Effects of Norepinephrine Infusions on Mesenteric Arterial Blood Flow and Its Tissue Distribution[1] (35694)

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Infusions of norepinephrine into the superior mesenteric artery or stimulation of the mesenteric periarterial nerves of cats or dogs produces a transient reduction in mesenteric blood flow but, as stimulation or infusion continues, flow returns to near control values (1–3). Studies based on India ink injections, changes in capillary filtration coefficient and isotope clearances suggested that a redistribution of intestinal blood flow occurred during the "escape" from the vasoconstrictor influence (4, 5). Vasoconstriction in the mucosa appeared to be well maintained throughout whereas blood flow in the submucosa increased. However, other observations (6, 7) have indicated that escape may be due to relaxation of the same vascular elements which were initially constricted.

The purpose of the present investigation was to determine whether norepinephrine escape occurred in animals other than the dog and cat and to reexamine the possibility that escape is associated with a redistribution of blood flow among the intestinal layers.

Methods. Two Sprague–Dawley rats, two rabbits, two monkeys (*Macaca mulatta* and *Aotus trivirgatus*) and 18 cats were used in the study. The rats, rabbits, and cats were anesthetized with intraperitoneal sodium pentobarbital and the monkeys with intravenous sodium pentobarbital 30 mg/kg after premedication with intramuscular Sernylan 5 mg/kg. Catheters were inserted into a common carotid artery and external jugular vein for arterial pressure measurement and intravenous administration of supplemental anesthesia, respectively. The abdomen was opened in the mid-line. Anastomotic connections between the superior and inferior mesenteric arteries were divided. The superior mesenteric artery was dissected free from the enveloping nerves which were cut. A noncannulating electromagnetic flow probe was placed on the vessel, and flow was determined with a Biotronex BL-610 flowmeter used in conjunction with a Beckman S11 Dynograph recorder. The zero flow reference was checked by mechanical occlusion of the artery downstream from the probe. Norepinephrine was infused into the mesenteric artery via a catheter in one of its proximal side branches except in the rat studies when the catheter was inserted into a femoral artery and its tip positioned in the abdominal aorta just above the origin of the mesenteric artery. The norepinephrine infusion rate was 1 μg/min in the cat experiments and 0.2 to 5.0 μg/min in the other animals.

The studies of flow distribution in the intestine wall were made in cats using the indicator fractionation method of Sapirstein (8). Approximately 0.1 mCi ^{86}Rb (as the chloride) was injected as an intravenous bolus while mesenteric arterial flow was being recorded. Forty-five seconds later the animal was killed with saturated potassium chloride injected intravenously as rapidly as possible. An annular segment from the mid-ileum was removed and mesenteric fat was trimmed off. The contents of the lumen were removed and the segment was incised along its length opened flat, blotted and weighed. The mucosa and submucosa were separated from the muscularis serosa by dissection, and the mucosa was separated from the submucosa by scraping. The clean separation of the layers was verified histologically (Fig. 1). Each lay-

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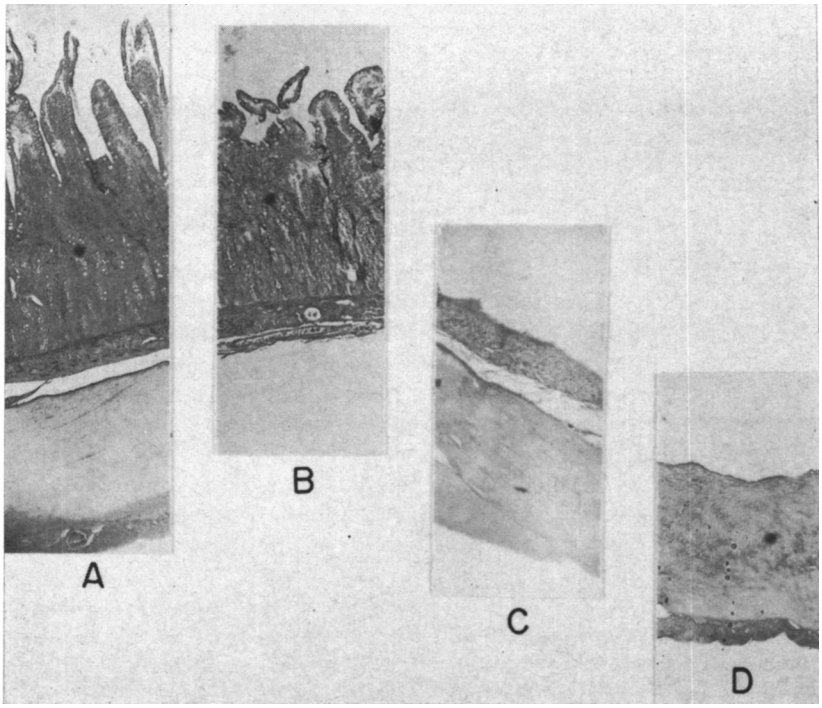

FIG. 1. Transverse sections of cat ileum. A, full thickness. Note cleavage plane between circular muscle and submucosa. B, after removal of muscle coat by dissection. C, after removal of mucosa by scraping. D, muscle coat only.

er was weighed, dissolved in sulfuric acid, and counted in the well of a Picker Spectroscalar. The cats were divided into three groups, each of six cats. In the first group ^{86}Rb was administered during a period of stable flow during the infusion of saline 0.1 ml/min into the mesenteric artery. In the second group ^{86}Rb was administered during the escape plateau occurring during the intramesenteric arterial infusion of norepinephrine 1 μg/min delivered in saline 0.1 ml/min. The third group was treated in the same way as the second except that the cats received the beta adrenergic blocking agent propranolol (Inderal, Ayerst Laboratories) 0.5 mg/kg intravenously 15 min before the norepinephrine infusion.

An approximation of the blood flow rate to the different layers of the ileum can be obtained if it is assumed that (1) 85% of the blood flow delivered by the mesenteric artery supplies the intestine. This figure is based on work which indicates that the mesenteric lymph nodes constitute 10–20% by weight of the structures supplied by this vessel and that the blood flow per gram of nodal tissue is similar to that of the intestine (9). (2) The distribution of the counts in the excised segment is representative of the distribution in the whole small intestine. If these assumptions are correct then the flow in any layer is equal to superior mesenteric artery flow (determined by flowmeter) $\times$ 85/100 $\times$ counts in/layer/counts in total segment.

Results. Presence of escape. Mesenteric escape was demonstrated in all the animals studied. Representative tracings are shown in Fig. 2.

Blood flow distribution. The results are set out in Table I. A marked degree of escape occurred during norepinephrine infusion, and the flow rate during the escape plateau was actually higher than in the preinfusion period. The calculated distribution of flow among mucosa, submucosa, and muscle during the escape period did not differ significantly from the distribution observed in the control group of animals ($p > .05$). The degree of es-

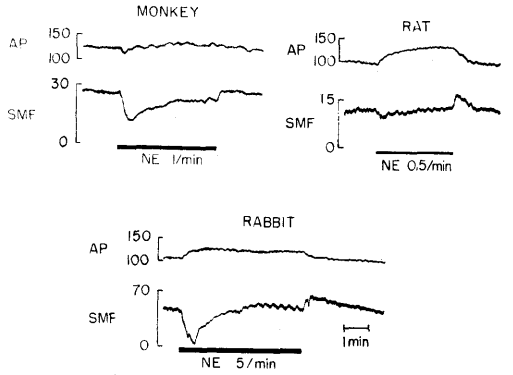

FIG. 2. Mesenteric blood flow changes induced by norepinephrine (NE) infusions in the monkey, rat, and rabbit. AP = aortic pressure (mm Hg), SMF = superior mesenteric artery flow (ml/min). Doses are in micrograms.

cape produced by norepinephrine after propranolol was significantly less than that induced by norepinephrine alone ($p<.01$) but again the distribution of the reduced flow did not differ significantly from the controls.

Discussion. It has been suggested that mesenteric escape is important in controlling intestinal secretion and absorption and in maintaining portal venous blood flow to the liver during states of increased sympathetic activity (4, 10). Hepatic arterial flow may be considerably reduced by sympathetic nerve stimulation or by norepinephrine infusions, and the hepatic arterioles exhibit a relatively weak tendency to escape from the initial constriction (11, 12). If the mesenteric vessels behaved similarly, portal flow would also be reduced and the combined reduction in both sources of blood supply to the liver might produce an undesirable degree of ischemia of this organ. The mesenteric escape phenomenon limits the reduction in portal flow and its importance is suggested by the present observation that it is not confined to cats and dogs but also occurs in other species.

The mechanism of escape has attracted much attention. One view is that mucosal flow is diminished throughout the period of adrenergic stimulation and that total flow returns to normal because of increased flow through submucosal exchange vessels. This is not supported by the data summarized in Table I which indicate that the distribution of flow among the layers during the norepinephrine escape plateau did not differ significantly from the distribution in control animals.

The estimation of blood flow by means of lipid-insoluble indicators has been criticized on the grounds that at high flow rates their distribution may be diffusion-limited rather than flow-limited (5). Nevertheless, estima-

TABLE I. Blood Flow and its Distribution (Means ± SE) in Six Control Cats and During the Escape Plateau of a Norepinephrine Infusion Before (Six Cats) and after Propranolol (Six Cats).

		Controls	During NE escape plateau	During NE escape plateau after propranolol
Total intestinal blood flow[a] (ml/min)		68 ± 8	70 ± 6[b]	34 ± 5[c]
% Segment weight	Mucosa	48 ± 3	49 ± 3	46 ± 1
	Submucosa	13 ± 3	13 ± 1	15 ± 1
	Muscle	39 ± 2	38 ± 2	39 ± 2
% Total flow distributed to	Mucosa	64 ± 4	66 ± 4	57 ± 5
	Submucosa	12 ± 2	7 ± 2	13 ± 2
	Muscle	24 ± 3	27 ± 3	30 ± 3
Flow (ml/min) to	Mucosa	43 ± 7	47 ±10	19 ± 4
	Submucosa	8 ± 2	5 ± 2	4 ± 0.5
	Muscle	16 ± 2	16 ± 3	10 ± 2

[a] Superior mesenteric flow x 0.85 (see text).
[b] Blood flow immediately preceding infusion was 60 ± 6 ml/min.
[c] Blood flow immediately preceding infusion was 53 ± ml/min.

tions of renal blood flow in the rat, at flow rates of at least 5.0 ml/g/min using ^{86}Rb were consistent with those obtained by other methods (8). This flow rate is considerably higher than that reported for any of the intestinal tissues at normal total mesenteric arterial flow (13). The distribution of intestinal blood flow under control conditions in the present study, *i.e.*, mucosa 64%, submucosa 12%, muscularis 24%, was similar to that obtained by Kampp and Lundgren (13) who obtained values of mucosa-submucosa 80% and muscularis 20%, using the lipid-soluble isotope ^{85}Kr. It seems likely, therefore, that the ^{86}Rb method would be capable of detecting any substantial redistribution of flow. In fact, the percentage of distribution of flow and the calculated absolute flows through the intestinal layers during the norepinephrine escape plateau did not differ significantly from those in control animals. As in a previous study (3) pretreatment with propanolol reduced the degree of mesenteric escape but again the percentage of distribution of the reduced flow within the intestinal wall was not significantly altered.

These results are in direct conflict with those of Folkow *et al.* (4, 5). They are not compatible with a redistribution of blood flow from mucosa to submucosa although they do not exclude the possibility of a blood flow redistribution between the superficial and deeper parts of the mucosa. The discrepancy between our findings presumably lies in the inadequacy of one or the other method and indicates the need for further studies by an independent technique.

Richardson and Johnson have compared the "escape" phenomenon with that of autoregulation (6) and have also directly observed the changes in red cell velocities in mesenteric capillaries during norepinephrine infusions (7). They concluded that their results were best explained by supposing that "escape" was due to a relaxation of those same vascular elements which were originally constricted by norepinephrine. The present data support this view.

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