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TEMPORARY INTESTINAL ISCHAEMIA INDUCED BY PROXIMAL MESENTERIC ARTERY OCCLUSION

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Injury caused by low linear energy transfer ionizing radiation is dependent on the oxygen tension in the irradiated tissues and is decreased by a factor of 2 to 3 in anoxia (GRAY et coll. 1953, GRAY 1961). The limited tolerance of the small intestine to radiation severely restricts irradiation of abdominal and retroperitoneal tumours. Temporary mesenteric ischaemia and hypoxia during irradiation can protect the small intestine against radiation injury (STECKEL et coll. 1974, PENN et coll. 1975, FORSBERG et coll. 1978, 1979), and may permit higher therapeutic doses to tumours without causing unacceptable radiation enteritis. Mechanical occlusion of superior mesenteric artery branches (PENN et coll.), systemic or selective administration of vasoconstrictor drugs (STECKEL et coll., RAPPLEYE et coll. 1975, LOTE et coll. 1981), or mesenteric embolization of degradable starch microspheres (ARFORS et coll. 1976, FORSBERG et coll. 1978, 1979, LOTE et coll. 1980, LOTE 1981) can all induce temporary ischaemia. The relative efficacy of these methods for radiation protection of the small intestine is, however, uncertain. Therefore the effect of small intestinal ischaemia of 10 min duration by direct clamping of the superior mesenteric artery was evaluated in cats.

Material and Methods

Animal preparation. Seven adult cats of either sex weighing between 2.4 and 5.5 kg (mean 3.4 kg) were used after an overnight fast. The cats were anaesthetized with sodium pentobarbital (40 mg/kg). Plastic cannulas were inserted into the distal aorta through both femoral arteries. The left femoral vein was also cannulated and a slow saline infusion (10 ml/kg/h) established. The tip of another cannula was placed in the left ventricle of the heart from the right carotid artery; its position was checked by recording left ventricular pressures. A midline laparotomy followed by splenectomy was performed. An electromagnetic flow probe was positioned over the main trunk of the superior mesenteric artery, and an occluding snare was prepared 1 to 2 cm distal to the probe. A dowel flow probe was carefully positioned on the superior mesenteric vein. Throughout surgery the small intestine was manipulated as little as possible. The mesentery was left in place. The nerve plexus covering the proximal trunk of the superior mesenteric artery was incised longitudinally to permit artery isolation, but the nerve fibres were not sectioned.

Tissue blood flow. Carbonized microspheres (New England Nuclear, Boston) with diameter 15.5 ± 0.9 μm and labelled with ^{95}Nb, ^{103}Ru, ^{113}Sn, or ^{141}Ce were used to measure blood flow per g of tissue. The microspheres were suspended in 10% dextran with addition of Tween-80 to prevent aggregation. The sonicated suspensions contained 1.2×10^6 spheres/ml. After thorough mixing, 1.0 ml sphere suspension was injected into the left ven-

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tricle for each tissue flow determination. Simultaneously, a reference blood sample was withdrawn from the distal aorta at a constant rate as described by HEYMANN et coll. (1977) and confirmed in the cat by SEGADAL & SVANES (1979). Net activity in blood and tissue samples was determined in a multi-channel gamma spectrometer (INC Instruments SC 722, Oakland), and tissue blood flow was calculated from the following formula: QT = QR × (cpm T/cpm R), where QT is blood flow rate in the tissue sample, QR flow rate in the aortic reference sample, cpm T is counts/min/g in tissue, and cpm R is counts/min in the reference blood sample. Cardiac output (CO) was also determined by the microsphere technique by the following formula: CO = QR × cpm I/cpm R, where cpm I is counts/min of total amount of injected microspheres. During injection of carbonized microspheres, the haemodynamic state of the animal was carefully monitored. Isolated ventricular ectopic beats were occasionally observed, without any significant influence on arterial blood pressure or mesenteric arterial or venous blood flow.

Tissue samples. Small intestinal tissue samples were taken at 9 consecutive levels 10 to 90 cm from the ligament of Treitz to the caecum. The mucosa/submucosa layer was separated from the muscularis layer by simple stripping, and the tissue flow was determined separately in each layer. Transmural circular tissue samples were taken from the duodenum, caecum, transverse colon, and from the rectum 2 cm above the anus. Samples were also taken from the liver, pancreas, both renal cortices, myocardium, retroperitoneal adipose tissue, and lymph nodes at the aortic bifurcation.

Electromagnetic flowmetry. Arterial blood flow in the superior mesenteric artery was recorded by a flow probe positioned over the proximal part of the artery and connected to a square wave electromagnetic flowmeter (Carolina Medical Electronics, 501, King, North Carolina). A dowel flow probe connected to a parallel flowmeter was used to measure superior mesenteric venous blood flow. Corrected zero flow readings were confirmed by arterial and venous occlusions, respectively, at the end of each experiment. Central aortic blood pressure and pulse rate were determined with a Statham pressure transducer P23De connected to a Hewlett-Packard 7758 A recorder and directly calibrated against a sphygmomanometer.

Experimental procedure. Following the completion of instrumentation, the cats were heparinized (100 U/kg). The first (control) blood flow determination by labelled microspheres was then performed. Blood flow in the superior mesenteric artery and vein were continuously recorded. At time zero, the superior mesenteric artery was occluded distal to the electromagnetic probe by the prepared snare. Cessation of arterial flow was confirmed by flowmeter readings. After 3 to 5 min, the second blood flow determination by labelled microspheres was performed. At 8 to 10 min, the third blood flow determination was done. Ten min after initial arterial obstruction the occluding snare was removed and the superior mesenteric arterial flow permitted to recover. The fourth blood flow determination by labelled microspheres was performed on an individual basis 14 to 19 min after initial arterial occlusion when superior mesenteric arterial flow had reached a stable level following temporary intestinal ischaemia. At the end of the experiment, the animals were killed by cardiac injection of potassium chloride.

Statistics. Wilcoxon's paired rank sum test was used to test statistical probability. Each animal served as its own control. A p-value less than 0.05 was regarded as statistically significant.

Results

Superior mesenteric arterial and venous blood flow. Arterial blood flow in the superior mesenteric artery increased rapidly when the snare was removed 10 min after initial obstruction, and stabilized during the next 8 to 10 min (Fig. 1). Mesenteric venous blood flow was initially reduced from an average of 51 to 25 ml/min (range 13–44 ml/min), then stabilized at this level throughout the ischaemic period, and increased to slightly less than control values following ischaemia (Fig. 1). All animals maintained considerable mesenteric venous blood flow in spite of total superior mesenteric arterial occlusion. Only one animal (No. 5) showed a transient reactive hyperaemia.

Small intestinal tissue blood flow. Mesenteric arterial occlusion significantly reduced the mucosal blood flow throughout the entire length of the small intestine. However, the absolute mucosal blood flow in the proximal jejunum was only reduced to 0.72 ml/min/g, and the mucosal blood flow remained in the range of 0.2 to 0.4 ml/min/g along the small bowel (Fig. 1 c). Mean absolute mucosal flow reduction along the small intestine during the ischaemic

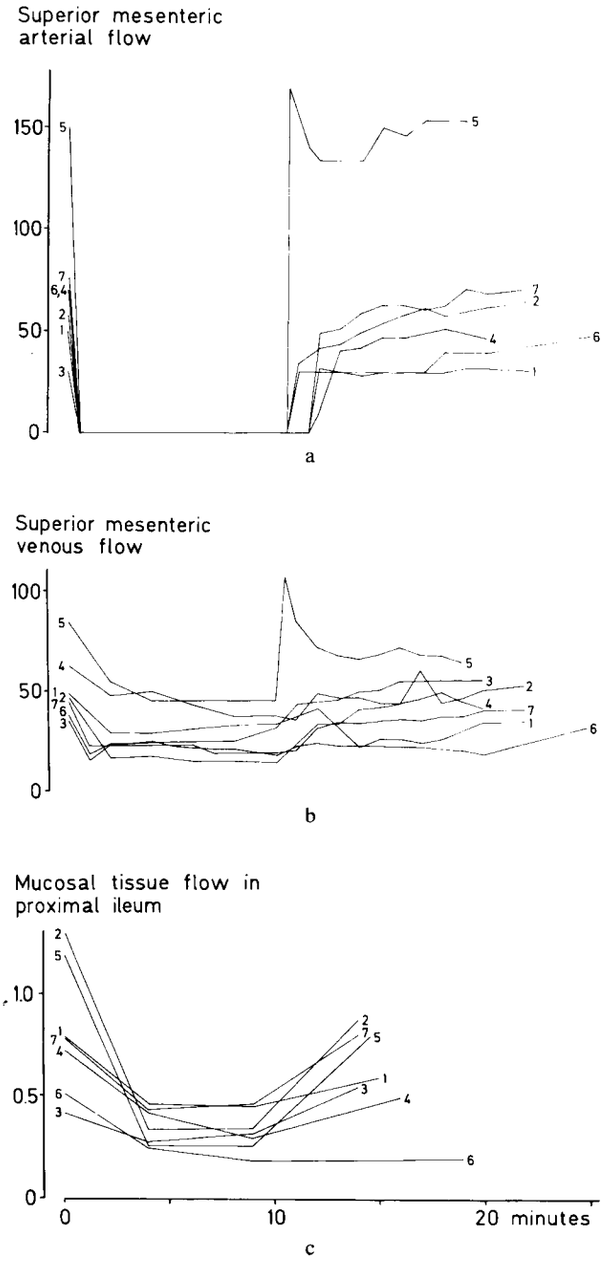

Fig. 1. a) Superior mesenteric arterial flow in ml/min (electromagnetic) before and following artery occlusion of 10 min duration in 6 cats (cat No. 3 was excluded for technical reasons). b) Superior mesenteric venous flow in ml/min (electromagnetic) before, during, and following superior mesenteric artery occlusion of 10 min duration in 7 cats. c) Blood flow in ml/min/g (carbonized microspheres) in mucosa 40 cm aboral to the ligament of Treitz before, during, and following superior mesenteric artery occlusion for 10 min in 7 cats.

period are given in Fig. 2. Flow reduction was less in the proximal jejunum and distal ileum (41 and 50%, respectively) than it was in the mid-segments of the small intestine, where a mucosal flow reduction of about 60 per cent was observed. The blood flow in the colon also decreased during mesenteric ischaemia, but clearly less than in the small intestine. No significant difference was observed between small intestinal blood flow determined at 4 min or at 9 min after initial arterial occlusion.

The blood flow reductions in the muscularis layers were more marked compared with the corresponding mucosal flow reductions (Fig. 2). This finding was more prominent 40 to 60 cm from the ligament of Treitz, in the bowel segments most remote from vessels with anastomoses to the superior mesenteric artery.

The blood flow to the duodenum did not change significantly during temporary mesenteric ischaemia, but it was reduced in the proximal colon (Fig. 2).

Blood flow in extra-intestinal tissues. Blood flow in retroperitoneal adipose tissue (0.16±0.13 ml/min/g, SE) and lymph nodes (0.27±0.05 ml/min/g) did not change during or after temporary mesenteric arterial occlusion, nor were cardiac output (418±100 ml/min) or myocardial tissue flow (2.40±0.08 ml/min/g) significantly altered.

Bilateral renal cortical blood flow by the microsphere method was determined in each animal to control the measurement accuracy. No significant difference in right or left renal tissue blood flow was found (Table).

Hepatic arterial blood flow increased ($p<0.02$) for the duration of mesenteric ischaemia and was still increased in all animals 4 to 9 min following arterial flow restoration (Fig. 3). Pancreatic tissue flow (0.87±0.16 ml/min/g) decreased to 0.54±0.22 ml/min/g ($p<0.05$) at 9 min after arterial occlusion and was still reduced (0.75±0.20 ml/min/g) at the end of the experiment.

Mean systolic aortic blood pressure transiently rose by 10 mmHg (range 0–15 mmHg) for 0.5 to 1 min after the mesenteric arterial occlusion. Pulse rate and systolic blood pressure were otherwise not changed during or following mesenteric ischaemia, and the animals remained haemodynamically stable throughout the entire experiment.

Discussion

The small intestine structure and mesenteric vascular anatomy in cat and man are very similar (NOER 1943, KNELLER et coll. 1972, HULTÉN et

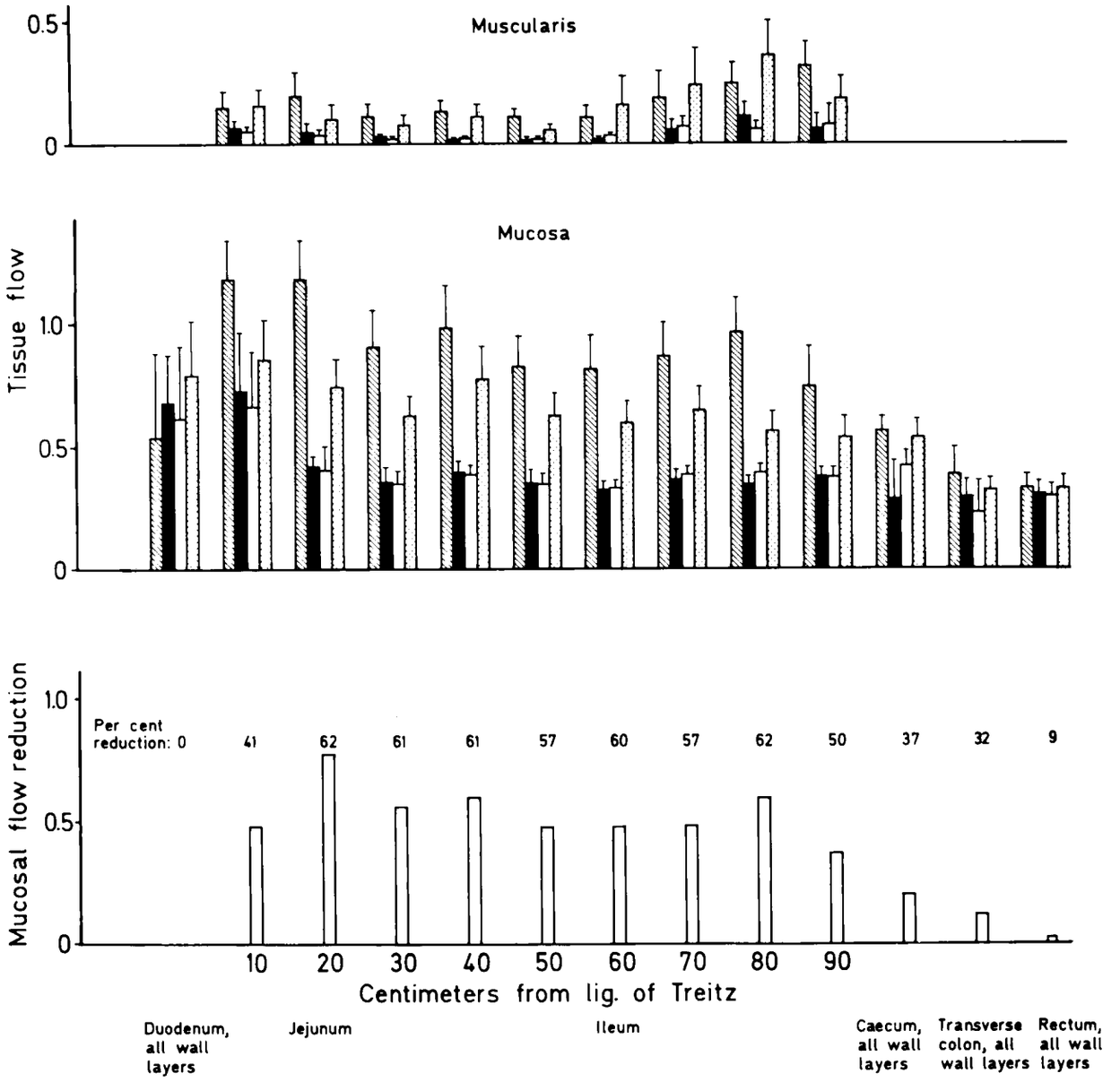

Fig. 2. Blood flow at 10 cm intervals along the gut before (▨), at 4 min (■), 9 min (□), and following (▦) initial superior mesenteric artery occlusion for 10 min in 7 cats (carbonized microspheres, $\bar{x} \pm SE$). Blood flow in ml/min/g in the muscularis layer (upper graph) and in the mucosa/submucosa layer (middle graph). Mean absolute and relative blood flow reductions in the mucosa/submucosa layer along the gut during superior mesenteric artery occlusion in 7 cats (lower graph).

coll. 1976, GRANGER et coll. 1980). In both species, the superior mesenteric artery supplies the gut from the duodenum to the midcolon and receives proximal anastomoses from the gastroduodenal and pancreaticduodenal arteries, and distal anastomoses from the inferior mesenteric artery. The superior mesenteric artery branches into fewer arcades in the cat (NOER), but the intramural vascular anatomy in the two species is otherwise essentially similar (NOER, HULTÉN et coll., GRANGER et coll.). Also, close similarity of average blood flow values in ml/min/g are reported (HULTÉN et coll., GRANGER et coll.). Thus, temporary proximal occlusion of the superior mesenteric artery most probably causes similar reductions in feline and human intestinal blood flow.

Superior mesenteric arterial occlusion in the an-

Table

Cortical tissue flow (ml/min/g) in right and left kidneys determined by microspheres before, during, and following temporary small intestinal ischaemia

Flow	Control	At 4.5 min	At 8 min	At 15 to 20 min
Right kidney	2.88±0.35	2.88±0.33	2.90±0.31	3.09±0.40
Left kidney	2.98±0.35	3.12±0.43	2.98±0.24	3.22±0.45

aesthetized cat clearly reduced the superior mesenteric venous flow and mucosal blood flow along the entire small intestine. However, collateral arteries maintained mean mucosal blood flow at 0.2 to 0.4 ml/min/g at all bowel levels. Since minimum flow was reached within 4 min at all levels, maximum collateral blood flow evidently was rapidly established and was not further increased by prolongation of the arterial occlusion. The observed mucosal blood flow reduction, and thus mucosal ischaemia and hypoxia, was less in the proximal jejunum and distal ileum, but rather uniform throughout the rest of the small intestine where mucosal blood flow was reduced by about 60 per cent.

Better preserved blood flow to both ends of the small bowel, which lie closer to anastomosing arteries, was expected. The reductions in pancreatic and colic blood flow during the superior mesenteric arterial occlusion indicate that perfusion of the small intestine was maintained at the expense of blood supply to these organs.

The results also confirm previous statements (LUNDGREN & SVANVIK 1973, CASUTO et coll. 1979) that the fraction of intestinal blood flow diverted to the mucosa/submucosa layer is increased during ischaemia. This finding is more prominent in the central segments of the ischaemic small intestine (Fig. 2). Although mucosal blood flow is relatively better preserved during ischaemia, the villous countercurrent exchange (JODAL et coll. 1978, LUNDGREN & HAGLUND 1978) may render the villous tips severely hypoxic during rather modest reductions in total mucosal flow (LUNDGREN & SVANVIK, CASUTO et coll.). In contrast, the epithelial regenerative zone at the villous base is not subjected to comparable hypoxia during ischaemia (JODAL et coll.) and is thus less protected against radiation injury. In this context, it is important that optimum hypoxic radiation protection demands virtual tissue anoxia (GRAY et coll., GRAY).

Ischaemia induced by proximal occlusion of the

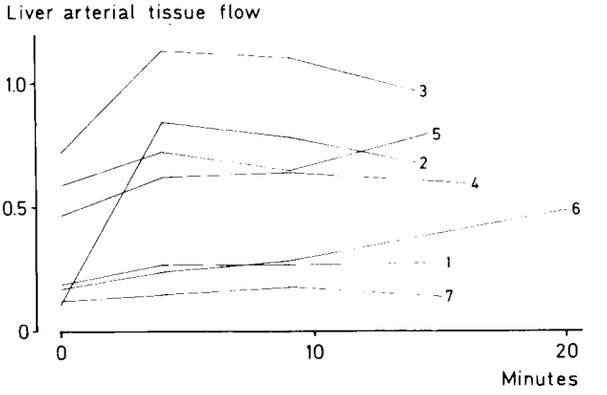

Fig. 3. Hepatic arterial blood flow in ml/min/g before, during, and following superior mesenteric artery occlusion of 10 min duration in 7 cats (carbonized microspheres).

superior mesenteric artery thus seems not sufficiently severe to provide optimum small intestinal protection to radiation. Moreover, blood flow through anastomoses would render the proximal and distal parts of the small intestine even less protected against radiation injury. By comparison, mesenteric arteriolar embolization of degradable starch microspheres (ARFORS et coll., LOTE et coll. 1980, LOTE) or mesenteric arterial vasopressin infusion (LOTE et coll. 1981) induce severe and uniform temporary small intestinal ischaemia. However, intraarterial vasopressin administration causes unwanted systemic vasoconstriction, which may reduce the flow also in target organs (LOTE et coll. 1981).

Intestinal ischaemia may reduce cardiac output and influence blood pressure and pulse rate (MARSTON 1977, HAGLUND & LUNDGREN). No such changes were seen in the present experiments, nor was myocardial blood flow reduced during or following the intestinal ischaemic event. The ischaemic period was probably not long enough for significant release of vasoactive intestinal products (MAR-

STON, HAGLUND & LUNDGREN). Increased hepatic arterial blood flow during intestinal ischaemia is regularly observed in the literature (COHN & KOUNTZ 1963, KOCK et coll. 1972, GELMAN & ERNST 1977).

In conclusion, temporary proximal occlusion of the superior mesenteric artery in the cat rendered the small intestine only moderately ischaemic due to abundant collateral flow. Also, ischaemia was unevenly distributed along the gut. The degree and distribution of such ischaemia, therefore, cannot be expected to provide optimum small intestinal hypoxic radiation protection. This conclusion also applies to artery occlusion achieved by inflatable balloons during selective catheterization of the artery.

SUMMARY

The severity and distribution of small intestinal ischaemia caused by temporary proximal occlusion of the superior mesenteric artery in cats were evaluated by electromagnetic flowmetry and carbonized microspheres. Average mucosal blood flow was reduced from 0.94 to 0.40 ml/min/g. Mucosal flow in the proximal jejunum and distal ileum was even less affected. Ischaemia induced by proximal occlusion of the superior mesenteric artery in cats was not severe enough to provide optimum conditions for intestinal hypoxic radiation protection, nor was such ischaemia evenly distributed along the gut.

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