was raised by adjustment of the clamp so that it was increased approximately twofold in one group of animals, and approximately threefold in another group. Pressure was kept elevated for about 40 min., then released, with recovery observations continuing for about 20 min. Peripheral resistance was calculated as a P/F ratio, where $P = \text{arterial} - \text{venous press.}$ in mm. Hg and $F = \text{flow through}$ the portal vein in ml./min.

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Venous pressure was set at 5 cm. water for initial weight, flow and pressure readings, which were taken at one-minute intervals. The experimental procedure was to elevate venous pressure in 5 cm. increments from 5 cm. to 30 cm. water, holding the pressure constant for 5 min. at each level. Venous pressure was then reduced to 5 cm. in one step and readings were continued for 10 min. A typical experiment is shown in figure 1.

Resistance was calculated as described, except that the flow was expressed per 100 Gm. tissue. Since the volume change recorded by this method is the sum of blood pooled plus interstitial fluid, these factors must be separated by empirical means. This is done by assuming that interstitial fluid accumulation is essentially a linear function of time as venous pressure is elevated and that all of the blood is pooled in the first minute of pressure elevation. The analysis of one such experiment is shown in figure 1. The slope of the line drawn through successive weight determinations at each venous pressure represents the increase of interstitial fluid. The vertical dashed lines represent the increase in blood volume. Also shown are changes in blood flow, and arterial pressure.
RESULTS

Influence of Portal Venous Pressure Elevation on Intestinal Hemodynamics. A group of 5 animals in which portal venous pressure was elevated moderately (average 2.15 X control) is summarized in figure 2. Here all values are given as per cent of control. Control averages and ranges were: blood pressure, 129 mm. Hg (101 to 165); heart rate, 164 (112 to 222); blood flow, 245 ml./min. (216 to 286); P/F, 0.496 (0.390 to 0.710); and portal venous pressure, 13.7 cm. (13.0 to 16.0). Following increase in portal pressure, blood flow fell to 50 per cent of control, but soon returned to a stabilized average of 70 per cent of control. Phase A in the diagram is taken to represent a period of flow deficit, reflecting storage of blood in the venous channels as the immediate consequence of venous pressure elevation. Arterial pressure declined progressively to 84 per cent of control. The P/F ratio, ignoring the immediate sharp increase which is believed not to reflect accurately the state of mesenteric vascular resistance, averaged 1.12 of control. Heart rate slowed to a small degree in this group.

When control venous pressure was restored, a brief period (phase B) of elevated flow occurred, believed to be caused by the release of blood trapped by the elevation of venous pressure. Blood flow then returned to a level slightly higher than control (1.08), with a stabilized P/F ratio of 0.93 of control. Arterial blood pressure recovered to 89 per cent of control during this period of observation.

A group of 4 animals in which portal pressure was increased to a greater degree (average 2.86 X control) is summarized in figure 3. Control averages and ranges for this group were: blood pressure, 145 mm. Hg (128 to 162); heart rate, 176 (155 to 204); blood flow, 198 ml./min. (130 to 249); P/F, 0.730 (0.569 to 0.932); and portal pressure, 11.0 cm. (9.2 to 13.1). With increase in portal pressure, flow fell immediately to 40 per cent of control during phase A, but equilibrated...
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in 2 min. to an average of 56 per cent of control. Arterial pressure declined to 84 per cent of control. The P/F ratio with stabilized flow averaged 1.37 of control. Heart rate showed minimal change.

Upon restoration of control venous pressure, a longer period of overshooting of flow occurred (phase B) than in the previous group. Flow was restored to an average of 0.80 of control in this group. After a brief decline in the P/F ratio during the release of pooled blood, the intestinal vascular resistance remained increased at 1.19 of control during the remainder of the recovery period. Blood pressure returned to 94 per cent of control.

Blood volume changes in the intestine were ascertained by the "flow deficit" method. Attention has been directed to vertically hatched areas in figures 2 and 3 relating to the mean blood flow curve. To obtain the pooling volume, the area under the dashed line, set at the level of the ensuing stabilized flow, was integrated in terms of the flow deficit per second. The pooled volume is accountable for the overshooting of flow following restoration of normal venous pressure, labeled phase B in the flow curve. This volume should be in reasonable agreement with the initial deficit volume.

The mean deficit volume change for the group with moderate portal pressure elevation (fig. 2) was calculated as 8.6 ml. of blood. The recovery volume was 6.8 ml. In the second group (fig. 3), with approximately threefold increase in portal pressure, the flow deficit volume was 23.6 ml. and the recovery volume was 23.2 ml.

The significant features of the above experiments may be summarized as follows: 1. Portal pressure increases of 2.14 and 2.86 times control resulted in a reduction of flow to 70 and 56 per cent of control respectively, and an increase in calculated vascular resistance of the intestine of 12 and 37 per cent. 2. There was an estimated increase of 6.8 and 23.2 ml. of blood in the small intestine. The results in the following section show that at least an equivalent amount of interstitial fluid accumulates during this time.

Depletion of the circulating volume by this amount could be an adequate stimulus to baroceptors, and hence cause a reflex increase in mesenteric vascular resistance. The possible role of extrinsic nervous mechanism is examined in the experiments of the following section.

The Role of Extrinsic Nerve Activity in Intestinal Hemodynamic Alterations Resulting from Increase in Venous Pressure. These studies were performed on segments of terminal ileum. A control experiment showing the increase in intestinal weight and the reduction in blood flow with elevation of venous pressure is shown in figure 1. Calculations of vascular resistance, blood volume and interstitial fluid volume were made as indicated.

Figure 4A shows the average change in peripheral resistance, estimated blood volume, and interstitial fluid volume as venous pressure was elevated from 5 to 30 cm. water in the first series of experiments. Initial peripheral resistance appeared higher in the denervated preparations, 5.09 peripheral resistance units (PRU), as compared with 3.97 PRU in the intact preparations. The difference was statistically significant ($p < 0.05$). This increase is probably a residual constriction from the preceding control venous pressure elevation, since denervation alone increases flow. In the intact preparation peripheral resistance increased 50.6 per cent, accompanied by cumulative increases of interstitial fluid of 7.4 Gm./100 Gm. tissue and blood volume of 4.1 Gm./100 Gm. tissue. After extrinsic denervation these factors were not significantly altered in the mean, although in one experiment the constrictor response was noticeably reduced.

In order to insure complete elimination of all sympathetic constrictor activity, the second series of experiments studied the effects of denervation plus treatment with phenoxybenzamine. Vascular resistance was initially 4.34 PRU in the control preparations and 5.21 PRU in the treated preparations. The difference was not statistically significant ($p > 0.05$). As in the first series, after
denervation plus phenoxybenzamine the constrictor response persisted or even increased in 4 out of 5 preparations, although it was reduced in one. However, the means of the 2 groups did not differ significantly (fig. 4B). Blood volume increased to approximately the same extent in both cases, but interstitial fluid formation was somewhat higher in the control group, but again not statistically significant. Thus, it appears that the constrictor response to venous pressure elevation is not primarily mediated by adrenergic nerves.

**DISCUSSION**

The blood volume changes as determined by the flow deficit and the weight methods are of the same order of magnitude. As determined by the first method, a twofold increase in venous pressure increased blood volume by 8.6 ml. From the data derived from the weight method it appears that a similar increase in pressure would increase blood volume 13.0 ml. (for a 500 Gm. small intestine). A threefold elevation of venous pressure increased blood volume 23.6 ml. as measured by the flow method, and 17.0 ml. as estimated by the weight method. Therefore, trapping of blood in the intestinal vasculature with elevation of venous pressure does not constitute a large volume as determined by either method. The formation of interstitial fluid appears to be of more significance, as evidenced by figure 4.

It is possible that increased interstitial volume would elevate tissue pressure and therefore partially offset the increase in trans-
mural pressure produced by venous pressure elevation. However, such elevation of tissue pressure is apparently not an important factor in our experiments. For example (fig. 1), at each level of venous pressure there was a gradual increase of interstitial fluid volume. However, the change in blood flow occurred only within the first minute of pressure elevation, when the blood was being pooled. Moreover, in one experiment using a denervated preparation, interstitial volume was decreasing as the experiment began and continued to fall until a venous pressure of 20 cm. water was reached. In this time vascular resistance increased 25 per cent. In the same preparation before denervation, resistance rose only 7 per cent over the same pressure range, although interstitial volume increased throughout. Thus, the increase in resistance appears not to be a result of fluid accumulation.

Inasmuch as venous outflow was measured in these experiments, it is possible that loss of large amounts of fluid from the capillaries with elevated pressure could reduce the apparent blood flow by the amount lost, and result in erroneous calculation of vascular resistance. To check this point, the exudate and secretions draining from the intestine during several experiments were measured and added to the increase of interstitial fluid volume to give an estimate of total fluid loss from the capillaries. Calculations show that the error from this source is in the order of not more than 2 per cent, which would fall within the limits of error of flow and pressure measurement.

Despite the indication of deviation of some of the circulating blood volume into the intestinal vasculature as the result of increased venous pressure, stimulation of baroreceptors and the initiation of extrinsic reflex vasoconstriction does not appear to be the important mechanism accounting for the venous-arteriolar response noted in the present investigation. This was clearly indicated by the persistence of this mechanism after denervation of the isolated segment. This conclusion was further strengthened by the continued response noted after presumptive elimination of adrenergic nerve activity following phenoxybenzamine infusion.

The venous-arteriolar response has been demonstrated to be reflex in origin in a number of other vascular beds. Haddy has shown that the increase in vascular resistance in the kidney with elevation of venous pressure is dependent primarily upon extrinsic innervation, although, as in our experiments, vascular resistance was never seen to decrease progressively with elevation of venous pressure. However, Haddy and Gilbert have reported that the constrictor response in the forelimb of the dog is abolished and replaced by passive dilatation after denervation.

Passive dilatation of the resistance vessels with venous pressure elevation apparently occurs in the lung bed. Also Read et al have recently reported that, irrespective of the venous-arteriolar response in certain beds, a decrease of total peripheral resistance in the dog is seen after elevation of vena caval pressure. The reader is referred to the latter report for a summary of the present status of knowledge of the venous-arteriolar response.

In skeletal muscle of the human this response persists after denervation and has been suggested by Gaskell and Burton to be a local reflex in nature, and by Patterson and Shepherd to be myogenic.

The existence of the venous-arteriolar response in the intestinal bed has been demonstrated in the present study in the whole intestine and in segments of terminal ileum. In contrast to the other vascular beds of the dog which exhibit this phenomenon, the intestinal response is apparently not under primary extrinsic or intrinsic adrenergic nervous control. The experiments do not eliminate the possibility that intrinsic reflex circuits insensitive to the action of phenoxybenzamine persist in function and cause a constriction of the resistance vessels (arterioles) as the result of venous pressure elevation. An alternative hypothesis is that myogenic constriction of the resistance vessels occurs with elevation of venous pressure. This was suggested as a normal mechanism in the
arterioles for response to changes in arterial pressure by Bayliss,9 and more recently by Folkow.10 However, it is not readily apparent why the arterioles should be more responsive to pressure changes occurring on the venous side than on the arterial side. Levy has recently suggested11 that venous pressure changes in the hind limb have only slight effects on the distending pressure of the arterioles. It is possible that such a myogenic response may be occurring directly in venules and venous tributaries, but such a conclusion is rendered insecure by the increase in blood volume which occurs during venous pressure elevation, a response suggesting rather passive dilatation of the capacity vessels. Our experiments to date can offer no final answer to the exact nature of the intrinsic mechanism which was manifested in these experiments.

**SUMMARY**

Measurement of blood flow through the portal vein of the dog during elevation of portal venous pressure demonstrated a reduction of flow greater than the decrease in the arteriovenous pressure gradient, indicative of an increase in mesenteric vascular resistance. Similar results were obtained when flow was measured in segments of terminal ileum. In the latter, simultaneous measurement of intestinal weight showed a progressive increase with venous pressure elevation, largely attributable to increase in interstitial fluid, but in part to the pooling of blood in the mesenteric capacity vessels. Reasons are given for the belief that the increased vascular resistance is not the result of segregation of interstitial fluid. Rather, it is concluded that with elevation of venous pressure the intestinal bed undergoes a venous-arteriolar response, previously described in certain other vascular beds. By this is meant an increased constriction of the resistance vessels as the result of increase in venous pressure.

Examination of the mechanism after denervation and adrenergic blockage by phenoxybenzamine in segments of terminal ileum demonstrated that the response was not dependent on extrinsic nerve activity. By exclusion, the mechanism is attributable to a local reflex, or, alternatively, to direct myogenic response (contraction of smooth muscle elements in the blood vessels to the stimulus of increased intraluminal pressure). Currently, the former hypothesis is favored (but not proved), because of the observation that venules and venous tributaries increase in capacity, and because of the probability that the effects of increased venous pressure will be felt slightly, if at all, by extension through the capillary bed to the arterioles. In conclusion, it is emphasized that experiments of a more definitive nature are required to resolve the ultimate mechanism.

**SUMMARJO IN INTERLINGUA**

Le mesuration del Flusco de sanguine a transverso le vena portal del can durante que le pression in le vena portal esseva elevate revelava un reduction del flusco plus grande que le reduction del gradiente de pression inter arteria e vena. Isto indicava un aumento del resistentia vascular mesenteric. Simile resultatos esseva obtenite quando le flusco esseva mesurate in segmentos de ileum terminal. In istos, le mesuration simultanea del peso intestinal revelava un augmento progressive con le elevation del pression venose, attributibile primarimente al augmento del fluido interstitial sed in parte etiam al acumulatou de sanguine in le vasos capacita- tori del mesenterio. Es presentate rationes que supporta le opinion que le augmentate resistentia vascular non es le resultato de segregation del fluido interstitial. In terminos positive, le conclusion del presente studio es que in le presentia de elevationes del pression venose, le vasculatura intestinal es le sito de un responsa veno-arteriolar (del typo previemente descritbe pro certe alteire vasculaturas). Iste formulation vole des- critber un augmentato constriction del vasos de resistentia como resultato del augmento in le pression venose.

Studios del mecanismo in question effec- tuate post disnervation e blocage adrenergic per phenoxybenzamina in segmentos de ileum terminal, demonstrava que le responsa non
DEPENDeva de un extrinsec activitate nervose. Per exclusion, le mechanismo es attribuibile a un reflexo local o, alternativemente, a un responsa myogene directe (contraction de elemento de muscular lisie in le vasos de sanguine sub le stimulo del augmentate presision intraluminal). Al tempore presente, le prime de iste due conceptiones es preferite (ben que sin prova), proque il ha essite observate que le venules e le tributaries venose augmenta lor capacitae e proque il es probabile que le effectos del augmentate pression venose es percipite levemente (si del toto) per un extension a transverso le vasculatura capillar usque al arteriolas. In conclusion il es signalate que experimentos de natura plus definitive es require pro clarificar le mechanismo completamente.

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