

Pancreatic vascular regulation in chronic pancreatitis in cats

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Abstract

In experimental obstructive chronic pancreatitis the normal hyperaemic response to secretory stimulation is lost, suggesting abnormal vascular regulation. Vascular regulatory mechanisms were investigated by observing the effect of increments in portal pressure on pancreatic blood flow in normal cats and cats with chronic pancreatitis. Normal cats maintained pancreatic blood flow until portal pressure was >15 mm Hg, after which it decreased. Total vascular resistance decreased until the portal pressure was 15 mm Hg and increased thereafter. These observations suggested that metabolic regulatory mechanisms prevailed while portal pressure was in the physiological range but myogenic mechanisms became dominant during portal hypertension. In chronic pancreatitis the basal pancreatic blood flow was reduced and was inversely proportional to portal pressure. Total vascular resistance increased as portal pressure increased. In chronic pancreatitis myogenic regulatory responses prevailed at all levels of portal pressure. In conclusion, intrinsic regulation of pancreatic blood flow was abnormal in cats with chronic pancreatitis. The loss of the predominance of metabolic regulation over the normal range of portal pressure may partly explain the reduction of pancreatic blood flow in response to secretory stimulation.

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The pathophysiology of chronic pancreatitis remains poorly understood. In an experimental model of chronic pancreatitis we showed that pancreatic blood flow was reduced.¹ Secretory stimulation and ethanol ingestion caused a further reduction, in contrast to the hyperaemic response observed normally.¹⁻⁵ This reduction in perfusion may be partly due to the lower metabolic demands of the fibrotic pancreas. This cannot, however, explain the reduction in perfusion in response to secretory stimulation or ethanol. It is possible that in chronic pancreatitis the regulation of the pancreatic microcirculation is abnormal.

The intrinsic control of the pancreatic microcirculation is normally determined by the relative contributions of the metabolic and myogenic regulatory mechanisms.^{3,6} To determine the relative importance of each

mechanism in cats with normal glands and cats with chronic pancreatitis, the effect of acute increases in portal pressure was investigated.⁶

Methods

PANCREATIC BLOOD FLOW MEASUREMENTS

Pancreatic blood flow was measured using a hydrogen gas clearance technique with an intraduct sensing electrode. This technique has been validated previously and is described in detail elsewhere.^{1,5,7-9} An insulated platinum electrode was inserted into the main pancreatic duct through an incision in the tail of the gland. The electrode tip was advanced to the mid-point of the body of the pancreas and secured. A silver-silver chloride reference electrode was positioned beneath the right hemidiaphragm. The signal was polarised so that current changes reflected changes in tissue hydrogen concentration. The current was amplified before being plotted on a chart recorder (Gilson Medical Electronics, Middleton, WI) and converted into a digital output for storage on a microcomputer (Apple IIe, Cupertino, CA).

Hydrogen (2.6%) in air was administered for 15 minutes via an endotracheal tube to achieve full tissue saturation. The cats were then allowed to breathe room air and mono-exponential desaturation curves were recorded over 15 minutes. From these hydrogen gas clearance curves, pancreatic blood flow was estimated using a computer software program that employed a modified Gauss-Newton non-linear regression algorithm for a mono-exponential system.¹⁰

EXPERIMENTAL PROTOCOL

Adult mongrel cats (weight 2-4 kg) were divided into two equal groups. In eight cats, chronic pancreatitis was induced.^{1,5,11-13} The animals were fasted for 24 hours and anaesthetised with intramuscular xylazine hydrochloride (1 mg/kg) and intraperitoneal sodium pentobarbital (25 mg/kg). The main pancreatic duct was narrowed in the neck of the gland to about 25% of its original diameter with a 4-0 silk ligature.¹¹ The abdomen was then closed and the animals were allowed to recover.

Experiments were performed five weeks later. At this time the typical histological changes of chronic pancreatitis had developed in the lobe drained by the main duct. This degree and duration of obstruction also produces functional abnormalities similar to that observed in patients with chronic pancreatitis.¹¹ The animals did not develop

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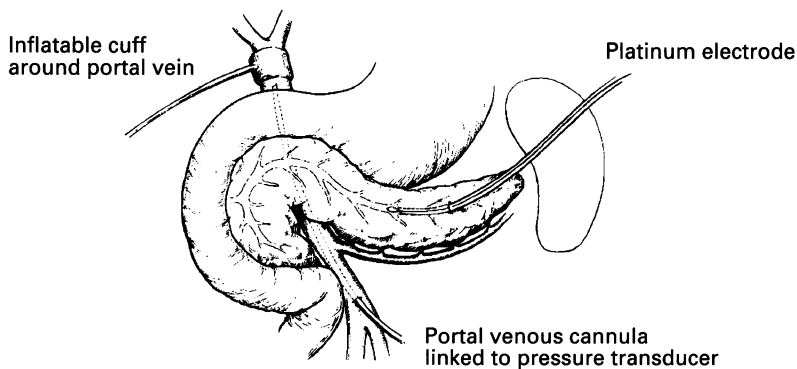


Figure 1: Diagram to illustrate the experimental method.

pancreatic insufficiency and maintained their weight and general health because drainage of the accessory lobe of the pancreas was not obstructed. The eight remaining cats who had not been operated on served as controls.

For the blood flow measurements, animals were anaesthetised as described above. A catheter was inserted into a femoral artery and connected to a pressure transducer (Statham Gould P23XL, Oxnard, CA) for the measurement of mean arterial pressure. A femoral vein was catheterised for the continuous infusion of pentobarbital (5 mg/kg/h) and administration of other drugs. A laparotomy was performed and a branch of the ileocolic vein was isolated. Through this vein a polyethylene catheter (external diameter 0.965 mm) was advanced in retrograde manner into the superior mesenteric vein. This catheter was connected to a second pressure transducer for the measurement of portal pressure and was zeroed to atmospheric pressure at the mid-axillary line of the animal. The portal vein was isolated in the porta hepatis and an inflatable cuff was placed loosely around the vein. The hydrogen sensing electrodes were placed as described previously for the measurement of pancreatic blood flow (Fig 1).

Animals were then allowed to stabilise and baseline pancreatic blood flow, arterial pressure, and portal pressure were measured. The portal vein cuff was inflated to produce stepwise 3 mm Hg increments in portal pressure: 12, 15, 18, 21, and 24 mm Hg. Pancreatic blood flow and femoral arterial pressure were measured at each increment of portal pressure

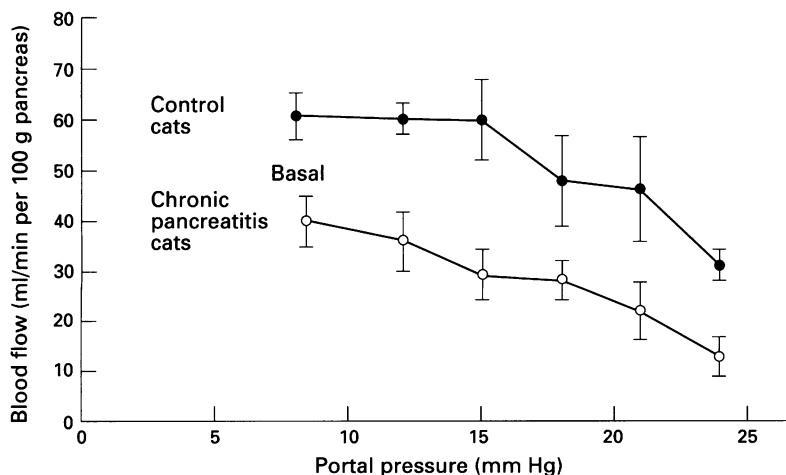


Figure 2: Effect of portal pressure on pancreatic blood flow in normal cats and cats with chronic pancreatitis.

after allowing 15 minutes for stabilisation. The cuff was then released and pancreatic blood flow, portal pressure, and femoral arterial pressure readings were repeated 15 minutes later.

Experiments were carried out according to guidelines established by the Office of Research and Development of the Sepulveda VA Medical Center in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. At the end of the experiment anaesthetised cats were killed with an overdose of intravenous potassium chloride.

DATA ANALYSIS AND STATISTICAL METHODS

All results were expressed as mean (SEM). Results were analysed using the Mann-Whitney U test. Pancreatic vascular resistance in the pancreas (R_p) was derived using the equation:

$$R_p = (P_A - P_V) / Q_p$$

where mean femoral arterial pressure (P_A) was assumed to be the same as the pressure in arteries supplying the pancreas. Portal pressure (P_V) was assumed to be the same as post-capillary venous pressure (there is a linear correlation between portal pressure and pancreatic capillary pressure).³ Q_p represented pancreatic blood flow. The units of resistance, mm Hg/ml/min per 100 g pancreas, is abbreviated to 'u' in the text.

Results

Resting portal pressure was the same in normal cats and cats with chronic pancreatitis (8.4 (0.5) mm Hg and 8.0 (0.3) mm Hg, respectively). Basal mean arterial pressure was also the same in each group (102 (4) mm Hg and 112 (6) mm Hg, respectively). Basal pancreatic blood flow in control cats (60 (6) ml/min per 100 g pancreas) was greater than in cats with chronic pancreatitis (42 (5) ml/min per 100 g pancreas) ($p < 0.05$). Total vascular resistance in normal cats (1.6 (0.1) u) was less than in cats with chronic pancreatitis (2.6 (0.2) u) ($p < 0.05$).

In normal cats, pancreatic blood flow was maintained until portal pressure exceeded 15 mm Hg (Fig 2). An increase in portal pressure above 15 mm Hg caused pancreatic blood flow to decrease. At a portal pressure of 24 mm Hg, pancreatic blood flow was 31 (7) ml/min per 100 g pancreas. This was significantly less than the basal pancreatic blood flow ($p < 0.05$). In cats with chronic pancreatitis, pancreatic blood flow was always lower than in normal cats ($p < 0.05$) and decreased even with small increases in portal pressure. At a portal pressure of 24 mm Hg, pancreatic blood flow was 13 (6) ml/min per 100 g pancreas ($p < 0.05$ v basal).

In normal cats, total vascular resistance fell as portal pressure increased until pressure reached 15 mm Hg. Thereafter, vascular resistance increased as portal pressure increased. In

chronic pancreatitis cats, total vascular resistance increased with each increment in portal pressure. Total vascular resistance at a portal pressure of 24 mm Hg was 3.8 (0.7) u ($p < 0.05$ *v* normal, NS *v* basal chronic pancreatitis).

Release of the portal venous cuff caused portal pressure to fall to basal levels in control cats (9 (1) mm Hg; NS *v* basal) but not in cats with chronic pancreatitis (11 (1) mm Hg; $p < 0.01$ *v* basal). Mean arterial pressure increased to 112 (6) mm Hg in normal cats, and 115 (9) mm Hg in cats with chronic pancreatitis (NS *v* basal in both groups). In normal cats, pancreatic blood flow returned to basal levels (54 (9) ml/min per 100 g pancreas; NS *v* basal). With the return of portal pressure towards baseline, pancreatic blood flow in cats with chronic pancreatitis rebounded above basal levels (53 (7) ml/min per 100 g pancreas *v* 42 (5) ml/min per 100 g pancreas) to approach levels seen after release in normal animals. This increase above baseline did not, however, achieve statistical significance ($p = 0.08$ *v* basal). In control cats, total vascular resistance after release of the portal cuff was higher than the basal value (2.2 (0.3) u; $p < 0.05$). In chronic pancreatitis cats, total vascular resistance was less than the basal value (1.9 (0.2) u; $p < 0.05$) but not different from that in control cats.

Discussion

The reduced pancreatic blood flow in chronic pancreatitis previously reported was confirmed.¹ Since basal portal pressure and mean arterial pressure were not changed, reduced pancreatic blood flow in chronic pancreatitis was caused by increased pancreatic vascular resistance. Pancreatic vascular resistance measured in this study was similar to that measured in dogs, 0.58–2.86 u.³ The cause of the increased vascular resistance in chronic pancreatitis is unknown and was not investigated here.

In chronic pancreatitis, reduced pancreatic blood flow may be due to the reduced metabolic needs of a fibrosed gland. This does not, however, explain the abolition of the normal hyperaemic response to secretory stimulation.¹ We have previously suggested that in chronic pancreatitis the pancreas behaves like a closed compartment in which ductal and interstitial pressure rises during secretory stimulation causing reduced pancreatic blood flow.^{1 5 12–14} An alternative, or an additional hypothesis is that vascular regulation may be abnormal in chronic pancreatitis.

In healthy tissues, intrinsic control of blood flow is maintained by a combination of myogenic and metabolic regulatory mechanisms.^{3 6 15} Myogenic reflexes control muscular tone in arteriolar resistance vessels in response to changes in vascular transmural pressure. Metabolic reflexes respond to local levels of metabolites. An increase in venous pressure allows evaluation of the predominant mechanism active in a particular vascular bed because these two regulatory mechanisms produce opposing effects on vascular resis-

tance. When myogenic mechanisms prevail, increased transmural pressure causes vasoconstriction and an increase in vascular resistance. The metabolic reflex would produce vasodilation and decrease the total vascular resistance.

In this study we observed that as portal pressure was increased to 15 mm Hg in normal cats, pancreatic blood flow remained stable. This occurred despite a fall in arterial pressure and was associated with a reduction in total vascular resistance in the pancreas. This suggested that the principal intrinsic regulatory mechanism of blood flow in the intact normal pancreas is metabolic over the normal range of portal pressures. This would be expected since in other tissues, skeletal muscle and the intestine, for example, which also need to respond rapidly to increased metabolic demand, metabolic regulatory mechanisms also prevail.¹⁵ However, as portal pressure increased beyond 15 mm Hg, arterial pressure continued to fall, pancreatic resistance increased, and pancreatic blood flow was reduced. This suggested that the metabolic regulatory responses were less important at higher portal pressure and myogenic regulation prevailed.

The compensatory response to increases in portal pressure up to 15 mm Hg in normal cats observed in the present study contrasts with the observations of Kvietyš *et al* in the isolated, perfused canine pancreas.⁶ An increase in venous pressure from 2.2 to 12.4 mm Hg in that study reduced pancreatic blood flow, while total vascular resistance increased. These investigators concluded that although metabolic mechanisms are active in the normal pancreas myogenic regulatory responses prevail. It is likely that their exclusion of extrinsic factors, especially the neurovascular connections to the pancreas, account for the disparity with our results.

The normal ability of the pancreas to maintain pancreatic blood flow as portal pressure increases was absent in chronic pancreatitis. Small increases in portal pressure above normal decreased the pancreatic blood flow and increased vascular resistance, suggesting that myogenic reflexes were prevalent. The cause of the loss of the metabolic component of vascular regulation in chronic pancreatitis is uncertain. It is possible that in chronic pancreatitis the gland is ischaemic at rest and metabolic reflexes are already maximal. In support of this suggestion was the observation that release of the portal venous cuff at the end of the experiments failed to produce a significant rebound hyperaemia. Alternatively, deranged regulatory mechanisms may reflect vascular damage in a chronically inflamed gland.^{16 17}

The loss of the predominance of metabolic regulation in chronic pancreatitis suggests that the gland would not be able to respond normally to increased metabolic demands during secretion. In previous experiments using the same feline model of chronic pancreatitis we observed that secretory stimulation was associated with reduced pancreatic blood flow.¹ This was highly abnormal since the normal response to secretory stimulation was

increased pancreatic blood flow. It is likely that the abnormal response was caused by both the observed increase in interstitial pressure and the loss of the normal intrinsic metabolic regulatory response observed in this study.

In conclusion, pancreatic vascular resistance is increased in cats with chronic pancreatitis. In normal cats metabolic regulation prevails over the normal range of portal pressure. In cats with chronic pancreatitis intrinsic regulation of pancreatic blood flow was abnormal with a loss of the predominance of metabolic regulation.

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