Localization of mesenteric hyperemia during digestion in dogs

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Many studies indicate that blood flow through the superior mesenteric vascular bed increases following a meal. This postprandial mesenteric hyperemia has been observed in men following oral glucose and protein feeding (2), and in conscious primates (26), dogs (5, 13, 14, 18, 24, 25), and rats (22) following oral feeding of their usual diets. In anesthetized cats or dogs, introduction of a food constituent into the duodenum also increases blood flow through the superior mesenteric artery (SMA) (11, 12), as well as through the duodenal segment containing the food (19). Likewise in anesthetized animals, placement of salt and peptone solutions (3, 4), hypo-, iso-, and hypertonic solutions of glucose (5), and isotonic glycine solution (23) in a small intestinal segment increases blood flow in the segment receiving the solution.

Studies performed prior to 1965 show that the increase in mesenteric blood flow is accompanied by increased cardiac output (7, 17, 20, 22) and blood flow through the limbs, kidney, heart, and carotid artery (1, 10, 18, 22). More recent studies, however, show that the cardiovascular system responds to feeding in two distinctly different phases. During presentation and ingestion of food, cardiac output, heart rate, aortic pressure, and vascular resistance in various vascular beds are altered in a pattern which mimics an increase in sympathetic neural activity (13, 14, 24-26). Within 5-30 min following a meal, cardiac output, heart rate, aortic pressure, and blood flow to the heart and kidney return to control levels while SMA flow starts to rise and reaches a maximum in 30-90 min (5, 13, 14, 24-26). Thus, the more recent studies suggest that while anticipation and ingestion of food elicit a generalized cardiovascular response, the cardiovascular effects of digestion are confined to the digestive organs.

Less information is available concerning the effect of a meal on celiac artery flow which is distributed to the liver, stomach, pancreas, spleen, and a part of the duodenum. Data are also not complete on blood flow distribution to the various areas supplied by the SMA, or on the distribution of flow within the wall of the small intestine during the digestive period. The present study was undertaken to clarify these points.

**METHODS**

Experiments were conducted on 58 mongrel dogs (15-25 kg), fasted for 24 h and anesthetized with either chloralose (75 mg/kg) and urethan (500 mg/kg) or pentobarbital sodium (30 mg/kg). All animals were ventilated with a positive-pressure respirator (IHarvard Apparatus Co., Millis, Mass.). The respirator was adjusted to achieve arterial blood pH between 7.38 and 7.45 before any experimental procedure. A femoral artery was cannulated for measuring aortic pressure. Effects of food on distribution of blood flow in the mesenteric organs were studied in six series of experiments utilizing four types of surgical preparations. In series 1 and 2, celiac and SMA blood flow were simultaneously measured while food was placed in the stomach (series 1) or duodenum (series 2). In series 3 and 4, SMA flow and flow through an isolated in situ segment of jejunum were simultaneously measured while food was placed in the duodenum (series 3) or in the isolated jejunal segment (series 4). In series 5, blood flows through two adjacent segments of jejunum were simultaneously measured while food was placed in one of the segments. In series 6, mucosal, submucosal, and muscle flow in the walls of three adjacent jejunal segments were simultaneously measured.
by use of radioactive microspheres, while food was in one of the three segments.

**Preparation of Digested Food**

Commercially available dog food (protein 12%, fat 7%, fiber 1.5%, ash 3%, linoleic acid 0.4%, moisture 78%) (Allen Products Co., Inc., Allentown, Pa.) was mixed in an electric blender until it became homogeneous. The pH of the homogenate was adjusted to approximately 7.0 with NaHCO₃. To each can of this homogenate was added 0.75 g of a pancreatic enzyme preparation (Viokase, Viobin Co., Monticello, Ill.), and the whole was gently mixed with a magnetic stirrer for 5-6 h to permit digestion. From 10 different cans to be used in experiments we prepared the digested food as described above and diluted aliquots from each can 1:2 and 1:4 with distilled water for the measurement of osmolality. These samples were centrifuged (19,250 × g) and the osmolality of the supernatants was determined using an osmometer (Advanced Instruments, Inc.). The osmolality of 1:2 diluted food ranged from 232 to 368 mosmol/kg and the mean ± SE was 291.3 ± 18.4 mosmol/kg. The osmolality of 1:4 diluted food ranged from 126 to 225 mosmol/kg and the mean ± SE was 189 ± 20.3 mosmol/kg. Since the osmolality of the 1:2 diluted and digested food was nearly isotonic with plasma, it was used when food was placed in the small intestine.

**Surgical Preparations and Experimental Procedures**

**Series 1 and 2.** The effects of intragastric placement (series 1) or intraduodenal infusion (series 2) of food on blood flow through the celiac and superior mesenteric arteries were studied in 26 dogs anesthetized with chloralose-urethan. Noncannulating electromagnetic flow transducers (Biotronex series 5000 connected to Biotronex BL-610 flowmeters) were placed around the celiac and superior mesenteric arteries after these arteries were carefully isolated from the adjacent tissue. Hydraulic occluders were placed around these arteries, distal to the transducers, so that zero-flow recordings could be obtained periodically. A needle inserted into the gallbladder allowed us to monitor its pressure with a Statham transducer. In the first series of experiments, either 200 ml of homogenized, nondigested food diluted with the same amount of water, or 200 ml of normal saline were introduced into the stomach through a nasogastric tube over a 3-min period. Aortic pressure and flow through the celiac and superior mesenteric arteries were continuously recorded on a Sanborn direct-writing oscillograph before, during, and after intragastric placement of food for at least 3 h. In the second series of experiments, normal saline or digested food diluted 1:2 with water was continuously pumped through a cannula into the proximal duodenal lumen at a rate of 4 ml/min. Aortic pressure and flow through the celiac and superior mesenteric arteries were continuously recorded before and during intraduodenal infusion of food for at least 2 h. In both series, a cannula in the distal jejunum provided an outlet for the chyme coming from the duodenum and jejunum. The presence of food in the cannula indicated that the food introduced into the stomach or duodenum passed through the jejunum.

**Series 3 and 4.** In 16 dogs, anesthetized with chloralose-urethan, the electromagnetic flow transducer and hydraulic occluder were placed around the SMA. In addition, a jejunal segment about 60 cm from the ligament of Treitz was isolated in situ, and the single vein draining the segment was cannulated after intravenous administration of heparin sodium (600 U/kg). The venous outflow from the isolated jejunal segment was diverted to a reservoir and the collected blood was returned by pump to the animal through a femoral vein at a rate equal to the venous outflow. A rubber tube was placed in the lumen of the isolated segment for introduction of food. Both ends of the segment were tied and cut away from the remainder of the jejunum. The cut end of the jejunal segment was tied. To provide an outlet for the chyme introduced into the duodenum, a cannula was inserted into the cut end of the remaining jejunal oral to the isolated segment. In series 3, digested food was pumped through a cannula into the proximal duodenal lumen at a rate of 4 ml/min, while the isolated jejunal segment contained 10 ml of normal saline. Flow through the SMA was continuously recorded and venous outflow from the isolated segment was measured periodically with a graduated cylinder and stopwatch (2-min samples) for at least 1 h. In series 4, 10 ml of digested food were placed in the lumen of the isolated jejunal segment but nothing was introduced into the duodenum. Blood flows through the SMA and isolated jejunal segment were simultaneously measured before and after placement of food for at least 16 min.

**Series 5.** Eight dogs were anesthetized with pentobarbital sodium. A loop of the jejunum about 30 cm aboral to the ligament of Treitz was exteriorized and divided into two segments such that each segment was drained by a single vein (6). After administration of heparin sodium, these veins were cannulated for measurement of venous outflow. The outflow was directed to a reservoir and the blood was returned to the animal through a femoral vein. A rubber tube was placed in the lumen of each segment for introduction and withdrawal of digested food and normal saline. At all other times, the tubes were connected to pressure transducers to monitor intraluminal pressure. Both ends of each segment were tied and the mesentery cut to exclude collateral flow.

The protocol consisted of three 15-min periods: precontrol, test, and postcontrol. In the control periods, both segments contained 10 ml of normal saline. In the test period, one segment contained 10 ml of digested food diluted 1:2 with water and the other segment contained 10 ml of normal saline. Venous outflow from each segment was simultaneously collected in graduated cylinders for 3 min with a 1-min interval between collections. After the volume was determined the blood was poured into the reservoir.

**Series 6** Ten dogs were anesthetized with pentobarbital sodium or chloralose-urethan (the findings were the same with either anesthetic). A loop of the jejunum about 30 cm aboral to the ligament of Treitz was exteriorized and divided into three segments according to the natural vascular pattern. A rubber tube was placed in
the lumen of each segment for introduction of solutions
to be studied and both ends of each segment were tied.
An indwelling catheter was inserted into the left ventri-

cle of the heart through the chest wall for injection of
microspheres. The presence of the catheter in the left
ventricle was confirmed by recording left ventricular

diastolic pressure.

One jejunal segment was left empty, one segment
contained 10 ml of digested food, and the third segment
contained 10 ml of an isotonic solution of nonabsorbable
polyethylene glycol (PEG). Twenty minutes after intro-
duction of the solutions, a bolus injection of carbonized
microspheres labeled with either \(^{85}\)Sr or \(^{141}\)Ce (approximately 1,760,000 microspheres) was made into the left
ventricle. Three minutes later, the other labeled
spheres were injected. The order of injection was alter-
nated in successive experiments. Two types of spheres
were used in this experiment to see if they yield similar
results. The microspheres were 15 ± 5 \(\mu\)m in diameter
and 1 ml of a stock suspension of the microsphere (3M
Co., St. Paul) had an initial radioactivity of about 0.1
mC (approximately 4,400,000 microspheres). A drop of
Tween 80 was added initially to this stock suspension to
prevent aggregation of the spheres. Just prior to the
injection, the stock suspension was shaken with a vortex
mixer and an aliquot of 0.4 ml was added to 2 ml of
20% dextran. This mixture was then treated with an
ultrasonic sonifier cell disruptor to achieve uniform dis-

dpersion of the microspheres just prior to injection.

Within 10 min after the injection of microspheres, the
dog was sacrificed by an intracardiac injection of satu-
rated KCl. The three jejunal segments were removed
from the animal and each segment was separated into
three portions: mucosa, submucosa, and muscle plus
serosa. This separation was accomplished by scraping
the mucosa and muscle from the submucosa with a
blunt instrument. Each tissue, in duplicate, was placed
in a preweighed, plastic counting tube. Each tube was
reweighed and the amount of radioactivity of \(^{141}\)Ce and
\(^{85}\)Sr was measured with a gamma scintillation spec-
trometer (Packard Instrument Company, Tri-Carb scint-
illation spectrometer, model 3002).

As reported previously (9), we found it technically
difficult to cut small samples of the whole wall of the
jejunum that contained representative weights of each
of the three layers. To avoid this source of error, we
calculated the total radioactivity of the jejunal wall from
the radioactivity of each tissue layer and the
weight distribution among the three layers (9). The
weight distribution of the three tissue layers of the
jejunal wall was obtained from 12 randomly selected
dogs. The relative weights of the three layers varied
little from animal to animal. They were as follows
(mean ± SE): mucosa, 63.1 ± 0.9%; submucosa, 11.9 ±
0.5%; muscle plus serosa, 25.0 ± 0.7%. With this mean
weight distribution and the radioactivity (cpm) per
gram of each tissue, the total radioactivity in the whole
wall in counts per minute per gram was calculated as
follows: total wall radioactivity = (0.631) (mucosal cpm/
g) + (0.119) (submucosal cpm/g) + (0.25) (muscle-serosal
cpm/g).

In all six series of experiments, the response to place-
ment of food was compared to control values using the
paired-\(t\) test.

RESULTS

The aortic pressure, which ranged from 110 to 175
mmHg, was not significantly altered during any of the
six series of experiments.

Series 1

In this series of experiments, the responses of celiac
and SMA flow to intragastric feeding were compared.
As shown in Fig. 1, the flow in the celiac artery in-
creased as food was introduced into the stomach. The

FIG. 1. Mean ± SE blood flows in
celiac and superior mesenteric arteries
following introduction of 200 ml food or
normal saline in stomach over a 3-min period (horizontal bar). Values are per-
cent of control. Mean control flows in
celiac artery, 15.4 ± 0.8; superior mes-
enteric artery, 14.3 ± 0.8 ml/min per
kg body wt. Asterisks indicate values
significantly different from control at \(P < 0.05\).
increased flow reached a plateau, about 10% above control, within 5 min and remained elevated for about 30 min. The flow then returned to the control level 60 min after the placement of food and remained near control for at least 2 h. The flow through the SMA, on the other hand, failed to change significantly for 20 min. At 30 min it reached a value 15-20% above the control level and remained there for the rest of the experiment. Saline was without effect on flow through either artery. Gallbladder pressure was not altered following intragastric placement of food or saline.

**Series 2**

Figure 2 shows the effects of infusion of digested food and normal saline into the duodenal lumen on blood flow through the SMA and celiac artery. The SMA flow started to rise soon after the infusion was begun and reached a plateau approximately 55-60% above the control in 60 min. The flow remained near this level as long as the food was infused. The flow in the celiac artery, however, was not significantly altered throughout the intraduodenal infusion of digested food. Infusion of normal saline did not alter the flow in either artery. Gallbladder pressure was not altered by intraduodenal infusion of food or saline.

**Series 3 and 4**

In these two series of experiments, digested food was either infused into the duodenum or placed into the isolated jejunal segment while blood flow through the SMA and isolated jejunal segment was simultaneously measured. As shown in Fig. 3, blood flow through the SMA significantly increased within 10 min of starting an intraduodenal infusion of digested food and reached a plateau, 20-25% above control, by 15 min. Flow in the isolated jejunal segment, which contained 10 ml of normal saline, remained unchanged throughout the infusion period. Placement of food in the isolated jejunal segment (no infusion into the duodenum) increased blood flow only in the segment. Flow to the SMA was not significantly altered (Fig. 3, lower panel).

**Series 5**

Table 1 compares the effects of luminal placement of digested food and normal saline in the double-segment preparation. Luminal placement of digested food significantly increased flow and decreased vascular resistance in the jejunal segment containing food but did not alter flow or resistance in the adjacent segment containing an equal volume of normal saline. Lumen pressure and venous osmolality were not significantly altered by the placement of food or saline. Average venous osmolality with saline in the lumen of either segment was 288.6 ± 3.1 and with food was 290.8 ± 2.7 mosmol/kg.

**Series 6**

Table 2 compares the distribution of radioactivity of microspheres in the wall of three adjacent jejunal segments (empty, digested food, nonabsorbable PEG). The radioactivity in the whole wall of the segment containing food was significantly higher (+35%, 85Sr; +50%, 141Ce) than in the segment containing the same volume of PEG. The radioactivity in the mucosal layer was also significantly higher (+44%, 85Sr; +57%, 141Ce) in this segment than in the PEG segment. The radioactivity in the submucosal and muscle-serosal layers of these two segments, however, was not significantly different. The radioactivities of the two nuclides in the whole wall and three tissue layers of the empty segment were not significantly different from those in the segment containing PEG. In this study two types of microspheres of similar size were injected sequentially to test for reproducibility of the results. As shown in Table 2, the two types of spheres gave similar results.
The first objective of our study was to determine if an increase in SMA flow during digestion is accompanied by a change in flow through the celiac artery. Introduction of food into the stomach did, indeed, increase celiac flow, but the increase lasted for only 30-60 min (Fig. 1). Intragastric placement of an equal volume of saline (Fig. 1) or intraduodenal infusion of food (Fig. 2) did not significantly alter celiac flow. These findings thus indicate that the presence but not the volume of food in the stomach increases celiac flow. The celiac artery perfuses the stomach, liver, spleen, pancreas, and a part of the duodenum. The study does not provide data relevant to distribution of the increased flow. However, it is probable that the increased celiac flow is due to an increase in gastric flow because intraduodenal infusion of food, bypassing the stomach, does not alter celiac flow (Fig. 2). Furthermore, Fara et al. (12) found that blood flow to the stomach is not altered following intraduodenal instillation of oil but SMA flow increases.

Although SMA flow increased following both intragastric and intraduodenal instillation of food, the times of onset of the increased flow in these two experiments differed (Figs. 1 and 2). While the increased SMA flow occurred within 10 min following intraduodenal infusion, the increased SMA flow did not become apparent until 30 min following intragastric placement of food; at that time celiac flow had already begun to return toward its control value (Fig. 1). The time of onset and duration of the increased flow in the celiac and superior mesenteric arteries thus appear to indicate that following a meal there is an initial increase in celiac flow (probably gastric flow) with no change in SMA flow, but as the chyme empties from the stomach and enters the small intestine, the celiac flow returns toward control while SMA flow rises.

Many investigators (5, 14, 24-26) have shown that in
conscious dogs SMA flow starts to rise within 5-15 min of feeding, reaches a peak (15-300% above the control) in 30-90 min and lasts for 3-7 h. The onset and duration of the increased SMA flow in the present study was similar to that observed by others in conscious dogs but the magnitude of the increase following intragastric placement of food was smaller. Following intraduodenal infusion of digested food, however, the magnitude was within the range observed in conscious dogs (5, 13, 14, 24-26). The lesser increase in SMA flow following intragastric placement of food in our study may have been due to delayed gastric emptying and/or to a decreased rate of intestinal digestion subsequent to the anesthesia. Recent preliminary studies show that digested food in the lumen is more effective in increasing jejunal blood flow than is undigested food (unpublished observations).

The second objective of our study was to determine if flow to all sections of the small intestine supplied by the SMA is increased during digestion. Figure 3 and Tables 1 and 2 clearly show that the increased flow is confined to the region exposed to food. Intraduodenal infusion of food increased SMA flow but did not alter flow to the isolated jejunal segment having no contact with food. Conversely, luminal placement of food in this isolated segment caused a significant increase in its flow without significantly altering SMA flow (Fig. 3). Although the isolated jejunal segment was perfused by the SMA, the increased flow in this segment was too small (7-10 ml/min) to be detected by the flow transducer on the SMA. The data in Fig. 3 thus indicate that the increased SMA flow during digestion appears to result from an increase in flow to the intestinal regions exposed to chyme. This possibility is further supported by the findings in series 5 and 6 (Tables 1 and 2). Luminal placement of food in one of the adjacent jejunal segments increased flow and decreased resistance only in the segment containing food. The increased flow was not due to increased luminal volume because placement of the same volume of normal saline (Table 1) or nonabsorbable polyethylene glycol (Table 2) did not significantly alter total flow to the segment. The increased flow was also not associated with significant changes in motor activity or venous osmolarity.

The third objective of our study was to measure flow in each layer of the intestinal wall after luminal placement of food. Radioactive microspheres were used to estimate flow to the mucosa, submucosa, and muscular-scarosa layers. The validity of the method has been verified previously by several investigators (8, 9, 15, 16). As shown in Table 2, radioactivity of 111Ce or 85Sr in the whole wall and mucosa of the segment containing food was significantly greater than that of segments which were empty or contained isotonic nonabsorbable PEG. Since radioactivity in a tissue is proportional to the number of microspheres trapped in capillaries which, in turn, is proportional to capillary flow, a greater tissue radioactivity indicates a greater capillary flow. At the time of injection of the spheres all three segments were subject to the same systemic influences (e.g., aortic pressure, portal venous pressure, arterial blood chemical constituents, and systemic neural activity). Consequently differences in total wall flow or its distribution can be reasonably attributed to differences in local conditions, i.e., lumen content. The study thus indicates that the presence of food in the jejunal lumen increases total wall flow by 35-50%, and the increase is mainly due to an increase in mucosal flow of 44-57%.

A recent hypothesis proposes that the cardiovascular response to digestion is confined to the vasculature of the digestive organs and that cardiac function and/or flow through other peripheral vascular beds are not altered during digestion (5, 13, 14, 24-26). Our findings also indicate that postprandial mesenteric hyperemia is confined to the area exposed to chyme. Furthermore, our findings show that this intestinal hyperemia results largely from an increase in mucosal flow. These data agree, in part, with those of Fara et al. (12), i.e., that intraduodenal instillation of food (oil in Fara's experiment) increases SMA flows but does not alter gastric or colonic blood flow. However, in contrast to our findings which show hyperemia occurring only in the area exposed to chyme, they found hyperemia in the jejunum when oil was instilled into the duodenum. Furthermore, in a cross-circulation preparation, they found increased SMA flow, not only in the animal receiving oil, but also in a recipient animal whose SMA was perfused by aortic blood of the animal receiving oil. These results clearly show that the mesenteric hyperemia induced by intraduodenal oil is at least in part mediated by blood-borne factors.

The discrepancy between our findings and theirs probably results from several differences in experimental conditions. The animals used were different (dog versus cat) and in addition they used only chloralose while we utilized chloralose-urethan for anesthesia. Fara et al. (12) have shown that some degree of vagal background activity is required for the apparent release of hormones necessary for the hyperemia in the remote organs. Urethan may have affected vagal activity in our experiments. However, as judged from heart rate and blood pressure, dogs under chloralose-urethan anesthesia do not appear to have lowered vagal activity. The most probable reason for the discrepancy appears in the type of food. Fara et al. used corn oil, while we used commercially available dog food which, when diluted 1:1 or 1:2, contained only 2.3-3.5% fat and 4-6% protein. The fat and protein content of this food may not be high enough to stimulate release of sufficient amounts of cholecystokinin into the circulation to cause hyperemia in the remote jejunum. In support of this possibility is the fact that in our studies gallbladder pressure was not changed following intragastric or intraduodenal instillation of food, whereas Fara et al. did find an increased gallbladder pressure following intraduodenal instillation of oil. The findings of our previous study (19) in which a liquid diet (Sego: protein 37%, fat 17%) or acid (HCl, pH 1.5) was used as the duodenal perfusate also support the possibility that composition of food is critical. Perfusion of the duodenal lumen with either the liquid diet or acid increased duodenal blood flow and decreased vascular resistance of a bioassay jejunum which was perfused by the duodenal venous blood. These vascular responses are similar to those that oc-
curred when cholecystokinin or secretin was infused intra-arterially to the donor duodenum. The type of food, more specifically the content of fat and protein in the food, therefore appears to be an important factor deciding the extent and mechanisms of postprandial mesenteric hyperemia.

Cholinergic nerves (12, 24) local mucosal nerves (21), active absorptive processes (21), and local or circulating humoral substances (12, 19) have been suggested as possible mediators of postprandial intestinal hyperemia. The present studies show that in anesthetized dogs the hyperemia is confined to the area of the intestine whose mucosa is exposed to food. The food used contained a relatively low concentration of fat and protein. Other studies (12, 19) have shown that food of higher concentrations of fat and protein can produce hyperemia in sections of the small intestine not exposed to food.

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