The Participation of the Venomotor System in Pressor Reflexes

By Robert S. Alexander, Ph.D.

In dogs anesthetized with chloralose, innervated loops of intestine were isolated so as to permit periodic interruptions of blood flow to record pressure-volume diagrams from the venous bed. Pressor reflexes were found to produce alterations in the venous distensibility diagrams which, on the basis of comparison with distensibility changes produced by constrictor drugs, are interpreted as direct evidence of venoconstriction accompanying pressor responses of the cardiovascular system.

INVESTIGATIONS of the functional role of the venomotor system have been handicapped by the lack of an adequate method for assessing its activity. Changes in the caliber of veins have been observed under various conditions,[1] but this is not adequate evidence of venomotor function unless these observations are correlated with an analysis of the associated hemodynamic factors. In the over-all regulation of the cardiovascular system, however, indirect evidence justifies the inference that there must be an important venomotor contribution to circulatory homeostasis, in addition to the well demonstrated adjustments of cardiac output and arteriole resistance.[2, 3]

Opportunities for a direct attack on this problem have been developed from studies of the distensibility of the splanchnic venous system[4] and the analysis of the influence of constrictor drugs on this distensibility.[5] Such distensibility determinations appear more relevant to the problem of venomotor activity than would flow resistance studies of the type employed in assessing arteriolar constriction, since venous capacity is a more significant variable than is venous resistance to blood flow.[6] The following observations on splanchnic venous distensibility in anesthetized dogs demonstrate directly the constriction of venous elements as part of the response observed in the common pressor reflexes.

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Methods

As described previously,[5] the physical characteristics of the splanchnic venous system demand rigorously controlled rates of distension and exact intervals between measurements if comparable distensibility determinations are to be obtained. This has been achieved in these experiments by injecting blood into the venous system of intestinal loops at the rate of 50 cc. per minute by means of a motor-driven syringe, all injections being spaced accurately at 10-minute intervals for both control and experimental observations. The injection procedure described below required less than 30 seconds; for the remainder of the 10-minute interval between injections, perfusion of the loop was maintained by the dog at its existing arterial blood pressure.

To preserve the sensitivity of cardiovascular reflexes, the dogs were anesthetized with chloralose following morphine sedation, employing 75 mg. of chloralose per kilogram for induction and 15 mg. per kilogram at 30-minute intervals for the following 2.5 hours. Using the same technic employed in earlier studies,[5, 7] a loop of ileum was exteriorized and all connections to the animal severed by ligation and cautery, except for careful preservation of the nerve plexus surrounding the mesenteric artery. The artery was cannulated and perfused with the animal's own blood by a connection with the carotid artery, and the mesenteric vein cannulated and the venous drainage returned to the dog by way of the jugular vein. Though it was impossible to prevent minor damage to the nerve plexus in isolating the artery for cannulation, maintenance of the afferent innervation of the loop was evidenced by reflex alterations in respiration which were readily elicited by slight manipulation of the isolated loop. Optical membrane manometers provided for continuous recordings of the arterial and venous pressures in the loop through "T" connections on the respective cannulas. A third manometer, recording the femoral arterial pressure of the dog, was used as an index to the pressor responses being elicited in the animal.

To make a distensibility determination, arterial

inflow was cut off by closing a stopcock in the arterial circuit, and then 15 seconds were allowed for drainage of blood from the loop and pressure stabilization. Venous outflow was then occluded by means of a second stopcock and, after a three-second interval, the injection was initiated by turning on the motor-driven syringe which injected blood through a "T" connection on the venous cannula. Cessation of arteriovenous flow and stabilization of the preparation prior to the injection was indicated by the absence of any change in arterial or venous pressure in the loop during the three-second interval between closing the venous stopcock and initiating the injection.

The recording of venous pressure during the injection yielded a record of pressure change as a function of time. Since the rate of injection was constant, the original recording could be converted to a pressure-volume diagram by inserting appropriate volume units on the time axis. As shown previously,[5] there is no retrograde flow of the injection to the arterial side of the loop; therefore these pressure-volume diagrams are direct measurements of venous distensibility.

To minimize intestinal motility, the dogs were atropinized and, except for experiments with hypercapnia and hypoxia, they were vagotomized. Movements of the exteriorized loop due to respiration were prevented by supporting the loop on a plastic platform mounted rigidly over the surface of the abdomen.

In experiments involving carotid sinus stimulation, one sinus was deafferented and the other sinus isolated by ligation of the common, the internal, and the external carotid arteries. In ligating the external carotid below the occipital artery and just below the small branch which courses over towards the carotid body, it was essential to employ an additional ligature above the occipital branch so as to permit strong anterior retraction of the root of the external carotid. This made it possible to pass the occluding ligature under the vessel posteriorly without danger of catching the underlying sinus nerve. The sinus was distended by injecting blood through a cannula in the ligated segment of the common carotid, sinus pressure being recorded by means of a three-way stopcock and a mercury manometer.

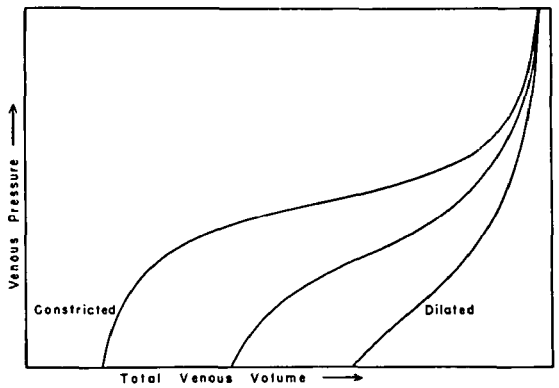

FIG. 1. Venous distensibility patterns with differing degrees of venomotor tone.

BASIS FOR ANALYSIS OF RESULTS

Recognition of venomotor activity in distensibility diagrams requires knowledge of the alteration in the form of the diagram which is associated with venoconstriction. This information has been presented previously,[5] as summarized schematically in figure 1. Contraction of the smooth muscle produces its greatest effect upon venous volume at low venous pressures, but has no influence at very high pressures where the venous wall has been stretched to the point at which the fibrous tissue is carrying the load. The constricted vein consequently exhibits a distensibility diagram that is much more sigmoid in form than is that of the dilated vein.

For quantitative reproduction in the laboratory of the scheme shown in figure 1, it would be necessary to obtain an accurate measurement of the total venous volume. Limited success in estimating this by gravimetric methods has been accomplished in the excised intestinal loop,[5] but such methods are not readily adapted to a loop with intact innervation. Distensibility diagrams are readily quantitated, however, in terms of pressure increments produced by in-

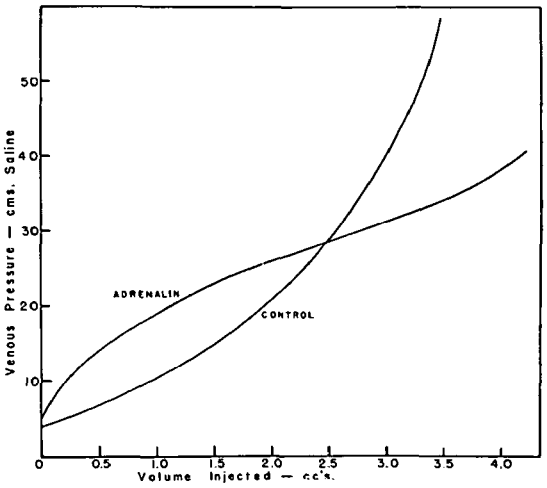

FIG. 2. Distensibility diagrams recorded during the injection of the venous system of an intestinal loop before and after the intra-arterial administration of 0.02 mg. of adrenaline.

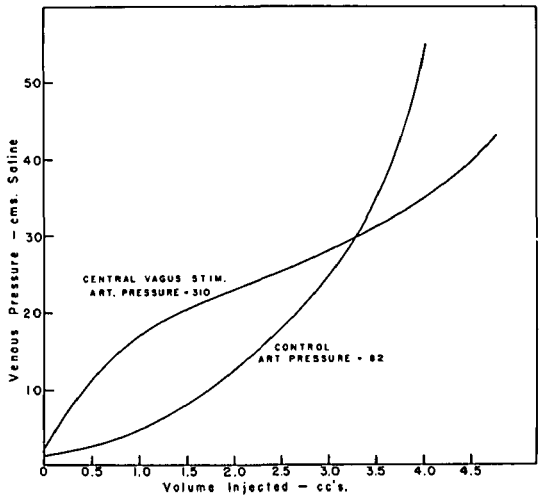

FIG. 3. Alteration in the venous distensibility of an intestinal loop associated with central vagus stimulation which elevated the arterial pressure of the dog from 82 to 310 mm. Hg.

jecting known volume increments, in spite of the unknown volume in the system at the start of the injection. This effectively shifts the origin of all curves shown in figure 1 to a common initial volume point at "zero" or the initial pressure, displacing the dilated curves to the left. The constricted diagram would then bow above and to the left of the dilated diagram at low pressures; as the pressure level is elevated, the constricted curve should cross to the right of the dilated diagram and exhibit a more gradual rise in pressure until high pressure levels are reached.

This pattern is illustrated in an actual experiment shown in figure 2, which presents pressure-volume diagrams obtained before and after the local administration of adrenaline into the intestinal loop of a dog. The altered pattern of the distensibility diagram shown in this figure will be used as an index to venoconstriction in the following analysis.

RESULTS OF REFLEX STIMULATION

Figure 3 illustrates the distensibility diagrams obtained from the innervated intestinal loop before and during strong stimulation of the central end of a cut vagus nerve. Nerve stimulation was started just after the arterial inflow to the loop was closed off for pressure stabilization; hence the only communication between the dog and the intestinal loop during the period of stimulation was by way of the nerves supplying the loop. Accompanying a rise in pressure in the dog of from 82 to 310 mm. Hg, there is noted a definite shift of the distensibility diagram to the constricted pattern. To visualize the true nature of the venoconstriction demonstrated in figure 3, the control curve should be transposed to the right so that the two curves would converge at high pressures, as in figure 1.

Altering pressure on an isolated carotid sinus had a similar action on the distensibility characteristics of the venous system of the

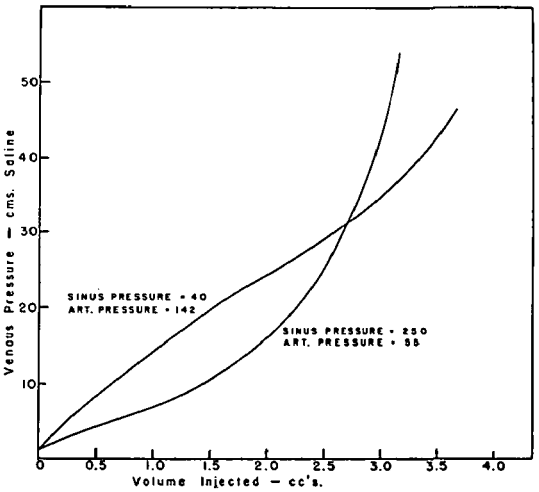

FIG. 4. Influence of hypertension and hypotension of an isolated carotid sinus upon venous distensibility.

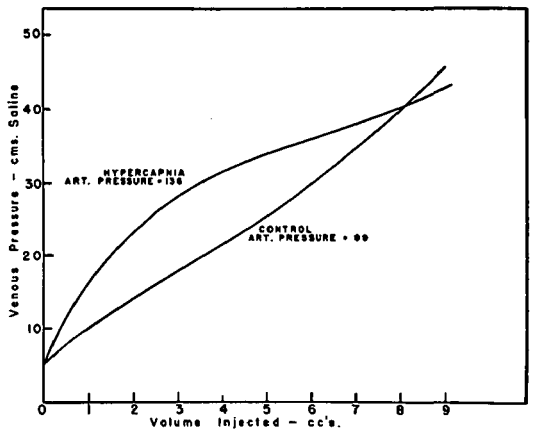

FIG. 5. Action of hypercapnia upon venous distensibility, associated with a rise in arterial pressure of the dog from 99 mm. Hg to 136 mm. Hg.

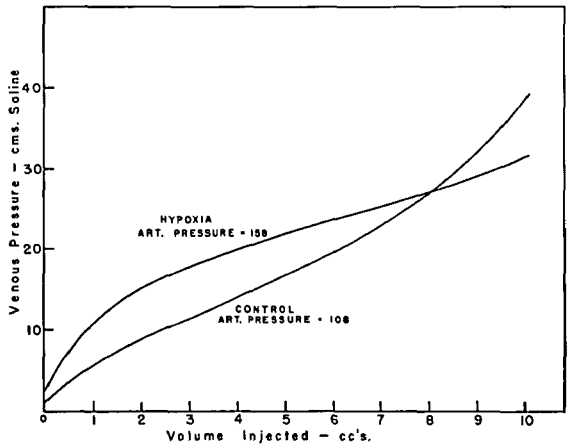

FIG. 6. Action of hypoxia upon venous distensibility, associated with a rise in arterial pressure of the dog from 108 to 158 mm. Hg.

intestinal loop. With pressure in the carotid sinus elevated to a level of 250 mm. Hg, vasomotor tone is inhibited, as evidenced by an arterial blood pressure of 55 mm. Hg in the experiment illustrated in figure 4. Associated with this, venous distensibility assumes the dilated pattern. Lowering the pressure in the carotid sinus to a level of 40 mm. Hg, reported to be the point of minimal stimulation of the pressoreceptor afferents,[8] evokes a pressor response in the animal with a rise in pressure to 142 mm. Hg. With this pressor response in the animal, the venous system of the intestinal loop exhibits a shift towards a more constricted pattern.

Figure 5 demonstrates a transformation to the constricted pattern of venous distensibility associated with extreme hypercapnia, produced by having the dog rebreath for 20 minutes into an oxygen-filled spirometer.

Figure 6 illustrates a pair of recordings obtained before and after a state of severe hypoxia had been produced by having a dog rebreath into an air-filled spirometer provided with a soda-lime absorber for removing carbon dioxide. The distensibility diagrams indicate that the pressor response observed under these conditions is accompanied by venous constriction.

DISCUSSION

These results demonstrate directly that reflex venoconstriction occurs in the venous bed as represented in the intestinal loop, thereby extending the conclusions of Peterson[9, 10] and of others that reflex constriction is exhibited by the great veins. The exact anatomic limit of the venous elements studied by our technic has not been identified. In all experiments, the manometer recording the pressure on the arterial side of the loop showed no evidence of any rise in pressure during the venous injection, confirming our previous observation that the injected blood does not flow retrograde to reach the arterial side of the preparation. Failure to observe more evidence of leakage of the injected blood[7] suggests that the injection may not reach the capillaries. On the other hand, cutting through the intestinal wall immediately after performing injections of India ink by our method reveals the presence of ink in minute vessels. Whatever may be the exact site of the retrograde block, this indicates that the greater portion of the significant venomotor elements must be included in these distensibility measurements.

In general, all reflex responses studied have demonstrated evidence of constriction in the venous elements of the intestinal loop accompanying a pressor response in the animal. The only exceptions encountered so far have been in responses to weak afferent nerve stimulation accompanied by small or biphasic responses in arterial blood pressure. Venous distensibilities recorded under such circumstances do not always indicate venoconstriction to be occurring simultaneously with the period of elevated arterial pressure. In a similar fashion, with progressive hypercapnia and especially with progressive anoxia, the peak of the rise and the subsequent critical fall in arterial blood pressure was not always correlated with the point of reversion of the distensibility diagrams from the pattern of venoconstriction to the pattern of venodilation. Such variability was illustrated by an animal in which venoconstriction appeared early and then disappeared in spite of a continued hypoxic rise in arterial blood pressure, while in another animal the peak of arterial pressure had passed and the pressure had fallen to a critically low level at the point at which venoconstriction was most prominent.

Such evidence suggests differential sensitivity between the venomotor elements of the intestinal loop and other regulatory factors in the cardiovascular system. There has been no evidence as yet, however, to suggest that a primary venodilation might be associated with a generalized arteriolar constriction.

It is therefore concluded that these distensibility studies offer substantial support for the frequently entertained hypothesis that the venomotor system may play a significant role in cardiovascular regulation. Should continued efforts to standardize the quantitation of these distensibility patterns prove successful, studies of venous distensibility should prove a valuable tool for throwing light upon the function of the enigmatic venomotor system.

Summary

Venous distensibility diagrams have been recorded from an isolated but innervated intestinal loop by performing injections with a motor-driven syringe while registering simultaneous changes in venous pressure. Distensibility diagrams exhibiting the pattern of venoconstriction have been observed following pressor reflexes evoked by central vagal stimulation, carotid sinus hypotension, hypercapnia, and hypoxia. Dilation of the venous bed occurred with carotid sinus hypertension.

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