Portal Pressure Responses to Catecholamines (36388)

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(Introduced by Samuel B. Formal)

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The effects of the endogenous catecholamines, norepinephrine (NE) and epinephrine (E), upon portal venous pressure remain controversial. From his studies in anesthetized dogs Green *et al.* (1) concluded that the elevation of portal pressure accompanying intraportal venous or intrahepatic arterial injections of these amines was secondary to activation of afferent and efferent venous sphincter mechanisms.

From his study in anesthetized cats Ross and Kurrasch (2) concluded that the hepatic sinusoidal sphincters were insensitive to physiological amounts of catecholamines. This study demonstrated the presence of beta adrenergic receptor sites in hepatic vasculature and it was concluded that the alterations in portal venous flow (and presumably pressure) were more relevant to alterations in blood flow through the spleen and gut than upon vascular changes within the liver. In an earlier study Ross (3) observed the effects of the catecholamines upon feline splenic blood flow and concluded that adrenergic splenic emptying was mediated through alpha receptor site stimulation. He cited the work of Green, Ottis, and Kitchen (4) as confirmatory in the dog. Actually, the latter investigators concluded that splenic emptying might be mediated by epinephrine rather than norepinephrine, which appeared to control splenic arterial inflow. Neither norepinephrine nor isoproterenol were significant stimulants of splenic emptying. In a previous report (5), concerning splanchnic hemodynamic events during catecholamine injections in dogs, we were impressed with the response exhibited by portal venous pressure to intravenous epinephrine, 1.0 μg kg^{-1}. This response, as Green, Ottis, and Kitchen observed, exceeded that seen with similar doses of either norepinephrine or isoproterenol. The present study was designed to measure, through a comparison of multiple doses and routes of injection, the effects of the endogenous catecholamines upon portal venous pressure in anesthetized dogs. The effects of splenectomy, as well as alpha and beta adrenergic receptor blockade, were included in order to further delineate the mechanisms underlying the portal pressure responses to catecholamines.

Materials and Methods.[1] Five mongrel dogs of either sex, with an average weight of 20 kg, were anesthetized with sodium pentobarbital, 30 mg kg^{-1}, iv, and the abdomen was opened through a midline incision. PE 160 catheters (Clay Adams, New York, NY) were placed in the left femoral artery and vein for systemic arterial and central venous pressure measurements. Portal venous pressure was measured with a similar catheter inserted into a branch of the superior mesenteric vein and advanced into the portal vein. The catheters were connected to pressure transducers (Statham, Hato Rey, Puerto Rico), calibrated with a mercury manometer. A similar catheter was inserted in the inferior vena cava via the right femoral vein for intravenous drug administration. The gastroduodenal artery was isolated and cannulated with a PE 20 catheter (Clay Adams). The

[1] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

TABLE I. Effects of Route of Injection of Catecholamine (0.1 μg kg^{-1}) on Portal, Arterial, and Vena Caval Pressures.[a]

	Route of injection					
	Before splenectomy			After splenectomy		
Pressure	HA	PV	VC	HA	PV	VC
			Norepinephrine			
PP	1.3[b]	2.4[b]	0.6	0.7	2.2[b]	−0.4
AP	6	10	20[c]	6	13	21[c]
VP	0.3	0.3	−0.2	0.1	0.2	0.5
			Epinephrine			
PP	1.5[b]	2.0[b]	1.8[b]	1.3[b]	2.2[b]	0.1
AP	4	5	−8	8	13	12
VP	0.0	0.3	0.2	0.5	0.5	0.2

[a] The effects of a small dose (0.1 μg kg^{-1}) of norepinephrine and epinephrine upon portal pressure (PP), arterial pressure (AP), and vena caval pressure (VP) are tabulated in terms of the change in mean pressure from control. The three routes of injection are the hepatic artery (HA), portal vein (PV), and inferior vena cava (VC), before and after splenectomy.

[b] Increase to a value significantly above control: $p < .05$; [c] $p < .01$.

catheter was advanced to the hepatic artery for intra-arterial drug administration. In addition to occluding the gastroduodenal artery, ligation of the right gastric artery made certain that subsequent drug injections went directly into the hepatic artery and liver. Following a 30 min postoperative interval, norepinephrine bitartrate (Levophed, Winthrop Laboratories, New York, NY), and epinephrine hydrochloride (Gold Leaf Pharmacal, Englewood, NJ) were injected sequentially into the hepatic artery, portal vein, and vena cava. Drugs were administered in doses of 0.1 and 1.0 μg kg^{-1} (base). Following control measurements of pressure in the portal vein, aorta, and vena cava the responses to norepinephrine and epinephrine were recorded on a polygraph (Sanborn, Waltham, MA). The animal was then splenectomized and the injection series was repeated in an identical manner. Before and after each series of drug injections the pressure transducers were opened to atmosphere for zero pressure determinations and the catheters were flushed with heparinized saline. The results were calculated in terms of the mean ± the standard error and their statistical significance assessed with the t test for paired data (6).

In a second set of experiments two animals were prepared in a similar manner except that the arterial injection catheter was placed in the left gastric artery and advanced to the splenic artery. The short gastric and the left gastroepiploic arteries were divided and ligated. During drug injections the hepatic artery was temporarily occluded hydraulically (7) to cause the entire dose to enter the splenic artery and spleen. Pressure responses to both doses of epinephrine were recorded before and after alpha adrenergic blockade with phenoxybenzamine (Dibenzyline, Smith, Kline, and French, Philadelphia, PA), 1.5 mg kg^{-1}, iv. The injection series was also performed before and following beta adrenergic blockade with propranolol (Inderal, Ayerst Laboratories, New York, NY), 0.5 mg kg^{-1}, iv.

Results. Control values for central venous, portal, and arterial pressures were 2.0 ± 0.6 (SE), 4.4 ± 0.3, and 143 ± 7 mm Hg, respectively. Injections of either dose of norepinephrine and epinephrine into either of the three routes caused a significant ($p <$ .05) increase in portal pressure except when norepinephrine, 0.1 μg kg^{-1}, was injected into the vena cava (Tables I and II). Both catecholamines, at a dose of 0.1 μg kg^{-1}, produced a maximum response ($p < .02$) when injected directly into the portal vein: 4.6 ± 0.2 to 7.0 ± 0.4 (NE) and 5.1 ± 0.4 to 7.1 ± 0.4 (E) mm Hg (Table I). The larger dose of both norepinephrine and epinephrine produced a maximum increase in portal pressure ($p < .001$) when injected into the vena cava: 5.2 ± 0.5 to 9.9 ± 0.8 (NE) and 4.9 ± 0.3 to 13.3 ± 0.7 (E) mm Hg (Table II).

Following splenectomy, except for epinephrine injections into the hepatic artery, administration of the small dose of either catecholamine into the hepatic artery or vena cava did not cause a significant increase in portal pressure (Table I). Either drug injected into the portal vein caused responses nearly identical with those prior to splenectomy: 4.8 ± 0.6 to 7.0 ± 0.6 (NE) and 5.0 ± 0.6

TABLE II. Effects of Route of Injection of Catecholamine (1.0 μg kg^{-1}) on Portal, Arterial, and Vena Caval Pressures.[a]

	Route of injection					
	Before splenectomy			After splenectomy		
Pressure	HA	PV	VC	HA	PV	VC
	Norepinephrine					
PP	1.8[b]	4.4[b]	4.7[bc]	2.0[b]	3.3[b]	3.1[b]
AP	17[b]	19[c]	46[c]	13[b]	15[c]	49[c]
VP	0.0	0.4	1.8	0.5	0.0	1.8
	Epinephrine					
PP	4.7[b]	5.7[b]	8.4[bc]	2.7[b]	3.6[b]	3.4[b]
AP	6	11[b]	34[c]	12	11[b]	36[c]
VP	0.6	0.3	2.3[b]	1.0	0.3	2.0[b]

[a] The effects of a large dose (1.0 μg kg^{-1}) of norepinephrine and epinephrine upon portal pressure (PP), arterial pressure (AP), and vena caval pressure (VP) are tabulated in terms of the change in mean pressure from control. The three routes of injection are the hepatic artery (HA), portal vein (PV), and inferior vena cava (VC), before and after splenectomy.

[b] Increase to a value significantly above control: $p < .05$; [c] $p < .001$.

to 7.2 ± 0.9 (E) mm Hg. Following splenectomy the previously observed increases in portal pressure in response to the large dose of both drugs injected into all routes were attenuated, with one exception: the large dose of norepinephrine, injected into the hepatic artery, caused a response similar to that seen prior to splenectomy (Table II). Both before and after splenectomy the only significant alteration in arterial pressure induced by the low dose of catecholamine attended norepinephrine injection into the vena cava (Table I). The low dose of catecholamine, did not alter central venous pressure under any circumstances tested. The large dose of norepinephrine increased arterial pressure through all routes of injection; the intravenous route provided for the largest response. Epinephrine responses were similar except that the intrahepatic injections did not cause a significant change in arterial pressure. Each catecholamine produced a significant rise in central venous pressure only when administered intravenously. This pattern of arterial and central venous pressure responses to the large dose of catecholamine was essentially unchanged by splenectomy (Table II).

In dogs prepared with a splenic artery catheter, injections of 0.1 and 1.0 μg kg^{-1} of epinephrine, into the portal vein, vena cava, and splenic artery all increased portal pressure (Fig. 1). The maximal response occurred when the large dose of epinephrine was injected into the splenic artery. Phenoxybenzamine attenuated the response of portal pressure to small doses of epinephrine, delivered through the portal vein or vena cava. The most striking change was the marked attenuation in portal pressure response to epinephrine injected through the splenic artery, subsequent to alpha adrenergic blockade. Phenoxybenzamine also attenuated the responses to the large dose of epinephrine delivered through each of the three routes. Beta adrenergic blockade appeared to enhance the portal pressure response to the large dose of epinephrine injected into the portal vein and vena cava (Fig. 2).

Discussion. Our results indicate that the effects of norepinephrine and epinephrine upon canine portal pressure are secondary to contraction of the spleen as well as constriction of portal venules. These data support the findings of both Green and Ross and coworkers. Green *et al.* (1) concluded, from canine experiments, that catecholamine-induced changes in portal pressure and flow were due to intrahepatic afferent and efferent venous sphincter contraction. On the other hand, Ross and Kurrash (2) reported that changes in portal blood flow, in cats, were due to alterations in intestinal and splenic outflow rather than vascular changes within the liver. In an earlier study, in dogs, Grindlay, Herrick, and Mann (8) observed that intravenous epinephrine caused a fall in portal blood flow despite an increase in splenic venous flow. They further reported that, following splenectomy, this decrease in portal flow was greater than that seen before splenectomy. These observations suggest that epinephrine's action on the mesenteric circulation is to decrease blood flow to the gut and hence venous return to the liver. Hepatic ischemia may be compensated by the simul-

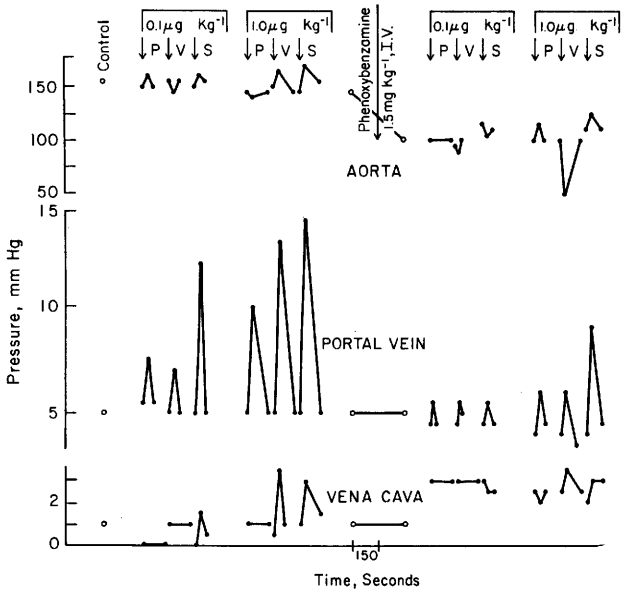

FIG. 1. The effects of 0.1 and 1.0 μg kg^{-1} of epinephrine upon arterial pressure, portal pressure, and central venous pressure were measured during drug injections into the portal vein, vena cava, and splenic artery both before and after alpha adrenergic blockade with phenoxybenzamine.

taneous mobilization of blood from the spleen.

The effects of epinephrine upon mesenteric and splenic circulations therefore achieve a net decrease in portal venous flow. The accompanying rise in portal pressure can be explained if epinephrine also acts simultaneously as an intrahepatic vasoconstrictor. This hypothesis is consistent with our finding that splenectomy attenuated portal pressure responses to a small dose of the catecholamine injected into the hepatic artery or vena cava, but not the portal vein. These observations are more obvious when a large dose of the catecholamine is injected through any route. Even though portal pressure responses are attenuated by splenectomy, pressure still rises significantly, indicating a mechanism other than mobilization of blood from the spleen. Since this effect is least following intrahepatic injections the locus of action may well be on the portal side, presumably at the level of the portal venules.

Another study by Ross (3) showed that adrenergic splenic emptying in the cat is the result of alpha receptor stimulation. He reported that his findings confirmed a previous study by Green, Ottis, and Kitchen (4) who, in fact, concluded that the emptying mechanism of the spleen was not alpha adrenergic receptor mediated since norepinephrine was minimally effective in evoking the response. The latter response was maximal following epinephrine injections. Although this suggested a beta adrenergic mechanism the author cited his previous studies with isoproterenol which failed to support this possibility. Our results reveal that alpha adrenergic blockade abolishes splenic contraction, as evidenced by portal pressure responses, while beta adrenergic blockade enhances this effect. These findings are seen through all routes of injection, except for epinephrine (1.0 μg kg^{-1}) injected into the splenic artery. This rise in portal pressure in the face of alpha blockade is presumably due to the availability of some unblocked receptors, since the response is greatly attenuated from that seen prior to alpha blockade.

Our results also show that epinephrine has a much greater effect on portal pressure than norepinephrine in near equimolar doses. Ahlquist *et al.* (9) and Davis, Gamble, and Withrington (10) have indicated that canine

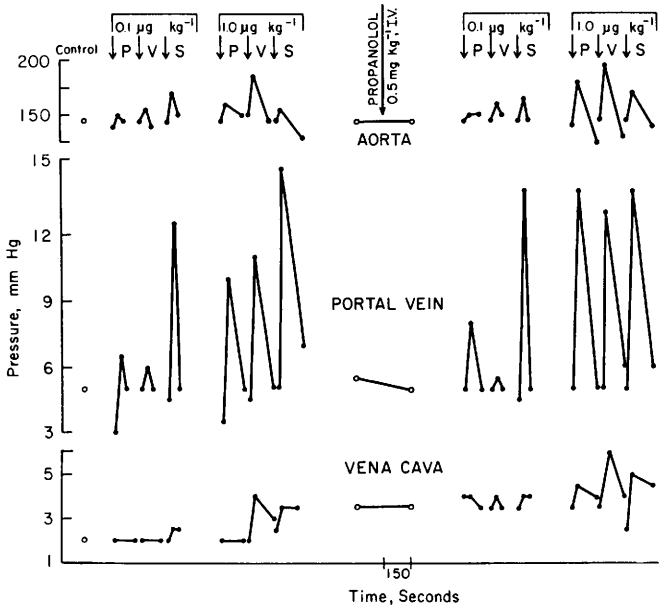

FIG. 2. The effects of 0.1 and 1.0 μg kg^{-1} of epinephrine upon portal pressure were recorded during drug injections into the portal vein, vena cava, and splenic artery both before and after beta adrenergic blockade with propranolol.

splenic contraction is more responsive to intra-arterial injections of epinephrine than norepinephrine, while Bickerton (11) showed that, in the order of relative potency, epinephrine exceeded both norepinephrine and isoproterenol in contracting the cat spleen *in vitro*. Furthermore, Geumei and Bashour (12) reported that there are beta receptors in the portal vein which, when activated, cause vascular smooth muscle contraction. Therefore, epinephrine should induce a greater increase in portal pressure than norepinephrine, since epinephrine has a greater effect on splenic contraction and presumably a greater affinity for beta adrenergic receptors present in the portal vein.

Summary. The effects of norepinephrine and epinephrine (0.1 and 1.0 μg kg^{-1}) upon portal, arterial, and central venous pressures were measured during drug injections into the portal vein, vena cava, and hepatic artery of anesthetized dogs. The small dose of norepinephrine and epinephrine evoked maximal increases in portal pressure when injected into the portal vein. Except for the responses to portal vein injections, which remained unchanged, these effects were attenuated by splenectomy. The large dose of epinephrine brought about portal pressure increases by all three routes of injection; the maximal change occurred following vena caval injection. These effects were attenuated by splenectomy and by alpha adrenergic blockade. Beta adrenergic blockade potentiated specific portal pressure responses to epinephrine. Norepinephrine elicited the same directional responses as epinephrine but they were lesser in magnitude. The data suggest that portal pressure responses to injected catecholamines are secondary to splenic contraction as well as direct effects on portal venules. The emptying mechanism of the canine spleen appears to be mediated by alpha adrenergic mechanisms.

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