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The Effects of Ethanol on Pancreatic Blood Flow in Awake and Anesthetized Dogs[1] (41751)

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Abstract. The pathophysiology of alcohol-induced acute pancreatitis is not clear. Ischemic injury has been suggested as a possible mechanism. To examine the effects of ethanol on pancreatic and splanchnic blood flow, measurements were made in fasted, conditioned awake dogs before and after iv infusion of ethanol (1.7 g/kg). At 30 min blood ethanol concentration ranged between 60 and 150 mg/dl and at 60 min between 166 and 350 mg/dl. Although cardiac output, aortic pressure, left atrial pressure, and arterial pH did not change, pancreatic flow declined by 39 ± 12 ml/min/100 g, $P < 0.05$ (from 173 ± 10 ml/min/100 g) at 30 min and was still depressed (by 27 ± 12 ml/min/100 g, $P < 0.05$) at 60 min. Concomitantly, hepatic arterial flow increased. While hepatic and pancreatic flow changed inversely, the correlation ($r = -0.17$) of these changes was not significant. At comparable blood ethanol concentrations in pentobarbital-anesthetized dogs hepatic arterial flow increased by 11 ± 3 ml/min/100 g, $P < 0.01$ (from 24 ± 5 ml/min/100 g), but pancreatic flow did not change. Thus, in the awake dog at blood levels that would produce mild to moderate alcoholic intoxication in man, ethanol reduces pancreatic flow. Although hepatic flow increases concomitantly, the relationship of these changes appears to be independent.

Local blood flow generally increases to areas of acute inflammation (1). In contrast to these changes, pancreatic blood flow appears to be reduced in experimental acute hemorrhagic pancreatitis (1–3). Ethanol, a causative substance in acute pancreatitis (4), has profound metabolic, hemodynamic, and regional blood flow effects. It would be of interest, therefore, to determine the acute changes of pancreatic blood flow produced by ethanol. Since the pancreas shares a common blood supply with other splanchnic organs, pancreatic flow might reflect primary effects in other regions. Accordingly, gastrointestinal blood flow was measured in conscious dogs before and following the intravenous administration of ethanol using the method of radionuclide-tagged microspheres (5). To determine the effects of anesthesia on these changes, comparable studies were also performed in the anesthetized dog.

Method. Healthy conditioned dogs, ranging in weight from 18–27 kg, were prepared 7 days before experimentation. Sterile catheters were positioned in a pulmonary vein and internal thoracic artery. To prevent catheter dislodgement a specially prepared jacket was worn by the dog. Catheter patency was maintained by daily irrigation of catheters which were then filled with sodium heparin. Additional heparin was administered prior to the experiment. Dogs were taken to the laboratory daily and exercised. During the day of the experiment the dogs were allowed to accommodate to the laboratory environment and placed in a specially designed sling for hemodynamic and blood flow measurements. Studies were performed after a 24-hr fast. After a period of 15–30 min, to allow each dog to accommodate to the sling, control measurements were made. Ethanol, 1.7 gm/kg, in a 25% (v/v) saline solution, was then infused intravenously over 60 min. Ethanol blood levels were measured using the enzymatic method (6). At 30 min, at an average blood ethanol level of 106 ± 6 mg/dl (range: 60–150 mg/dl) and at 60 min, at the time of the cessation of the infusion, when average blood ethanol level was 231 ± 18 mg/dl (range: 166–

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350 mg/dl), regional blood flow and hemodynamic determinations were repeated.

Dogs that had been fasted for 24 hr and weighed between 17 and 23 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intravenously administered. No additional anesthesia was given during an experiment. All dogs were intubated and ventilated with a Harvard respirator. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. Catheters were positioned in the inferior vena cava and descending aorta. A cannula was also placed in the left atrial appendage. To maintain catheter patency, sodium heparin was administered. All hemodynamic and chemical determinations were made in the same fashion as those obtained in the awake dog except that the anesthetized animal remained in a right lateral decubitus position rather than in a sling. Ethanol, 1.7 gm/kg, in a 25% (v/v) saline solution, was administered intravenously over 30 min, resulting in an average ethanol blood level of 219 ± 7 mg/dl (range: 152–264 mg/dl). Five additional dogs received an equivalent volume of saline without alcohol.

Regional blood flow was measured with 15 μm microspheres using the method of Rudolph and Heyman (5). Microspheres were labeled with strontium-85, cerium-141, iodine-125, or scandium-46. Between four and six million microspheres in 5 ml of a 63% sucrose suspension were rapidly injected into the left atrium; cannula was then flushed with 5% dextrose in water over a 15- to 20-sec period. Beginning 30 sec before and continuing for exactly 2½ min, a reference blood sample was withdrawn from the arterial catheter at 3.69 ml/min, using a Harvard withdrawal pump. After completing blood flow studies, animals were anesthetized with pentobarbital and sacrificed with potassium chloride. Multiple tissue samples were obtained from stomach, liver, spleen, pancreas, duodenum, ileum, proximal colon (cecum), distal colon (rectum), and renal cortex. Samples, which were between 1 and 2 g, were measured to the nearest milligram and placed in glass tubes and counted for 5 min in a 3-in. well-type sodium iodide scintillation counter. Appropriate energy windows and standard techniques were used for isotope separation (5). To reduce further any error that might be introduced by contaminant contributed by accompanying isotopes and background, the order of isotopes was randomized for each experiment.

Flow to each region (ml/min/100 g) was calculated using the formula:

$$Q_b = \frac{Q_r \times C_b \times 100}{C_r \times \text{wt}}$$

where Q_b = the tissue blood flow (ml/min/100 g), Q_r = reference blood flow (ml/min), C_b = total counts in the sample, C_r = total counts in reference sample and wt = weight of sample (grams). Total hepatic arterial and pancreatic blood flow were determined from organ weight estimated from the total body weight (7). Cardiac output (CO in liters/min) was calculated by the formula:

$$\text{CO} = \frac{Q_r \times C_i \times 10^{-3}}{C_r}$$

where C_i = total counts of isotope injected. Calculations of flow were performed with an IBM System III computer.

Arterial pH and PCO_2 were measured with a Radiometer Acid–Base Cart and oxyhemoglobin saturation with an A/O oximeter. Pressures were measured with a Statham P23Db strain gauge manometer with zero reference taken as the midchest. Data were analyzed with the Student t test for paired data, using Dunnett's table for multiple comparison with same control (8), to determine the significance of the flow changes produced by ethanol and the Student t test for unpaired data to compare the differences in the basal blood flow in anesthetized and conscious dogs. $P < 0.05$ was considered significant. Values are expressed as the mean ± standard error of the mean. The concomitant brain blood flow changes are the subject of another report (9).

Results. *Splanchnic flow in conscious dogs.* The ethanol infusion did not produce a significant change in cardiac output, aortic pressures or left atrial mean pressures in the conscious dog (N = 10). Arterial pH, PCO_2, or oxyhemoglobin saturation were also not altered. As shown in Fig. 1, at both low and moderate ethanol concentrations a redistribution of splanchnic flow occurred: Pancreatic flow declined by 39 ± 12 ml/min/100 g, $P < 0.05$ (from 173 ± 10 ml/min/100 g), and

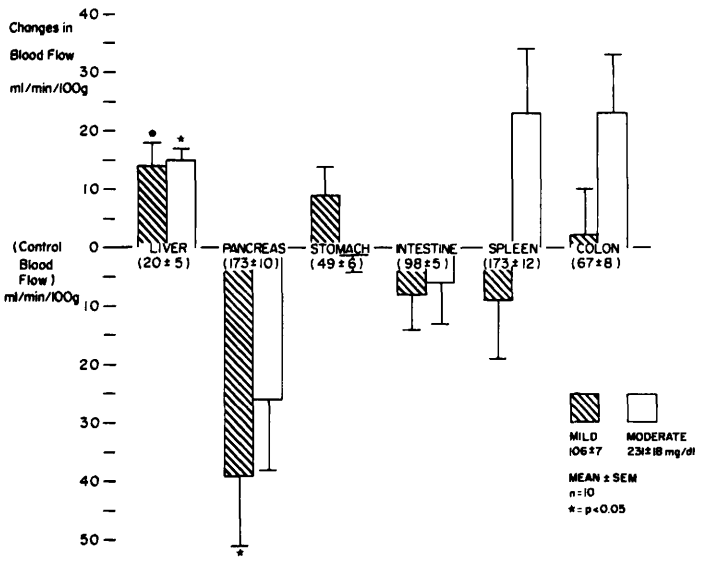

FIG. 1. Comparative changes of ethanol on splanchnic blood flow in conscious dog. Changes in flow at 30 min (mild intoxication) are contrasted with those at 60 min (moderate intoxication).

was still below control values, by 27 ± 12, $P < 0.05$, at peak ethanol levels. Concomitantly, hepatic arterial flow had increased above basal levels by 14 ± 4 ml/min/100 g, $P < 0.05$ (from 20 ± 5 ml/min/100 g), and by 15 ± 2 ml/min/100 g, $P < 0.05$, at peak ethanol levels. At moderate ethanol concentrations, proximal colon flow (by 23 ± 10 ml/min/100 g, $P < 0.05$, from 67 ± 8 ml/min/100 g) had also increased, whereas a concomitant increment of splenic flow (by 23 ± 11 ml/min/100 g, from 173 ± 12 ml/min/100 g) lacked statistical significance using Dunnett's table. At both ethanol concentrations blood flow to the stomach, duodenum, ileum, distal colon, and renal cortex did not change.

Correlative changes. Since the pancreas and the liver share a common arterial supply, the coeliac artery, and since ethanol produced a reciprocal change in blood flow to these organs—pancreatic flow declined when hepatic flow increased—the relationship between these changes was examined. However, as shown in Fig. 2, the correlation between the maximal change in pancreatic flow to the concomitant change in hepatic flow was not significant ($r = -0.17$, PNS); even when estimated organ weights were considered, no significant correlation was found ($r = -0.18$, PNS). Although flow to the spleen—an organ that shares a common arterial tributary with the pancreas—also increased at peak ethanol concentrations, this change occurred when the decline in pancreatic flow had become less pronounced. Thus, the decline of pancreatic flow could not be explained as a passive redistribution of flow, resulting from primary blood flow changes in organs with which the pancreas shares a common arterial blood supply.

Splanchnic flow in the anesthetized dog. Since previous experimental studies of

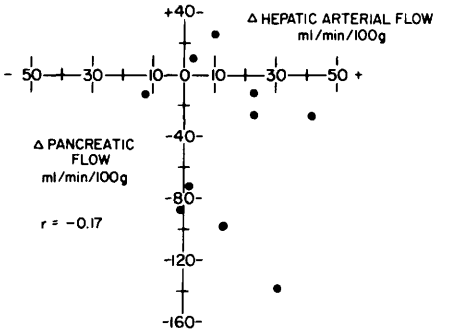

FIG. 2. Relationship between changes in pancreatic flow and hepatic flow. Peak change of pancreatic arterial flow, which occurred at 30 min of ethanol infusion, is correlated with concomitant hepatic flow change. This relationship was not significant. Means of samples from 10 dogs are displayed.

splanchnic blood have generally been performed in anesthetized animals, the findings obtained in awake dogs (N = 10) were contrasted with those obtained in anesthetized dogs (N = 9). Ethanol infusion in the anesthetized animal produced a decline in pH (from 7.41 ± 0.01 to 7.38 ± 0.01, $P < 0.05$) but no change in aortic mean pressure, cardiac output, PCO_2, or oxyhemoglobin saturation. As Fig. 3 demonstrates, neither saline nor ethanol produced a change in pancreatic blood flow in the anesthetized dog. By contrast, anesthesia did not alter the effect of ethanol on blood flow to the liver or proximal colon: Hepatic arterial (by 11 ± 3 ml/min/100 g, $P < 0.01$, from 24 ± 5 ml/min/100 g) and proximal colon (by 22 ± 9 ml/min/100 g, $P < 0.05$, from 65 ± 7 ml/min/100 g) blood flow increased. Also, as observed in the anesthetized dog, stomach, intestine, and renal cortical flow did not change. Table I shows that when basal blood flow was not significantly altered by anesthesia, regional blood flow changes produced by ethanol were similar in both anesthetized and conscious dogs. However, in anesthetized dogs, with basal pancreatic flow lower than that produced by ethanol in conscious dogs, no further change in flow occurred after ethanol administration.

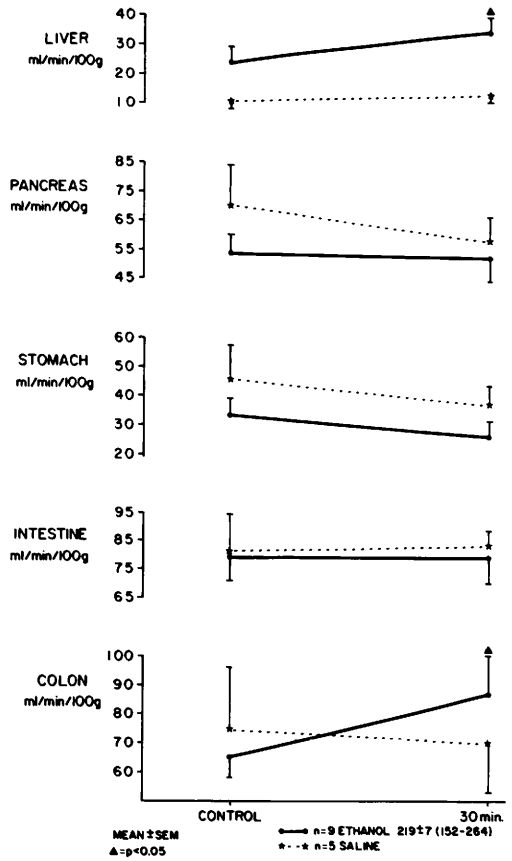

FIG. 3. Changes in splanchnic blood flow in anesthetized dogs. Effects of saline and ethanol on splanchnic blood flow are compared. Colon and liver blood flow increased after ethanol, whereas pancreatic flow did not change. Saline did not alter blood flow. Average and (range) of blood ethanol shown.

TABLE I. ORGAN BLOOD FLOW BEFORE ETHANOL

	Anesthetized dog (N = 9) (ml/min/100 g)	Awake dog (N = 10) (ml/min/100 g)
Pancreas	54 ± 6[a]	173 ± 10*
Colon	65 ± 7	67 ± 8
Intestine	79 ± 8	98 ± 5
Stomach	33 ± 6	49 ± 6
Liver	24 ± 5	20 ± 5

[a] Mean ± SEM.
* $P < 0.001$.

Discussion. An intravenous infusion of ethanol in conscious dogs, with blood concentrations reaching those found in man with mild to moderate alcohol intoxication, produced a redistribution of splanchnic blood flow: Hepatic arterial flow increased after ethanol administration whereas pancreatic blood flow declined. By contrast, a similar infusion in anesthetized dogs reaching comparable blood levels did not change pancreatic flow even though hepatic arterial flow had increased. In both awake and anesthetized dogs ethanol also increased blood flow to the proximal colon. Thus, pancreatic blood flow was found to decline after ethanol administration and this effect was obscured by pentobarbital anesthesia.

The effects of ethanol on hepatic (10–15) and pancreatic (16) blood flow have been studied before but not concomitantly. Previous studies (13–15), but not all (10–12), in baboon (14), man (13), and dog (15)—both with (14) and without anesthesia (13, 15) have generally demonstrated that hepatic blood flow increases after ethanol administration. Also in

a study similar to ours, Horwitz and Myers (16) found a decline in pancreatic flow at blood levels comparable to our peak levels. These investigators (16) did not observe such a response, however, at lower concentrations. The explanation for this difference is not apparent, although in that study ethanol was administered as a bolus over 10 min rather than by a slow infusion over 60 min.

Since concomitant systemic hemodynamic changes were not observed in these studies, the decline in pancreatic flow must have been a reflection of local vascular changes. The failure to demonstrate an association of the decline in pancreatic flow with the blood flow changes in the other organs with which the pancreas shares a common blood supply suggests that passive local redistributional effects would not be the explanation for the decline in pancreatic flow. However, although tissue samples were obtained from all splanchnic organs, the intact organs themselves were not weighed. Therefore, the actions of ethanol on *total* portal flow could not be measured, which limits the conclusions that can be derived from our observations of the regional flow changes.

The neurohumoral effects of ethanol also appear to have been excluded, at least in part, by the studies of Horwitz and Myers (16). In those studies alpha, beta, histaminergic, and prostaglandin blockade did not obviate an ethanol-induced decline in pancreatic flow (16). However, neither opiate receptor nor vagal blockade was performed in these studies. Since naloxone may attenuate the acute intoxicating effects of ethanol (17) and the reduction of pancreatic exocrine secretion by intravenous ethanol can be abolished by atropine (18), a direct or indirect role of these neurohumoral mechanisms must still be considered as possible explanations for the effects of ethanol on pancreatic blood flow.

Horwitz and Myers (16) also assessed the effects of a mannitol infusion on pancreatic blood flow after ethanol administration. Although cardiac output was not altered by the mannitol infusion and flow to other splanchnic organs was not changed, there was a partial reversal of the ethanol-induced decline in pancreatic flow. Pancreatic blood flow, however, was still substantially lower than the flow rate before ethanol administration. Also, the effect of mannitol on pancreatic flow before ethanol administration was not examined. Thus, their suggestion that cell swelling might be responsible for the decline in pancreatic flow must be still viewed as being unproven.

Although our study and that by Horwitz and Myers (16) demonstrated a decline of pancreatic flow after ethanol administration, neither study established that pancreatic ischemia was produced. Because concomitant pancreatic oxygen extraction and oxygen consumption were not measured, it is possible that the fall in pancreatic flow was merely a reflection of an ethanol-induced reduction in pancreatic oxygen demand. Also, since intravenous ethanol has been shown to decrease pancreatic exocrine secretion (18), the changes in blood flow observed with ethanol administration may be a reflection of the reduced metabolic requirements resulting from this effect.

The mode of ethanol administration in our study can be viewed as another limitation when extrapolating our findings to man. While intravenous ethanol did not alter stomach or small intestinal blood flow, the application of ethanol to stomach mucosa (19) increases blood flow to this organ. Also, small intestine blood flow has been shown to increase when alcohol is given to dogs through an exteriorized loop of jejunum (20). Moreover, while intravenous ethanol administration reduces pancreatic exocrine secretions, this finding is not observed when ethanol is delivered by a gastrointestinal route (18). These differences suggest that when ethanol is taken by mouth, the early gastrointestinal blood flow changes, at least, might be different from those observed when this substance is given by intravenous administration. Nevertheless, even if this is so, after ethanol absorption is completed, the effects of *blood* ethanol might be paramount and pancreatic flow might therefore decline.

Also, when alcohol is ingested in the human, cardiac output generally *increases* (21, 22). In our study cardiac output did not change. Such a difference in total flow might be associated with different flow patterns in some regions than those we observed. Accordingly, this disparity must be viewed as another limitation when extrapolating our observations to the human. Thus, additional investigations are needed to clarify these relationships before it can be concluded that ethanol use may pro-

duce pancreatitis by the mechanism of ischemic necrosis.

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