Comparison of Changes in Mesenteric Resistance Following Splanchnic Nerve Stimulation with Responses to Epinephrine and Norepinephrine

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This is a study of the characteristics of the splanchnic nerve supply to the mesenteric vascular circuit. The flow and pressure responses in the dog's superior mesenteric artery to splanchnic nerve stimulation and to intraarterial injections of epinephrine and norepinephrine, before and during various levels of adrenergic blockade, are analyzed. The results suggest that the splanchnic nerve contains only vasoconstrictor fibers, the mediator of which is probably norepinephrine, but that it also contains fibers which induce the release of epinephrine from the adrenal gland. No evidence for the presence of cholinergic dilator fibers was found.

Von BASCH\(^1\) claimed in 1873 that the inhibitory action on the gut which resulted from splanchnic nerve stimulation was dependent upon coincident vasoconstriction. No difference in the response was obtained with the right and the left splanchnic nerves.\(^2\) Bayliss and Starling\(^3\) reported that section of the splanchnic nerves resulted in vascular dilation in the intestine; they felt that the vasoconstriction obtained on stimulation was independent of the inhibitory action observed. In connection with experiments on hepatic blood flow, Burton-Opitz\(^4\) also reported a drop in blood flow from the intestine after stimulation of the greater splanchnic nerve. These results, in general, have been supported by other investigators.\(^5,6\) Richins\(^7\) reported that direct microscopic observations of the small vessels of the intestinal wall revealed a dilation after the administration of ergotoxine phosphate (0.5 ml. of a 1/1000 solution), thus suggesting the possibility of a tonic sympathetic vasoconstrictor activity.

An earlier paper from this laboratory\(^8\) compared the effects of intra-arterial sympathomimetic amines and of ischemia on the blood vessels of the canine mesenteric vascular bed with those of skeletal muscle, cutaneous and renal beds before and during adrenergic blockade. A recent paper\(^9\) reported the effects of sympathetic nerve stimulation before and during adrenergic blockade on the vasculature of canine skeletal muscle. The present paper reports results of a similar study on the mesentery, and compares the results with those obtained in skeletal muscle which was shown to be supplied by both adrenergic constrictor fibers and cholinergic dilator fibers by way of the lumbar sympathetic chain.

**METHODS**

Fourteen dogs, weighing 13.0 to 24.5 Kg. (average 18.5) were anesthetized with 30 mg./Kg. of sodium pentobarbital intravenously and received 40 mg./Kg. of Mepesulfate initially plus 20 mg./Kg. every half hour thereafter to prevent coagulation. Artificial respiration was given throughout each experiment. The rate of blood flow was measured with the electromagnetic flowmeter of Denison, Spencer and Green\(^10\) and recorded in the superior (cranial) mesenteric artery; lateral pressures in the mesenteric artery and the portal vein were measured with strain gages using technic similar to those described previously.\(^11\) The pressure drop across the flowmeter cannula and connecting tubing was 0.179 mm. Hg/ml./minute. The sensitivity of the flowmeter was 72.6 ml./min. for full scale deflection. Checks
of "zero" flow were made about every 30 minutes throughout each experiment; the mean rate of drift was 3.65 ml/min/hr. Initial and final calibrations of the flowmeter revealed no error in most experiments and an average change of ±6.75 per cent in three.

The greater splanchnic nerve was exposed, a ligature was placed around it immediately caudal to the point where the last ramus from the sympathetic chain joins the nerve and the nerve was severed just cephalad to the ligature in all but two experiments. The nerve was stimulated between the ligature and the point where the nerve passed into the crus, by means of a Grass stimulator, model S4A, using square waves with a frequency of 20 per second and a duration of 15 msec.

Solutions for injection were made up daily using sterile, pyrogen-free saline as a diluent. Commercial epinephrine and levarterenol were given in 3 μg doses in 0.3 ml volume within 10 seconds ± 2 seconds.

Responses to the adrenergic drugs and to splanchnic stimulation recorded before the blocking drug served as the control data for each experiment. These procedures were repeated after each of the logarithmically increasing doses (0.1, 0.3, 1, 3, 10, 30 and 100 mg.) of the adrenergic blocking drug, Lidar. In eleven experiments the left splanchnic nerve was used, in three the right splanchnic nerve.

**RESULTS**

**Control data.** Control blood flow in the 14 dogs ranged from 10.2 to 64.0 (av. 32.07) ml./min. Control aortic pressure ranged from 70 to 150 (average 105.2) mm. Hg; control portal pressure ranged from 9.2 to 27.0 (av. 13.9) mm. Hg. For all pressures zero pressure was referred to a point 6 cm. ventral to the skin over the spine.

Resistance in the whole mesenteric-portal circuit ("total") was computed in PRU

\[
\text{PRU} = \frac{\text{mesenteric artery pressure}}{\text{mesenteric artery flow}}
\]

from the ratio:

\[
\frac{\text{mesenteric artery pressure}}{\text{mesenteric artery flow}}
\]

The "gut" resistance was computed from the ratio:

\[
\frac{\text{mesenteric artery pressure} - \text{portal vein pressure}}{\text{mesenteric artery flow}}
\]

In all cases calculations were made of the "liver" resistance, i.e.,

\[
\frac{\text{portal vein pressure} - \text{vena cava pressure}}{\text{mesenteric artery flow}}
\]

The changes in the "liver" resistances closely paralleled those in the "gut" and "total" circuits, but since the vena cava pressure was assumed to be zero rather than actually measured, we have omitted "liver" resistances from the paper. Control resistance for the "total" circuit ranged from 1.0 to 12.25 (average 4.5) PRU; and control resistances for the "gut" were 1.44 to 10.8 (average 4.85) PRU.

In view of the relatively small flows measured in the mesenteric artery, India ink was injected into the metered portion of the mesenteric artery at the end of ten of the experiments. The portion of the gut which was stained varied from 3 to 8 feet in length (average 6.4 feet). This represented approximately two thirds of the small bowel, usually the more distal portion.

**Responses to Splanchnic Nerve Stimulation**

**Control Responses:** The averages and standard errors of all responses in all dogs to left splanchnic nerve stimulation are shown in figures 1 and 2. The responses to right splanchnic nerve stimulation in the "total" bed were similar in all details to those to left splanchnic nerve stimulation.

The voltage used to stimulate the splanchnic nerve was varied from 3 to 6 volts in an attempt to duplicate the response to 3.0 μg. of epinephrine. The response was always pure constriction. In every case, coincident with the onset of stimulation, flow declined rapidly and both aortic and portal pressures rose, indicating a primary vasoconstrictor response in both "total" and "gut" circuits. In most cases, approximately 15 seconds after the onset of stimulation, a secondary increase in both flow and aortic pressure occurred. Upon cessation of stimulation flow often increased further without much change or with a small decline in aortic pressure.* Resistances calculated at

* Since the aortic pressure was recorded downstream from the flowmeter the dip may have been due to the increased pressure loss caused by the increased flow past the frictional resistance in the flowmeter and connections.
the peaks of the increase in flow were always less than those for the initial response, indicating, either a decrease in the initial constriction or, in some cases, a secondary dilation.

Portal pressure, which had declined following the initial response, sometimes showed a small increase coincident with the post stimulus rise in flow. Aortic and portal pressures gradually returned to control values over a 3 to 5 minute period. Pulse pressure and the amplitude of the flow pulsations were increased and heart rate tended to slow during the secondary rise in aortic pressure.

Slow oscillations of flow and of aortic and to a lesser extent of portal pressure with a cycle length of 10 to 20 seconds often appeared during the stimulation and persisted for two or more minutes. When such oscillations were present, prior to stimulation, they were often accentuated during the stimulus. Since the peaks and valleys of flow and pressure coincided it could not be determined that these oscillations were initiated in the mesenteric bed; rather they appeared to be secondary to Traube-Hering waves in the aortic pressure.

Responses during Adrenergic and Cholinergic Blockade. (fig. 1 and 2). Ilidar, 0.1 mg., reduced the magnitude of the initial constrictor response to stimulation of the right but had no significant effect on the responses to stimulation of the left nerve. This dose did not unmask any further secondary dilator responses. Increasing doses of the blocking drug progressively diminished the magnitudes of the constrictor responses to both nerves until they were finally abolished at approximately 30 mg. of Ilidar. Additional significant secondary dilator responses began to appear after 1.0 mg. of Ilidar; these increased progressively as doses of the blocking drug were increased to a

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**Fig. 1.** Plot of average changes (11 animals) in peripheral resistance of "total" bed (mesenteric artery to inferior vena cava) following stimulation of left greater splanchnic nerve. (V = 4, D = 15 msec., F = 20/sec.)

Ordinate scale, per cent of control PRU units. Vertical bars, ± standard error of mean. Abscissa, prior dose of Ilidar in mg.

Upper solid line, average of all constrictor responses; lower solid line, average of all dilator responses; dashed line, average of all initial responses. Deviation of dashed line from upper solid line towards lower solid line indicates degree of "reversal", i.e., conversion of the initial response from one of constriction to one of dilation.

**Fig. 2.** Average changes (9 experiments) of peripheral resistance, in the "gut" bed (mesenteric artery to portal vein) following stimulation of left greater splanchnic nerve (V = 4, D = 15 msec., F = 20/sec.). Scales same as in figure 1.
maximum at 10 mg. The initial constrictor responses were converted to apparent dilatation only when 100 mg. of Ilidar was used. Atropine, in doses of 80 µgms. to 10 mg., did not abolish the primary dilator responses in the two experiments in which it was used.

Prior to adrenergic blockade, splanchnic stimulation induced a striking increase in both portal and aortic pressures which were diminished both in amplitude and duration but not abolished by the succeeding levels of blockade. Portal venous pressure rose about in proportion to arterial pressure, hence the change in "gut" resistance was about the same as "total" circuit resistance.

Epinephrine and Norepinephrine: The responses to epinephrine (EPI) and to norepinephrine (NOR), levarterenol, were similar to those published previously. EPI and especially NOR often induced cyclic oscillations of pressure and flow (Traube-Hering waves).

The amplitude of any existing Traube-Hering waves of both portal and aortic pressures was increased for approximately two minutes. Peaks and valleys in flow corresponded fairly closely to these fluctuations in pressures.

Figures 3 and 4 show the average and standard error of all responses in all dogs of the present series in response to 3.0 µg. of EPI and NOR at the various levels of adrenergic blockade used.

Comparison of Responses to Nerve Stimulation and EPI and NOR: In the control period, primary vasoconstriction was generally greatest for NOR, next for EPI, and least for splanchnic stimulation. As adrenergic blockade was increased to moderate levels the constrictor responses to EPI were abolished and replaced by marked vasodilation, whereas those responses to NOR and to splanchnic stimulation remained the same except for magnitude. With increase in dose of the blocking drug,
to around 30 to 100 mg. the constrictor responses to NOR and to splanchnic stimulation were abolished and converted to a weak apparent dilator response.

The principal differences between splanchnic stimulation and intra-arterial EPI and NOR were: (1) in the control state the initial vasoconstrictor response was of less magnitude with splanchnic stimulation; (2) in the control response and the first two levels of adrenergic blockade there was no significant secondary dilator response to splanchnic stimulation, but there were with EPI and NOR; (3) the magnitude of the apparent nerve-induced primary dilator response ("reversal") with large doses of the blocking drug was not as great as was that to EPI but was slightly greater than that to NOR and (4) the primary constrictor response was not replaced by a dilator one in all dogs as was the case with EPI and NOR. The response curves for splanchnic stimulation (figs. 1 and 2) closely resembled that of NOR (fig. 4) in both the magnitude of the response and the level of adrenergic blockade at which the various responses were altered.

Neither with nerve stimulation nor with the drugs used was there any change in flow which could be attributed to peristalsis.

**DISCUSSION**

The control response obtained in the mesentery with splanchnic stimulation closely resembled the type 1 response obtained in skeletal muscle by Youmans, Green and Denison. This primary vasoconstrictor response was observed in 100 per cent of the control responses in the mesentery, but in only 67 per cent of the control responses in skeletal muscle. The response was of shorter duration in the mesentery than in skeletal muscle. During progressive adrenergic blockade in both skeletal muscle and in the mesentery apparent dilator responses developed. Atropine abolished the dilator responses in skeletal muscle, but had no effect on those in the mesentery.

The responses to NOR in both the control state and during adrenergic blockade in the mesentery were quite similar to those in skeletal muscle, and comparable doses of the blocking drug were required to abolish the constrictor responses in both the mesentery and skeletal muscle.

A somewhat larger dose of the adrenergic blocking drug was required to "reverse" the response to EPI (conversion to primary vasodilation) in the mesentery than in skeletal muscle; but the dilator responses were about equally resistant to blockade.

In the mesentery, significant apparent dilator responses to nerve stimulation began to appear at the same level of adrenergic blockade that EPI reversal began to be noted, but the primary constrictor responses were not completely abolished until a dose of Lidar (30 mg.) was reached which was necessary to abolish the constrictor responses to NOR.

The increase in flow and the apparent dilator responses seen during the period of nerve stimulation were never seen without an accompanying rise in arterial pressure. These apparent dilator responses, therefore, may not have been actual reductions of constrictor tone, but may have been due to a mechanical dilation produced by the rise in arterial pressure.

The rise in arterial pressure and apparent dilation in the control state and after small doses of adrenergic blocking drug occurred only after a latent period of about 15 seconds, sufficient to have allowed EPI, released from the adrenal gland by the nerve stimulation, to have reached the mesenteric circuit by recirculation. As the dose of the blocking drug was increased this latent period for the apparent dilator response became progressively shortened almost to "zero" but was never seen without an accompanying rise in aortic pressure and never preceded the rise in aortic pressure. Despite abolishing the constrictor responses to intra-arterial injections of 3 μg. of each of EPI and NOR, and the constrictor responses to nerve stimulation, and despite abolishing the pressor responses to EPI and NOR, 30 to 100 mg. of the blocking drug failed to abolish the pressor responses and the bradycardia and increased pulse pressure responses to nerve stimulation.

**CONCLUSIONS**

In view of the fact that the resistance to blockade of the constrictor responses to nerve
stimulation corresponded more closely to NOR than to EPI, it would appear that the mediator of the neurogenically-induced vasoconstriction is more likely NOR than EPI.

Since atropine was without effect on the apparent mesenteric dilator responses to nerve stimulation, whereas it caused complete abolition of the dilator responses in skeletal muscle, the presence of cholinergic dilator fibers in the splanchnic nerves, were not demonstrable.

The apparent dilator response to nerve stimulation during the action of fairly large doses of adrenergic blocking drugs seems to be explained best by (1) a dilator effect of EPI released from the adrenal gland and recirculating through the mesenteric bed and (2) by the rise in arterial pressure induced by the effects of vasoconstrictor impulses and/or EPI resulting from splanchnic nerve stimulation and affecting portions of the visceral circulation and, perhaps, other portions of the body which had been incompletely blocked by the adrenergic blocking drug.* From careful examination of all of the records, it appears that the most likely explanation for the increase in flow (apparent dilation) in response to nerve stimulation after administration of larger doses of the blocking drugs was the mechanical effect of rise in aortic pressure.12

The respective resistances in the small intestine and in the liver (assuming the vena cava pressure to be "zero") did not vary significantly from that of the bed as a whole, or from each other, as a result of splanchnic stimulation. This would seem to indicate that the two beds are both about equally innervated by the splanchnic nerves.

**Summary**

Blood flow in the cranial (superior) mesenteric artery was measured with an electromagnetic flowmeter during splanchnic stimulation and intra-arterial injections of 3μg. of epinephrine (EPI) and norepinephrine (NOR).

Flow was recorded during the control state and after the establishment of various levels of adrenergic blockade which was created by the intra-arterial injections of logarithmically increasing doses of Lidar, ranging from 0.1 to 100 mg.

During the control state, splanchnic stimulation caused a vasoconstriction which was accompanied by an increase in the aortic and portal pressures, recorded by strain gages in the cranial mesenteric artery and portal vein. Injection of 3.0 μg each of EPI and NOR also produced a vasoconstriction of this vascular bed.

During adrenergic blockade, there was a progressive diminution of the primary vasoconstrictor responses to nerve stimulation until it was completely abolished. At the same time, there appeared a secondary apparent dilator response which was never completely abolished. With the largest dose of blocking drug, there was also a primary apparent dilator response which was neither prevented nor abolished by atropine. These apparent dilator responses have been explained on the basis of a striking increase in aortic pressure which appeared during splanchnic stimulation and/or the release and recirculation of epinephrine from the adrenal gland.

The fact that the levels of adrenergic blockade at which alterations were made in the responses to splanchnic stimulation were similar to those at which alterations also appeared in the responses to levarterenol, suggests that the mediator of the neurogenic response more closely resembles levarterenol than epinephrine.

The respective resistances in the small intestine and in the liver did not vary significantly from that of the bed as a whole or from each other, as a result of splanchnic stimulation. This would seem to indicate that the two beds are both about equally innervated by the splanchnic nerves.

**Acknowledgement**

The Mesesulfate, formerly called Treburon, was supplied through the courtesy of Hoffman-LaRoche, Inc., Nutley, N. J.

The epinephrine was Adrenalin Chloride 1:1000.
Le fluxo sanguine in le arteria mesenteric cranial (superior) esseva mesurate per medio de un fluxometro electromagnetic durante stimulation splanchnic e post injectiones intra-arterial de 3 µg de epinephrina e de norepinephrina.

Le fluxo esseva registrate durante le stato de controlo e post le establimento de varie nivellos de blocage adrenergic create per le injection intra-arterial de logarithmicamente augmentate doses de Ilidar ab 0,1 a 100 mg.

Durante le stato de controlo, stimulation splanchnic causava un vasoconstriction que esseva accompagnate per un augmento del pressiones aortic e portal, registrabile in le arteria mesenteric cranial e le vena portal. Le injection de 3 µg de epinephrina e de 3 µg de norepinephrina etiam produceva un vasoconstriction de iste lecto vascular.

Durante le blocage adrenergic, il occurreva un progressive diminution del primari responsa vasoconstrictor a stimulation nervose usque a lor disparition complete. Simultaneamente il appareva secundari responsa dilatator apparente che nunquam dispareva completemente. Con le plus grande doses del droga blocante, il etiam occurreva un primari responsa dilatator apparente che esseva ni prevenite ni abolite per atropina. Iste apparente responsa dilatator ha essite explicate super le base de un frappante augmento del pression aortic che appareva durante le stimulation splanchnic e/o le relaxation e recirculation de epinephrina ab le glandula adrenal.

Le facto que le nivellos del blocage adrenergic al quales alterationes occurreva in le responsas al stimulation splanchnic esseva simile a nivellos al quales alterationes occurreva etiam in le responsas a levarterenol, pare indicar che le mediator del responsa neurogenic es plus affin a levarterenol que a epinephrina.
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