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EFFECTS OF ENDOTOXIN ON THE HEMODYNAMICS OF THE STOMACH *

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Endotoxin induces many profound vascular effects, including venous pooling, changes in resistance to blood flow in many organs, and circulatory collapse leading to death. Prominent among the early vascular effects of endotoxin is the rapid development of hepatic and intestinal congestion (2–4). One apparent mechanism of splanchnic blood pooling in endotoxin shock is hepatic venoconstriction. Liver engorgement subsides with time, but intestinal venous congestion continues, suggesting some persistent effects of endotoxin, either directly on the blood vessels of the gut, or indirectly on these vessels through nervous or humoral mechanisms (2, 5, 6).

The gastric circulation, like the intestinal, is in direct continuity with the portal vein and might be expected to exhibit responses to endotoxin similar to those of the gut vasculature. In order to differentiate the direct hemodynamic effects of endotoxin from indirect neurohumoral influences on the circulation of the stomach, the gastric vasculature was studied both in continuity with the general circulation and as an isolated vascular bed.

METHODS

Thirty mongrel dogs of both sexes, weighing 8 to 20 kg, were studied acutely. The animals were anesthetized with pentobarbital sodium (35 mg per kg), and heparin sodium (5 mg per kg) was administered intravenously. Artificial respiration was administered by a tracheal cannula when required. The stomach and its major blood vessels were exposed by a left subcostal incision. Splenectomy was routinely performed, and the splenic and hepatic arteries were ligated near their origins.

The right gastric and right gastroepiploic arteries and veins, the multiple branches of the left gastroepiploic artery and vein, and both ends of the stomach were also ligated. Blood flow to the stomach was thereby maintained through the left gastric artery by a Sigmamotor pump interposed between the right femoral artery and the celiac axis. Particular care was exercised to avoid undue trauma to the periarterial nerves while inserting the cannula. Gastric blood flow was held constant for each dog. Mean flow for 21 dogs was 39 ± 4 (SD) ml per minute. Gastric artery pressure varied considerably more than flow in this group of animals and averaged 126 ± 40 mm Hg. This procedure will be referred to as "single circulation" studies, since the blood perfusing the stomach returned to the general circulation.

In 9 other animals the venous drainage from the stomach was shunted into a pump-oxygenator (Kay-Cross disc oxygenator, Pemco, Inc.) primed with the blood of a donor animal before being returned to the left gastric artery. This constituted a vascular circuit independent of the general circulation. The results from these 9 animals will be considered as "dual circulation" studies. The isolation of the gastric from the general circulation was demonstrated by comparing the blood volumes collected from the coronary vein with the minute volume perfused by the pump. In addition, India ink was not observed beyond the confines of the stomach after injection into the perfusion system.

Mean pressures were obtained from the coronary vein, perfusion tubing proximal to the left gastric artery, and left common carotid artery by a strain gauge connected to a Sanborn Twin-Viso recorder. A 20-minute stabilization period followed the start of gastric artery perfusion. The next 30 minutes comprised the experimental observation period. *Salmonella typhosa* 0901 endotoxin (0.6 mg per kg Bacto Lipopolysaccharide, Difco Laboratories) was injected in one bolus into either the perfusion system proximal to the left gastric artery or into a femoral vein at the onset of the observation period.

The division of experiments into single and dual circulation studies is outlined in Table I.

Single circulation (21 animals). In 10 dogs pressures were monitored from 20 minutes before to 30 minutes after injecting endotoxin into the left gastric artery. In 5 additional animals endotoxin was injected into a fe-

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TABLE I

Experimental design

Experiments	Number
Single circulation	
Endotoxin in gastric artery	10
Endotoxin in femoral vein	5
Endotoxin and phentolamine in gastric artery	3
Control (no endotoxin)	3
Total	21
Dual circulation	
Endotoxin in gastric circulation	3
Endotoxin in general circulation	3
Control (no endotoxin)	3
Total	9

moral vein, and pressures were recorded as above. Endotoxin was injected into the left gastric artery in 3 other dogs while phentolamine methanesulfonate was being infused simultaneously into the left gastric artery in doses which did not alter systemic arterial pressure (1.5 to 3.0 μg per minute). In the remaining 3 animals no endotoxin was administered; the results from these 3 animals served as controls.

Dual circulation (9 animals). In 3 animals endotoxin was administered into the closed circuit gastric circulation. Endotoxin was injected into the femoral vein and never reached the stomach circulation in 3 other dogs. The remaining 3 animals received no endotoxin; these dogs served as controls for the dual circulation experiments.

RESULTS

Single circulation. The injection of endotoxin into the left gastric artery of 10 dogs caused a rise in coronary venous pressures, followed within 2 minutes by an increase in left gastric artery pressures and a decrease in common carotid artery pressures. Peak venous pressures were reached approximately 5 minutes after injection and exceeded preinjection levels by more than 20 mm Hg. Venous pressures then returned to initial values over the subsequent 15 minutes. Left gastric artery pressures continued to rise to maximal values for 10 minutes after injection and then decreased, but were still nearly twice preinjection values at 30 minutes. Compared with preinjection levels, the average gastric vascular pressure had increased by 116 mm Hg at 10 minutes and 82 mm Hg at 30 minutes after endotoxin. Systemic pressures reached a nadir 10 minutes after injection when they averaged 24% below starting pressures. Subsequently, average carotid arterial pressure returned to 13% below initial pressure at 30 minutes. The results for these 10 animals appear in Table II.

Gastric vascular pressures responded in a qualitatively similar fashion when endotoxin was injected systemically into the femoral vein of 5 dogs (Table II). The average gastric artery pressure increased 46 and 17 mm Hg above initial values after 10 and 30 minutes, respectively. Average carotid arterial pressures in this group of 5 dogs were nearly identical with those pressures observed in the 10 animals previously cited at 10 and 30 minutes after injecting endotoxin. Mean coronary venous pressure rose 40% above the preinjection value at 5 minutes, and at 30 minutes was 40% below the initial level. Systemic arterial pressures were 24 and 22% below control at 10 and 30 minutes, respectively.

In 3 animals in whose perfusion system a local phentolamine infusion was maintained after local

TABLE II

Comparison of locally and systemically administered endotoxin on pressures in the left common carotid artery, left gastric artery, and coronary vein over a 30-minute observation period *

	Time (*min*)						
	0	5	10	15	20	25	30
Local administration of endotoxin (10 dogs)							
Left gastric artery pressure							
Mean	104	174	220	206	196	186	186
S.E.M.	28	19	20	18	17	16	16
Left common carotid artery pressure							
Mean	140	111	107	116	117	122	122
S.E.M.	8	12	12	12	10	10	12
Coronary vein pressure							
Mean	10	30	21	14	11	10	9
S.E.M.	1	2	2	1	1	1	1
Systemic administration of endotoxin (5 dogs)							
Left gastric artery pressure							
Mean	167	183	213	208	195	188	184
S.E.M.	18	17	21	14	19	23	22
Left common carotid artery pressure							
Mean	138	105	105	112	110	113	108
S.E.M.	9	20	21	17	15	18	18
Coronary vein pressure							
Mean	15	21	16	13	11	11	9
S.E.M.	1	1	1	1	1	1	1

* Pressures are expressed in mm Hg. S.E.M. signifies one standard error of the mean.

TABLE III

*Pressure changes in the left gastric artery, the coronary vein, and left common carotid artery in 3 control animals and 3 animals given endotoxin while phentolamine was infused**

Dog	Flow	Pressure (*mm Hg*)																				
		Left gastric artery							Coronary vein							Carotid artery						
no.	*ml/min*	*mins*: 0	5	10	15	20	25	30	0	5	10	15	20	25	30	0	5	10	15	20	25	30
		Control																				
11	41	126	148	140	140	146	152	156	15	20	22	22	23	23	19	144	160	160	160	160	156	154
12	34	140	130	120	124	128	124	124	15	17	17	18	17	16	16	132	136	144	144	144	132	136
13	34	140	140	126	110	120	110	128	17	16	16	16	20	22	23	144	148	138	144	144	144	140
Mean	36	135	139	129	125	131	129	136	16	18	18	19	20	20	19	140	148	147	149	149	144	143
		Phentolamine and endotoxin																				
14	35	128	142	140	124	108	116	120	12	18	18	9	7	5	5	126	116	104	100	98	92	94
15	28	86	96	108	132	140	150		8	12	10	10	10	10		124	126	120	120	112	112	
16	41	160	144	176	184	152			19	23	23	15	17			136	116	138	130	108		
Mean	35	125	127	141	147	133	133	120	16	21	17	11	11	8	5	129	119	121	117	106	102	94

* The gastric circulation was in continuity with the systemic in both series.

injection of endotoxin, the gastric arterial pressure increased 16 mm Hg, and systemic pressure decreased 8 mm Hg 10 minutes after injecting endotoxin (Table III).

Dual circulation. From the onset of infusion in the dual circulation experiments, it was apparent that the gastric vascular bed was behaving in a manner different from that observed in single circulation studies. Twenty minutes after the pump-oxygenator was started, gastric arterial pressures were considerably higher than the pressures obtained in the single circulation experiments. Furthermore, the gastric artery pressures continued to rise. In the control animals with dual circulations, the rise was 63% in 30 minutes. For this reason gastric arterial pressures following injection of endotoxin by either the local or systemic route of administration were compared in the single and dual circulation experiments as a change from the control animals for each series. In the 9 animals comprising this series of isolated gastric circulation studies, venous pressure was atmospheric throughout. These results appear in Table IV.

Left gastric and common carotid arterial pressures remained unchanged in 3 dogs of this group when endotoxin was injected into the left gastric artery and did not reach the systemic circulation. Ten minutes after injection, arterial pressure in the stomach was 33% lower than in the 3 control dogs of the dual circulation study.

In the 3 dogs in which endotoxin did not reach the gastric circulation after injection into a femoral vein, left gastric artery pressure increased by 11%, and systemic arterial pressure decreased by 17% ten minutes after the administration. Compared with the control dogs, gastric artery pressure was 14% less at 10 minutes and 26% less at 30 minutes.

DISCUSSION

The results of this investigation indicate that endotoxin profoundly increases resistance to blood flow in the gastric vascular bed of the dog. Within 10 minutes after the local injection of endotoxin into a gastric artery, vascular resistance doubled while systemic arterial pressure declined 24%.

Hemodynamic changes similar to these have been described in the lung and forelimb (7, 8); opposite effects of endotoxin have been observed in the coronary circulation (9). The mechanism of these vascular alterations is not fully under-

TABLE IV

Contrast between local and systemic administration of endotoxin on gastric artery pressures in single and dual circulation experiments

	Per cent change from control		
	10 minutes	20 minutes	30 minutes
Single circulation			
Local endotoxin	+114	+103	+97
Systemic endotoxin	+35	+24	+10
Dual circulation			
Local endotoxin	−33	−48	−63
Systemic endotoxin	−14	−20	−26

stood, although many mediators have been suggested, including endotoxin itself, catecholamines, serotonin, histamine, the sympathetic nervous system, and others (2, 5, 6). In addition, there is evidence that endotoxin alters the vascular responsiveness to vasoactive substances (10).

Within the limits of the experimental conditions described herein, several factors might have been responsible for the rapid increase in gastric vascular resistance observed following endotoxin administration in the animals with a single circulation. The rise in venous pressure, presumably due to hepatic venous congestion, might have elevated resistance in the stomach. A second possibility is that endotoxin could have acted directly on the gastric vasculature to constrict the bed or to release a local humoral vasoconstrictor. Alternatively, endotoxin could have activated distant nervous or chemical mechanisms which mediated the increase in gastric vascular resistance.

It appears unlikely that the elevation of venous pressure per se was a major factor in raising arterial pressure in the stomach. Although venous pressure rapidly tripled after the injection of endotoxin, the magnitude of the increase was only 20 mm Hg and reached its peak far in advance of maximal arterial pressure. Furthermore, the latter pressure remained elevated long after venous pressure had returned to normal. A venoarteriolar reflex exerts a nearly immediate effect rather than the sequence observed here (11). In preliminary investigations in this laboratory, a threefold rise in coronary venous pressure was not accompanied by increase in gastric arterial pressure of the magnitude observed after endotoxin.

When endotoxin was restricted to the isolated gastric circulation, resistance did not increase. Ten minutes after injecting endotoxin, resistance was essentially identical to preinjection values and was considerably less than the resistance observed in the 3 control dogs with dual circulations. This suggests that endotoxin had neither direct vasoconstrictor properties in the stomach, nor did it release any local vasopressor material.

The increase in gastric vascular resistance, therefore, must have been secondary to a distant mechanism of endotoxin, whether nervous or humoral. If the effects of endotoxin on the stomach were mediated primarily by the sympathetic nervous system, the separation of the stomach vasculature from the general circulation should not have blocked the response of gastric arterial pressure to endotoxin limited to the systemic vessels. Ten minutes after the systemic injection of endotoxin in the dual circulation preparation, gastric arterial pressure was only 11% higher than preinjection pressure, and was lower than control animal pressures despite systemic hypotension.

Additional evidence for a remote mechanism of endotoxin action on the gastric vasculature is suggested from the single circulation experiments (Table II). In these experiments the gastric vascular pressure responses following systemic intravenous and local intra-arterial endotoxin injections were qualitatively similar. Their quantitative differences may be explained by the difference in the mode of administration. The less marked response after systemic injection could be expected because of the initially lower endotoxin concentration in the gastric circulation, which remained lower as other organs rapidly cleared the endotoxin from the general circulation (12). Half the circulating endotoxin is removed from the blood in the first ten minutes following femoral vein injection (12). Furthermore, there is ample evidence indicating that blood vessels exposed to endotoxin demonstrate an altered reactivity to vasoactive substances including catecholamines (10, 13).

It therefore appears that endotoxin elicits a release of humoral vasoactive substances at sites other than the stomach. The ability of phentolamine to block the gastric vasoconstrictor effects of endotoxin in the intact animal suggests the presence of pressor agents. Endotoxin has been shown to induce the release of histamine, serotonin, and catecholamines (6, 14, 15). Work in this laboratory has indicated that histamine is a vasodilator of the stomach vessels, whereas norepinephrine vasoconstricts (16). A current hypothesis is that endotoxin induces an imbalance in the normal ratio of these vasoactive substances, thereby leading to small vessel injury and circulatory collapse (5). Whether one or more of these agents are released in quantities adequate to induce the changes observed in the intact animals after injection of endotoxin is not evident from these studies.

The results from the dual circulation experiments were not altogether satisfactory. They

demonstrate, however, that exclusion of the gastric vascular bed from the general circulation prevents the acute vasoconstriction observed in the single circulation studies. The gradually rising gastric artery pressure was observed in all animals in the dual circulation studies which persisted from the onset of an independent gastric circulation throughout the experimental observation period in the control dogs and in the animals in which endotoxin was limited to the systemic circulation. It is difficult to explain this progressive increase in gastric artery pressure. We are inclined to believe that it may represent an artifact due to the differences in technique from the single circulation experiments, the response of the gastric vasculature to the donor animals' blood, or the changes effected by the disc-oxygenator. Nevertheless, it must be stressed that this gradual and continuous increase in pressure was clearly of a different character from the abrupt rise in pressure observed in the single circulation experiments.

SUMMARY

The vascular effects of endotoxin on the perfused dog stomach were investigated by employing an acute preparation in which blood flow was held constant. Both gastric artery and coronary venous pressures rapidly increased in response to *Salmonella typhosa* endotoxin administered into either the left gastric artery or femoral vein. The responses of the gastric artery to endotoxin were blocked by locally infused phentolamine. Endotoxin, whether administered locally or systemically, failed to raise the gastric arterial pressure in the isolated gastric vascular bed. These data suggest that the increased gastric vascular resistance observed after administering endotoxin is mediated by circulating vasoactive substances elaborated at sites remote from the stomach.

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