Experimental Acute Pancreatitis

The Changes in Pancreatic Oxygen Consumption and the Effect of Dextran 40

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A canine model was devised to measure the oxygen consumption of the pancreas in experimentally induced pancreatitis. Over the 120 minute investigation period the oxygen consumption fell by 63% in the presence of a diminishing pancreatic blood flow and constant arteriovenous percentage saturation across the pancreas. Dextran 40 has been previously shown to maintain the pancreatic circulation. Accordingly a second group of dogs was treated with Dextran 40 (1.5 ml/kg) 60 minutes after induction of the pancreatitis. This produced a significant increase in the pancreatic oxygen consumption and widening of the arteriovenous difference. Dextran 40 appears to reverse the hypoxia of the pancreas noted in acute experimental pancreatitis.

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MANY ASPECTS OF THE pathophysiology of acute pancreatitis are poorly understood[4,13] and little is known about the oxygen consumption of either the diseased or normal pancreas.[28] A variety of therapeutic agents have been advocated in the treatment of acute pancreatitis and include Dextran 40,[1,7,13,31] Trasylol,[17,21,27] vasopressin,[3,25] and albumin.[9,18] However, these drugs were assessed purely on their ability to reduce the mortality and morbidity of the pancreatitis with little attention being paid to their mode of action and effects, if any, on the underlying pathophysiology of pancreatitis.

Recent work has investigated the hemodynamic changes occurring in acute experimental pancreatitis,[7] and a prominent feature was the rapid fall in the pancreatic arterial blood flow. This was refractory to treatment with plasma while low dose Dextran 40 appeared to significantly diminish the pancreatic ischemia.[7]

Accordingly, this study was undertaken to serially measure the oxygen consumption of the pancreas in dogs with acute experimental pancreatitis. In view of the beneficial effect noted with the Dextran 40, a second group of animals treated with Dextran 40 was also investigated.

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Materials and Methods

Acute pancreatitis was produced in anesthetized dogs by injecting 20 ml of homologous bile under pressure into the pancreatic duct.[7] The pancreatic arterial blood flow was measured with an electromagnetic flow probe around the gastroduodenal artery.[7] This vessel has two end arteries, the right gastroepiploic artery and the pancreaticoduodenal artery. The former vessel supplies part of the greater curvature of the stomach and this vessel was ligated. The latter artery is the main vessel supplying the pancreas.[8] Hence, the flow probe situated around the gastroduodenal artery directly measured the pancreatic arterial blood flow. The two additional vessels supplying the pancreas from the splenic artery and duodenal mesentery respectively[7,8] were also ligated.

A cannula was introduced through a left femoral arteriotomy into the aorta at the level of the coeliac axis. Blood collected from this cannula indicated the arterial oxygen tension (Pa_{O_2}) and the percentage oxygen saturation of the blood entering the pancreas. A fine cannula was inserted into a vein lying on the surface of the uncinate process of the pancreas and advanced towards the pancreaticoduodenal vein. Blood from this second cannula provided the pancreatic effluent samples. A 30 minute stabilization period was allowed after setting up the dog model. Simultaneous venous and arterial blood samples were collected and the pancreatic arterial blood flow measured. The percentage oxygen saturation and the hemoglobin were

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measured in both the venous and arterial samples using an International Laboratories (Lexington, Massachusetts, U.S.A.) 182 Co-Oximeter and the arterial oxygen tension (Pao_2) was estimated using an International Laboratories (Lexington, Massachusetts, U.S.A.) 213 Digital pH Blood Gas Analyzer.

Oxygen consumption was calculated using the formula: Pancreatic blood flow × Hemoglobin × Difference between the arterial and venous percentage saturation × 1.34/100 and expressed as milliliter of oxygen consumed per minute by the pancreas.[19]

Prior to induction of the pancreatitis, two blood samples were taken at ten minute intervals and they represented the control values for the normal pancreas. Further blood samples were taken 15, 30, 60, 90 and 120 minutes after induction of the pancreatitis.

The dogs were divided into two groups, each of six animals. The first group was infused only with 50 ml. saline per hour and acted as the "saline treated" group. In the second group, Dextran 40 (1.5 ml/kg) was added to the saline infusion starting 60 minutes after induction of the pancreatitis and they were the "Dextran treated" group. Two additional dogs who underwent a laparotomy, but in whom pancreatitis was not induced had serial estimations of oxygen consumption made for two hours (control).

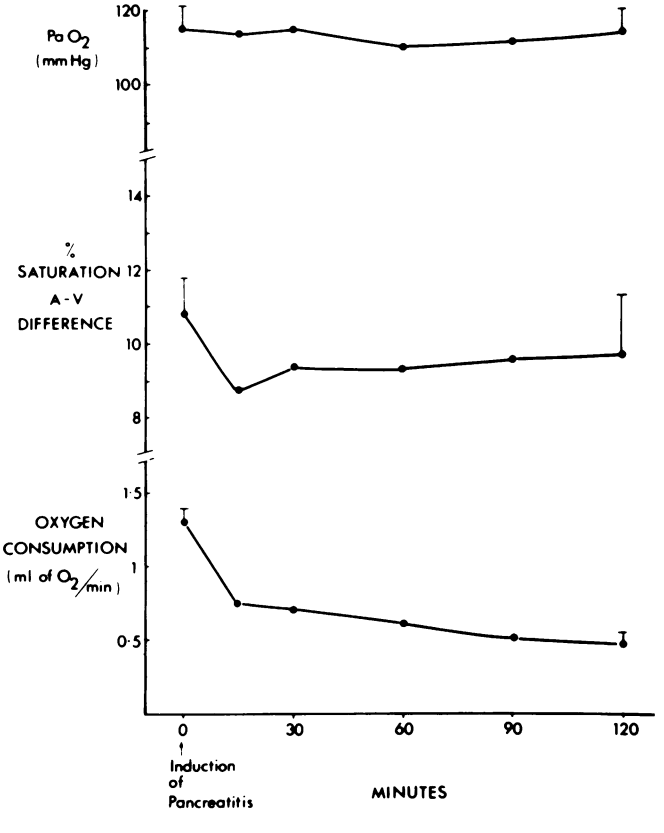

FIG. 1. Changes in arterial PO_2, arteriovenous oxygen saturation difference and oxygen consumption of pancreas before and after induction of acute experimental pancreatitis.

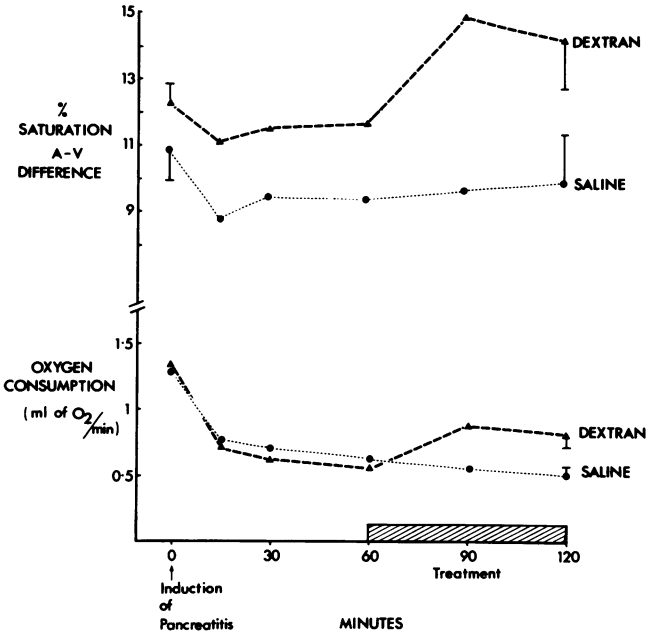

FIG. 2. Changes in arteriovenous oxygen saturation difference and oxygen consumption of pancreas in acute experimental pancreatitis before and after treatment with dextran.

Results

The Po_2 in the arterial blood exceeded 110 mmHg in all the dogs throughout the period of the study (Table 1). The difference between the percentage saturation in the arterial and venous blood samples (A-V difference) prior to induction of pancreatitis in the two groups was not significantly different with values of 10.8 and 12.3% respectively (Figs. 1 and 2 and Table 1). Induction of pancreatitis produced no significant change in the A-V difference in the "saline only" dogs. The mean value at 120 minutes was 9.7%. In contrast, when the Dextran 40 was infused into the group II dogs, the A-V difference increased to 14% at 120 minutes which was significantly wider ($p < 0.05$) than the "saline only" dogs.

The mean oxygen consumption of the normal pancreas in the two groups was 1.3 ml O_2/minute. Induction of pancreatitis produced a rapid fall in the oxygen consumption to 0.74 ml O_2/minute at 30 minutes in the "saline only" group ($p < 0.001$). This continued to fall to a mean value of 0.48 ml O_2/minute at 120 minutes. The oxygen consumption fell by a similar degree over the first 60 minutes in the group II dogs, at which time treatment with Dextran 40 was commenced. This resulted in an increase in the oxygen consumption over the subsequent 60 minutes from 0.57

TABLE 1. *Serial Changes in Acute Pancreatitis*

Time (minutes)	0*	15	30	60†	90	120 ± SD	p at 120 min.
PaO_2							
control	119	115	110	116	119	114	
group I	115	115	110	112	114	115	
group II	113	114	111	114	112	113	
Oxygen consumption							
ml 0/min control	1.15	1.2	1.1	1.15	1.1	0.98	
group I	1.3	0.74	0.71	0.6	0.5	0.48 ± 0.15	0.001
group II	1.3	0.71	0.61	0.57	0.85	0.76 ± 0.17	
A-V difference							
control	9	9.2	9.1	8.6	8.1	8.7	
group I	10.8	8.8	9.3	9.3	9.3	9.7 ± 4	0.05
group II	12.3	11.1	11.5	11.6	14.8	14.1 ± 3.6	

* Start of pancreatitis.
† Start of Dextran 40 (1.5 ml/kg).

ml O_2/minute to 0.76 ml O_2/minute ($p < 0.05$). The Pao_2, A-V difference and oxygen consumption remained constant in the two dogs in whom pancreatitis was not induced.

Discussion

Little is known about the pathophysiology of acute pancreatitis,[2,4,7,13] and information is scanty and controversial regarding the oxygen consumption of either the normal or diseased pancreas.[28] Frogge and coworkers[10] reported that the oxygen consumption of the unstimulated dog pancreas was 0.025 ml O_2/minute/g. This did not alter when either secretin or pancreozymin was given. In this present study the oxygen consumption of the pancreas during the control period was 1.3 ml O_2/minute. Since the average weight of the pancreas in a 15 kg dog is about 35 g the results in these two studies are similar.

The serial changes occurring in oxygen consumption in acute pancreatitis have not been previously reported. Over the 120 minutes the oxygen consumption in the saline group fell from a mean of 1.3 ml O_2/minute to 0.48 ml O_2/minute. This 63% fall in the oxygen consumption was not related to systemic hypoxia since the Pao_2 remained in excess of 110 mmHg throughout this study.

The pancreatic blood flow has already been shown to fall rapidly in experimental pancreatitis[7,13,23,25] with a 45–72% fall[7,25] in the three hour period after inducing the pancreatitis. This was a selective change since over the same time period the percentage of the cardiac output reduced from 3 to 1.6%.[7]

These findings are in contrast to the increased blood flow and increased oxygen consumption noted in other inflammatory conditions. Patients with severe sepsis often have a raised cardiac output and increased oxygen consumption,[30] and systemically septic dogs have an increased oxygen consumption even in the presence of a diminished cardiac output.[30] In dogs with a septic hind limb, the cardiac output was increased by 50% and the majority of it was through the septic area.[15]

The oxygen consumption of an organ may be altered by changes in the hemoglobin, pancreatic blood flow and the A-V difference. The hemoglobin increased by a mean of 1.5 g/dl during the period of investigation, while the pancreatic blood flow has already been shown to significantly fall in acute pancreatitis. Hence it might be expected for the pancreas to extract more oxygen from the slower flowing blood in an attempt to maintain a constant tissue oxygen tension. This mechanism, reflected by a widening of the A-V difference, has been demonstrated in dogs with a critical arterial stenosis producing an ischemic limb.[19]

However, the A-V difference remained constant in the group I dogs. Arteriovenous shunting is a histological feature of acute pancreatitis,[24,26] and a constant A-V difference in the presence of progressive pancreatic ischemia and hypoxia tends to confirm the functional effect of this histological observation.

Imrie and workers[16] have recently reported the high incidence of systemic arterial hypoxia in patients with acute pancreatitis. This hypoxia remained for up to one week and was associated with an increased mortality.

Day et al.[6] have emphasized the damaging effect of hypoxia on dogs given bile induced pancreatitis. Both hypoxia and hypercapnia can stimulate the sympathetic nervous system with the release of epinephrine. This produces further vasoconstriction which will potentiate the ischemia within the pancreas. Indeed, stimulation of the sympathetic nervous system either centrally or peripherally has been shown to enhance the development of a lethal hemorrhagic pancreatitis from a mild nonlethal type,[12] while a sympathectomy has the reverse effect.[14]

Dextran 40 has been shown to reduce the mortality

and morbidity of acute experimental pancreatitis[1,31] and maintain the pancreatic blood flow.[7,13] It also has a beneficial effect in hemagglutination states.[5,11,29,31] Dextran 40 also has been demonstrated to reverse or prevent experimentally produced intravascular aggregation with a resultant return in the oxygen consumption towards normal.[20] This latter property may be of considerable importance since Murphy et al.[22] have recently reported that a degree of intravascular coagulation may be a feature in acute pancreatitis.

In our study, treatment with Dextran 40 was started 60 minutes after induction of the pancreatitis in the group II dogs. This produced a significant increase in the oxygen consumption which was greater at 120 minutes than the group I dogs ($p < 0.001$). The A-V difference also widened with treatment by Dextran 40 from 11.6 to 14% and this was significantly greater than the group I dogs at 120 minutes ($p < 0.05$).

The increase in the A-V difference in the presence of a maintained but reduced pancreatic blood flow suggests that the Dextran 40 was producing a real increase in the pancreatic microcirculation with increased oxygen consumption by the now hypoxic pancreas. This work gives further evidence that acute pancreatitis may not be a typical inflammatory condition, but rather a primary vascular lesion.

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