Posterior Hypothalamic Effect on Gastrointestinal Blood Flow in the Conscious Cat[1] (37314)

ROBERT B. GILSDORF, LOUIS F. URDANETA, ARNOLD S. LEONARD,
AND JOHN P. DELANEY

Department of Surgery, Minneapolis Veterans Administration Hospital, and the University of Minnesota Hospital, Minneapolis, Minnesota 55417

Stimulation of the posterior hypothalamic area of the midbrain has been shown to produce significant cardiovascular effects with increases in blood pressure, pulse rates, peripheral resistance and cardiac output (2, 8, 9). Cobbald *et al.* showed that changes in mesenteric vasculature are a major factor in this response, with increased resistance and decreased capacitance during posterior hypothalamic stimulation (PHS) (2, 8). This vascular responsiveness has led some investigators to question if demonstrated changes in secretion and motility and certain pathologic changes occurring with PHS are largely due to changes in blood flow (10, 11, 14, 15, 18). Fluorescence micrography, however, also demonstrates anatomically direct motor and secretory cell innervation by adrenergic fibers; their functional significance remains uncertain (16).

For the purpose of further defining how the posterior hypothalamic area affects gastrointestinal function, this study of the effects of PHS on blood flow to various tissues of the gastrointestinal tract was undertaken.

Materials and Methods. Using an indicator distribution method, gastrointestinal tissue blood flows were estimated in 30 awake, adult cats weighing 1.95–3.89 kg (average 3.12). Each cat was prepared for study by inserting a polyvinyl catheter (0.066 in. o.d. × 0.034-in. i.d.) into the superior vena cava and another into the proximal aorta via the brachial artery and vein. The catheters were tunnelled subcutaneously to the interscapular area and there fixed to the interspinous ligament with a heavy nonabsorbable suture.

Each animal also had a bipolar stainless steel electrode placed in the posterior hypothalamic area using the coordinates described in the atlas of Bleier (1). Once placed, the electrodes were fixed to the skull with dental acrylic into which an electrical contact plug was imbedded. The exact position of the tip of the probe was marked at the end of each experiment by a direct current burn and determined at autopsy by serially sectioning the brain. Only those cats with electrodes accurately positioned in the posterior hypothalamic area were retained in the study.

After the placement of the vascular catheters and hypothalamic electrode, a two-week recovery period was allowed. During this time the cats were introduced once or twice to a small isolation cage in which blood-flow estimations were to be performed later. "Practice runs" served to acquaint the animal with the experimental circumstances so that undue anxiety or motor activity did not occur when actual studies were done. As a check on the function of the electrodes, a brief period of stimulation was given cats during this practice stand. Only those cats that exhibited increases in pulse rate and in arterial pressure with PHS were used in the stimulated group. Five cats showed no cardiovascular or visible response to electrical stimulation during this preliminary stand and were therefore designated to the control group. A faulty electrode was assumed to be the cause of this failure to respond because, at autopsy, the electrodes were properly positioned in all five cats. All other animals were randomly placed in the control or stimulated groups.

At the time that flows were to be measured,

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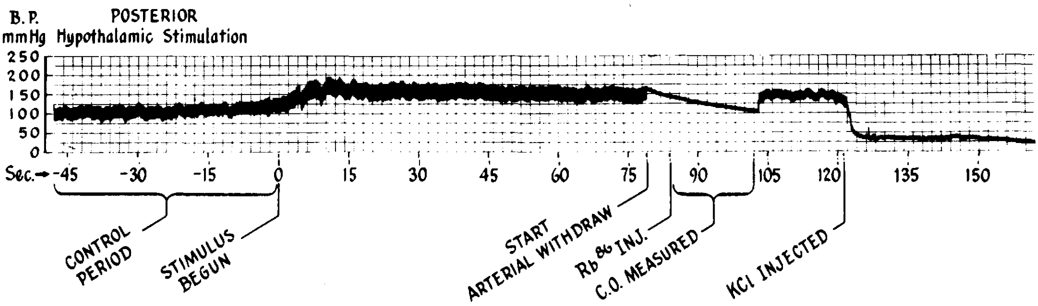

FIG. 1. Blood pressure tracing during flow measurement experiment. The tracing shows the pressure and pulse increase during posterior hypothalamic stimulation.

the cat was placed in the special cage and cannula connections were made. A 30-min rest period was then allowed during which the blood pressure was monitored (Fig. 1). Withdrawal of arterial blood at the rate of 0.63 ml/sec was begun. Ten seconds later a fixed volume of ^{86}Rb in saline was flushed as a bolus into the superior vena cava using a Krogh–Keys syringe pipette. Radioactivity in the withdrawn arterial blood was detected with a beta-sensitive crystal scintillation detector attached to a Picker rate meter and recorded on a Texas Instrument Servoriter. Thus an isotope dilution curve was drawn for calculation of cardiac output. Thirty seconds after the injection of the ^{86}Rb the animal was killed acutely with a 20-ml bolus of saturated solution of potassium chloride containing 500 mg of pentobarbital.

In 10 of the animals, electrical stimuli were delivered to the posterior hypothalamic electrode by means of the square wave pulse generator delivering a current of 0.8 to 1 mA (3–8 V) with 1-msec pulse duration, at 50 Hz. These parameters of stimulation were used because they had produced maximal changes in gastric and pancreatic secretory functions in previous studies by Gilsdorf *et al.* and Leonard *et al.* (11, 14). Stimulation was started 90 sec before the measurement of blood flow and continued until sacrifice. Twenty cats received no electrical stimulation and served as controls.

After sacrifice, the various tissues were excised and cleaned of areolar tissue and fat. Segments of the gastric corpus, mid-small intestine and mid-colon were separated by sharp dissection into three layers (mucosa, submucosa, and muscularis) and each layer was analyzed separately. Each tissue sample was weighed and digested in hot nitric acid.

Cardiac output was determined by the Stewart principle of radioisotope dilution as described by Conn; and tissue blood flow was calculated as described by Sapirstein and modified by Delaney and Grim (3, 19, 5). Tissue blood flow was expressed as ml/g/min.

A "perfusion ratio" was also calculated. This is defined as the ratio of the fraction of the cardiac output perfusing a tissue to the fraction of the body weight represented by that sample. The perfusion ratio gives a concise indication of the distribution of the cardiac output by stating the relative share of cardiac output on a weight basis and tends to negate variations in organ size and in cardiac output.

The statistical significance of the differences in the measured blood flows and perfusion ratios were determined using Student's *t* test.

Results. The average cardiac output in the control cats was 840 (SE 94) ml/min. The average cardiac index was 263 (SE 21) ml/min/kg. The 10 cats receiving PHS had an average cardiac output of 846 (SE 104) ml/min or 242 (SE 23) ml/min/kg. The lack of significant change in cardiac output was observed despite significantly elevated systolic (+40%) and diastolic (+47%) pressure in all of the animals in the stimulated group. The mean pulse rate was 127% of the prestimulation rate.

TABLE I. The Effect of Hypothalamic Stimulation on Tissue Blood Flow.

	Control		Posterior hypothalamic stimulation		
	Mean	SE	Mean	SE	% of control (* = $p < 0.05$)
Esophagus	.40	.04	.42	.06	105
Stomach					
Corpus	.77	.08	.61	.09	79
Mucosa	1.23	.13	.89	.14	72
Submucosa	.52	.07	.51	.09	98
Muscularis	.55	.11	.35	.04	64
Antrum	.54	.04	.42	.05	78
Small bowel					
Duodenum	1.02	.07	.82	.13	80
Jejunum	.89	.06	.71	.10	80
Ileum	.81	.05	.66	.10	81
Mucosa	.97	.07	.68	.12	70*
Submucosa	.75	.06	.54	.08	72
Muscularis	.59	.06	.56	.15	95
Colon	1.04	.07	.62	.06	60*
Mucosa	1.65	.19	.84	.09	51*
Submucosa	.88	.11	.53	.06	60*
Muscularis	.75	.09	.43	.06	57*
Other					
Gallbladder	.35	.04	.29	.03	83
Pancreas	1.36	.15	.97	.13	71
Mesentery	.23	.03	.13	.01	57*

Tissue blood flows are listed in Table I and the perfusion ratios in Table II.

During PHS all organs except the esophagus showed decreases in mean blood flow. The only organ with a statistically significant ($p < 0.05$) decrease in blood flow in all layers was the colon. Flow during stimulation was 0.62 (SE 0.06) ml/g/min or 60% of all control group mean value. Each of the three layers showed a significant decrease. The mucosa of the small bowel and the fatty mesenteric tissue also showed significant decreases to 70% of the control value and 57% of the control value, respectively.

The colon and the mesentery also had significant decreases in calculated perfusion ratios, 68 and 69% of control, respectively. The change in the perfusion ratio of the ileum also was statistically significant, 78% of control.

Discussion. Two facets of this study deserve separate comment: (a) The establishment of normal gastrointestinal organ blood flows in the awake cat. (b) The effects of posterior hypothalamic stimulation. The radioisotope indicator fractionation method has been validated for estimating blood flow to the tissues of the gastrointestinal tract by Delaney and Grim and by Sapirstein (5, 19). Their observations were made on dogs and rats, establishing normal gut blood flows for these species. Gastrointestinal blood flows in cats have not previously been studied by the isototope dilution methods. Delaney measured gastric blood flow in unanesthetized dogs, but except for that study, all observations of blood flow to individual gastrointestinal organs have been made on anesthetized animals. A comparison with other reported studies has been made in Table III (4, 6, 12, 13, 17, 21).

These data in our study show relatively small standard errors indicating that the experimental circumstances were reasonably comparable from one animal to another. Blood

TABLE II. The Effect of Hypothalamic Stimulation on Perfusion Ratios.

	Control		Posterior hypothalamic stimulation		
	Mean	SE	Mean	SE	% of control (* = $p < 0.05$)
Esophagus	1.51	.07	1.78	.26	118
Stomach					
Corpus	2.86	.19	2.71	.29	95
Mucosa	4.46	.32	4.02	.50	90
Submucosa	2.15	.20	2.29	.41	107
Muscularis	1.87	.22	1.59	.19	85
Antrum	2.12	.15	1.94	.22	92
Small bowel					
Duodenum	4.03	.27	3.48	.39	86
Jejunum	3.53	.19	2.91	.27	82
Ileum	3.36	.20	2.62	.31	78*
Midbowel					
Mucosa	3.96	.28	2.97	.35	75*
Submucosa	3.26	.36	2.28	.26	77
Muscularis	2.50	.23	2.20	.48	88
Colon	3.98	.24	2.73	.29	69*
Midcolon					
Mucosa	6.15	.57	3.71	.40	60*
Submucosa	3.25	.34	2.33	.24	72
Muscularis	2.85	.27	1.94	.26	68*
Other					
Gallbladder	1.52	.19	1.28	.12	84
Pancreas	5.20	.36	4.57	.58	88
Mesentery	.83	.07	.56	.05	67*

flows measured in this study are generally slightly higher than previously reported values.

Arranged in order, the pancreas has the highest blood flow, 1.36 ml/g/min, followed by the colon, duodenum, jejunum, ileum, gastric corpus, gastric antrum, esophagus, gallbladder and mesenteric fat. The perfusion ratios show nearly the same relationships. Delaney and Custer have previously noted the relatively high colonic blood flow in relation to the other splanchnic viscera of the dog (6).

The changes observed in tissue blood flow with PHS, although significant in certain organs, were not generally as striking as reported by Cobbald *et al.* and Folkow *et al.*, who observed posterior hypothalamic influences on cardiac output and small bowel blood flow in the anesthetized cat (2, 9). Several fundamental differences exist between their studies and ours. A balance was used to measure the volumes of small bowel segments as an index of vascular capacitance; venous outflow measurement was used to estimate blood flow; and they used a slower frequency in the electrical stimulation than was employed in the present study. In their studies they observed decreased blood flow, decreased capillary capacitance and filtration coefficients, and increased resistance in the small bowel. The effect began approximately ten seconds after beginning the stimulation but then decreased after one or two minutes. They explained this as an "autoregulatory escape."

Using the isotope fractionation method requires selection of a single moment for tissue blood flow measurement and does not permit observation of changes in the flow over extended periods. Flow was measured in this study in the 2–3 sec period occurring after 90 sec of stimulation. The data presented thus represent blood flow at one point in time

TABLE III. Blood Flow in the Gastrointestinal Tract Measured by Isotope Distribution Technique.

Animal:	Awake cat	Anesthetized dog					Awake dog	Anesthetized rat		
Investigator:	Present	Delaney	Delaney	Goodhead	Papp	Sapirstein	Delaney	Debreczeni	Jansky	Steiner
Reference no.:	study	(5)	(6)	(12)	(17)	(19)	(5)	(4)	(13)	(21)
Esophagus	.40		.21							.60
Stomach (intact)			.51			.40				.40
Corpus	.77	.32	.41				.55			
Antrum	.54	.61	.56				.38			
Mucosa	1.23	1.13					1.04			
Submucosa	.52	.50					.31			
Muscularis	.55	.25					.19			
Small bowel (intact)			.72					.81	.82	
Duodenum	1.02		.70	1.10						1.10
Jejunum	.89			1.03						.90
Ileum	.81			.92						.70
Mucosa	.97									
Submucosa	.75									
Muscularis	.59									
Colon (intact)	1.04		.82	1.23						
Mucosa	1.65									
Submucosa	.88									
Muscularis	.75									
Gallbladder	.35		.39							
Pancreas	1.36		.60		.76	1.00			1.01	

during autonomic stimulation and do not reflect earlier or later changes which could be different in either or both magnitude and direction. This period of time could have been during a period of autoregulatory escape and the moderate observed changes thus explained. Further studies in which blood flow is measured at earlier times during stimulation would be necessary to ascertain if this were the case.

Furthermore, electrical stimulation of a hypothalamic region, as done in this study, is not as specific as one would like, despite rigid criteria for electrode placement. Stimulation may affect tracts from adjacent regions or immediately adjacent nuclear complexes and thereby modify the primary effects. Donovan has commented on the nonspecific nature of hypothalamic stimulation (7). The techniques employed in this study have been shown to significantly influence other parameters of gastric, pancreatic, and small bowel function. In view of the small changes in tissue blood flow observed, it is difficult to attribute gastric and pancreatic secretory changes induced by hypothalamic stimulation, described by Gilsdorf *et al.,* Leonard *et al.,* Porter *et al.,* and Sen and Anand, to changes in blood flow alone (11, 14, 18, 20). A primary neural effect on cellular secretory mechanisms is more likely. The high blood flow rate of the colon and its responsiveness to hypothalamic stimulation would make hemodynamic changes more likely factors in the pathogenesis of functional abnormalities of that organ.

Summary. Cats receiving PHS were found to have significantly less blood flow to the colon mucosa (51%), submucosa (60%), and muscularis (57%) and to small intestinal mucosa (70%) than control cats.

No significant differences were detected in the blood flow to the tissues of the esophagus, stomach, gallbladder, or pancreas.

Despite significant increases in blood pressure (147% of control) and pulse (127% of control) cardiac output was not different in the two groups.

Tissue blood flows in the control group ranged from the high in the pancreas of 1.36 ± 0.15 ml/g/min followed by the colon, duodenum, jejunum, ileum, and gastric corpus to the low in the gastric antrum of 0.54 ± 0.04 ml/g/min.

It is concluded that posterior hypothalamic stimulation can affect tissue blood flow in the gastrointestinal organs but the magnitude of the changes is not sufficient to provide the sole explanation for reported physiologic and pathologic changes associated with such stimuli.

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