Ethanol-Induced Alterations in Pancreatic Blood Flow in Conscious Dogs

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SUMMARY Because ethanol abusers are susceptible to pancreatitis in animal models, and interruption of the pancreatic circulatory supply may also cause pancreatitis, we studied the effect of ethanol infusion on pancreatic blood flow. We administered ethanol 0.5 g/kg and 1.5 g/kg iv, to 35 conscious dogs (ethanol blood levels, 117 ± 10 (SD) and 297 ± 67 mg/100 ml, respectively). Measurements were made of aortic pressure and regional blood flow by the radioactive microsphere method in the pancreas, stomach, spleen, intestines, adrenal glands, and kidneys. Pancreatic flows were 172 ml/min per 100 g control, 156 ml/min per 100 g after 0.5 g/kg ethanol and 108 ml/min per 100 g after 1.5 g/kg ethanol. After the higher dose, the decrease in pancreatic flow of 64 ml/min per 100 g or 37% was statistically significant (P< 0.01); pancreatic vascular resistance rose by 113% (P< 0.001). There were no significant changes in flow or resistance in the other organs studied. Similar changes in pancreatic flow and resistance occurred after 1.5 g/kg ethanol in groups of dogs pretreated with phenoxybenzamine, an α-adrenergic antagonist; propranolol, a β-adrenergic antagonist; cimetidine, a histamine H2 receptor antagonist; and meclofenamate, a prostaglandin synthetase inhibitor. The changes in pancreatic blood flow and resistance were substantially reversed by 25% mannitol, 3 ml/kg, iv, after infusion of ethanol. We conclude that ethanol, in high doses relevant clinically, selectively elevates pancreatic vascular resistance, probably by inducing perivascular cellular swelling. Circ Res 50: 250-256, 1982

ALTHOUGH it has been common knowledge that ethanol abusers are uniquely susceptible to pancreatitis, the reason for this association has not been clear. On the basis of data from animal models, several investigators have suggested that circulatory disturbances may be a major factor in the etiology of acute hemorrhagic pancreatitis. Either generalized (Smyth, 1940; Block et al., 1954; Pfeffer et al., 1962) or localized (Mengury et al., 1957) pancreatic necrosis have been observed when the pancreatic arterial supply was occluded by various methods. Accordingly, we investigated the possibility that ethanol might cause changes in pancreatic flow or resistance which could be relevant to ethanol-induced pancreatitis in clinical settings.

Ethanol was administered parenterally to conscious, resting dogs, and regional flow changes in the pancreas were compared with those in other abdominal organs. The blood levels of ethanol attained in these animals were in the range of what is commonly encountered in clinical settings. We found that high doses of ethanol cause a substantial elevation in vascular resistance in the pancreas without altering vascular tone elsewhere in the abdomen. This is the first report of a relationship between ethanol exposure and a potentially adverse physiological reaction in the pancreas.

Methods

Sterile thoracotomies under halothane anesthesia were performed on 35 adult mongrel dogs weighing 13.7-25.5 kg. Polyvinyl 18-gauge catheters were implanted in a jugular vein, the left atrium, and the thoracic aorta. Seven to 12 days were allowed for recovery before experiments began.

Regional blood flow in selected abdominal organs was determined by the radioactive microsphere technique, as we have described previously (Buckberg et al., 1971; Fixler et al., 1976; Morgan et al., 1978). Four radioactive labels, 85Sr, 46Sc, 141Ce, and 125I, were used with inert microspheres, measuring 10-20 μm in diameter. For each regional flow measurement, a bolus of labeled microspheres was injected into the left atrial catheter and flushed in with 15 ml of saline over approximately 10 seconds. Total counts injected were calculated, using weighed aliquots from continuously agitated injectate solutions. Blood was withdrawn with a Holter pump from the aorta, beginning just before the microspheres were injected and continuing for 90 seconds thereafter. Cardiac output was measured directly from timed volume collections of this blood (Fixler et al., 1976; Morgan et al., 1978). After the experiment, an overdose of barbiturate was administered to each dog. After death, the pancreas, stomach, spleen, portions of the large and small intestines, right adrenal gland, and both kidneys were removed. The organs were homogenized and counted in a Packard 5230 well-type γ scintillation counter, using differential spectrometry (Buckberg et al., 1971; Fixler et al., 1976, Morgan et al., 1978). Each sample contained at least 600 microspheres, and samples were measured in triplicate. In each
dog, flows measured in the two kidneys varied by less than 15%. Aortic pressure was continuously monitored with a Statham P23Db transducer and a Beckman oscillograph, except when aortic blood was sampled. The aortic pressure reported was obtained just prior to microsphere injection. Regional vascular resistance was calculated as the quotient of the aortic pressure in mm Hg divided by regional flow in ml/min - 100 g tissue weights.

During the experiments, the dogs, after an overnight fast, lay in a sling to which they had been accustomed previously. No sedation was given prior to study. An initial microsphere injection was made while the dog was resting quietly. Ethanol 0.5 g/kg body weight then was infused into a peripheral vein through an implanted catheter or a percutaneously inserted catheter over a 10-minute period. The infusate was a 50% ethanol solution made by mixing equal amounts of pure ethanol and one-half normal saline. Ten minutes after this infusion ended, a second bolus of microspheres was injected. Immediately afterwards, an additional 1.0 g/kg of ethanol was administered over 10 minutes, and 10 minutes after this second infusion ended, a third microsphere bolus was injected.

After a group of dogs had been studied by the protocol above, other groups of dogs were studied with the same dosages of ethanol after administration of an α-adrenergic-blocking agent (phenoxybenzamine), a β-adrenergic-blocking agent (propranolol), a prostaglandin synthetase inhibitor (meclofenamate), and a histamine H2 antagonist (cimetidine). A preceding control measurement was obtained in each dog prior to administration of these agents. Dosages were: phenoxybenzamine 2.0 mg/kg iv, 30 minutes before ethanol infusion; propranolol 1.0 mg/kg iv, 20 minutes before ethanol infusion; meclofenamate 5.0 mg/kg, iv, 5 minutes before ethanol infusion; cimetidine 15 mg/kg, iv, 20 minutes before ethanol infusion.

The dose of phenoxybenzamine completely blocked the pressor response to phenylephrine, an α-adrenergic agonist, at an infusion rate which elevated aortic systolic pressure by 30 mm Hg prior to administration of the α-receptor antagonist. The dose of propranolol completely blocked the heart rate induced by isoproterenol, a β-adrenergic agonist, infused at 2 μg/min, iv. The dose of meclofenamate reduced urinary prostaglandins in anesthetized dogs by at least 80%. The dose of cimetidine has been shown in numerous studies to decrease gastric secretion markedly. Also, this dose plus chlortrimeton, an H1 histamine receptor blocker, prevented the hypotension induced by histamine phosphate (4 μg/min × 5 minutes, iv) at a dose of chlortrimeton which did not, by itself, block the hypotension.

Finally, a group of dogs was infused with ethanol, as above, and, beginning 10 minutes after the second dose, 3 ml/kg of 25% mannitol were administered over 10 minutes. Measurements were obtained immediately at the end of the mannitol infusion.

Blood ethanol levels were measured according to the method of Kingsley and Current (Kingsley and Current, 1950). Statistical analyses were performed by both one- and two-way analysis of variance.

Results

Effect of Ethanol on Regional Blood Flow in Abdominal Organs

Our initial study was designed to evaluate the effect of ethanol infusions on regional blood flow in the pancreas and other abdominal organs. Nine dogs were studied at two levels of ethanol infusion. Blood ethanol values in eight dogs, following the first ethanol infusion (of 0.5 g/kg), were 117 ± 10 (sd) mg/100 ml and following the second infusion (of an additional 1.0 g/kg) were 298 ± 67 mg/100 ml. These are similar to values we have noted previously with this dosage (Horwitz and Atkins, 1974) and correspond to levels commonly encountered with moderate social drinking and advanced intoxication, respectively, in humans. There were no significant differences from the pre-ethanol control value in either regional flow or regional vascular resistance in the stomach, spleen, large and small intestines, adrenal gland, or kidney. However, regional flow in the pancreas fell by 64 ml/min per 100 g (−37%) and regional resistance in the pancreas rose by 113% after the higher dose of ethanol (Fig. 1 and 2). Both these changes were significant by two-way analysis of variance (P < 0.01). At the lower level of ethanol infusion, changes in pancreatic flow were inconsistent. Although pancreatic resistance rose in seven of the nine dogs, the rises were variable and not statistically significant. Mean aortic pressure rose at the higher ethanol dose (+21 mm Hg (P < 0.01)) but was not altered significantly at the lower dose (Table 1). Cardiac output did not change significantly at either dose.

On the basis of these experiments, we concluded that in normal, conscious dogs exposed to blood alcohol levels of approximately 298 mg/100 ml, there is a sharp rise in vascular resistance in the pancreatic bed, unaccompanied by resistance changes in other abdominal organs, and that this results in a substantial fall in pancreatic blood flow.

Effects of Sympathetic Blocking Agents, a Prostaglandin Synthetase Inhibitor, and a Histamine H2 Antagonist on Ethanol-Induced Changes in Pancreatic Blood Flow

Our subsequent experiments were designed to seek out the mechanism by which the changes in pancreatic blood flow occurred. We considered several possibilities—changes in sympathetic nervous system activity, changes in prostaglandin-mediated activity, and histamine-mediated effects—as possible mechanisms. Accordingly, we administered phenoxybenzamine, an α-adrenergic antagonist, propranolol, a β-adrenergic antagonist, meclofenamate, a prostaglandin synthetase inhibitor, and cimetidine, a histamine H2 receptor blocker before
giving ethanol infusions. Aortic pressure rose significantly during the second ethanol infusion after pretreatment with meclofenamate and cimetidine, but not phenoxybenzamine. None of these drugs altered pancreatic flow prior to ethanol infusions when resting control and post-blocking drug values were compared. In six dogs pretreated with phenoxybenzamine, pancreatic flow fell significantly after ethanol 1.5 g/kg (Table 2). Pancreatic vascular resistance rose in five of the six phenoxybenzamine dogs, but this was not a statistically significant change (Table 2, Figure 3). In six dogs pretreated with meclofenamate, pancreatic flow fell after ethanol 1.5 g/kg in five (not statistically significant) but pancreatic vascular resistance increased significantly ($P < 0.05$, Table 2 and Fig. 3). In four of five dogs pretreated with cimetidine, pancreatic flow fell and pancreatic resistance rose, but in neither case was the change statistically significant (Table 2, Fig. 3). By a one-way analysis of variance, there was no difference in the magnitudes of the changes in flow or resistance in the pancreas, or in the other organs studied, between the group given ethanol alone or the groups given phenoxybenzamine, meclofenamate, or cimetidine. The two dogs given propranolol cannot be compared statistically with the other groups, but after the second dose of ethanol, substantial falls occurred in pancreatic flow ($-82$ and $-97$ ml/100 g per min) and pancreatic resistance rose sharply in both dogs. Cardiac output
TABLE 1  Effects of Ethanol Infusion on Aortic Pressure and Cardiac Output

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ethanol 0.5 g/kg</th>
<th>Ethanol 1.5 g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \bar{x} ) AOP (mm Hg)</td>
<td>102 ± 3</td>
<td>106 ± 4</td>
<td>123 ± 5*</td>
</tr>
<tr>
<td>C.O. (liters/min)</td>
<td>2.85 ± 0.21</td>
<td>2.52 ± 0.15</td>
<td>2.75 ± 0.28</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Phenoxybenzamine pretreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>88 ± 4</td>
<td>88 ± 2</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>( \bar{x} ) AOP (mm Hg)</td>
<td>2.38 ± 0.36</td>
<td>2.39 ± 0.25</td>
<td>2.38 ± 0.20</td>
</tr>
<tr>
<td>C.O. (liters/min)</td>
<td>2.24 ± 0.19</td>
<td>2.24 ± 0.20</td>
<td>2.18 ± 0.39</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Meclofenamate pretreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95 ± 4</td>
<td>98 ± 9</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>( \bar{x} ) AOP (mm Hg)</td>
<td>2.86 ± 0.39</td>
<td>2.52 ± 0.34</td>
<td>2.45 ± 0.37</td>
</tr>
<tr>
<td>C.O. (liters/min)</td>
<td>2.17 ± 0.10</td>
<td>2.65 ± 0.37</td>
<td>2.65 ± 0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine pretreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>90 ± 2</td>
<td>96 ± 4</td>
<td>106 ± 7</td>
</tr>
<tr>
<td>( \bar{x} ) AOP (mm Hg)</td>
<td>2.04 ± 0.19</td>
<td>1.73 ± 0.10</td>
<td>1.93 ± 0.10</td>
</tr>
<tr>
<td>C.O. (liters/min)</td>
<td></td>
<td></td>
<td>2.24 ± 0.20</td>
</tr>
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<td></td>
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</tbody>
</table>

Definitions: \( \bar{x} \) AOP = mean aortic pressure, C.O. = cardiac output, Control = original value before any intervention ± SE.

* Significant difference (P < 0.05) by analysis of variance from pre-ethanol value (post-drug except in "No Drug Pretreatment" group).

Effects of Mannitol after Ethanol Infusion

We considered the possibility that cellular swelling related to fluid shifts might have influenced the changes in pancreatic flow or resistance. To assess this, we gave hypertonic mannitol, an osmotically active agent which does not enter cells, shortly after ethanol infusions, to see whether the decrease in flow could be reversed by this agent.

In seven dogs, mannitol was administered after the second ethanol infusion. Serum osmolalities by freezing point depression were done in two dogs. Pre-ethanol levels were 282 and 289 mOsm/kg H2O, levels post-ethanol were 288 and 301, and levels at the end of the mannitol infusion were 308 and 306, respectively. Aortic pressure rose after ethanol 1.5 g/kg 94 ± 4 to 119 ± 7 mm Hg (+25 mm Hg, P < 0.05). Cardiac output was unchanged (2.54 ± 0.40 liters/min control, 2.52 ± 0.35 liters/min with ethanol, 2.72 ± 0.15 liters/min with mannitol). As in all the other groups, the pancreatic flow decreased (—43%) and resistance rose (+163%) after the second ethanol infusion (Fig. 4). However, after a subsequent 10-minute infusion of hyperosmotic mannitol, flow rose in six of the seven dogs to a level that was no longer statistically different from the pre-ethanol control values (Fig. 4). The pre-ethanol mean value was 154 ml/100 g per min, and post-mannitol, it rose to 110 ml/100 g per min. Pancreatic resistance fell by 46% post mannitol.

There was a significant difference between control

### TABLE 2  Ethanol and Pancreatic Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>No drugs (n = 9)</th>
<th>( \bar{x} ) Phenoxybenzamine (n = 6)</th>
<th>( \bar{x} ) Meclofenamate (n = 6)</th>
<th>( \bar{x} ) Cimetidine (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>( \bar{x} ) 172 ± 38 0.90 ± 0.13</td>
<td>107 ± 16 0.95 ± 0.18</td>
<td>228 ± 59 0.57 ± 0.21</td>
<td>94 ± 20 1.28 ± 0.34</td>
</tr>
<tr>
<td>Ethanol 0.5 g/kg</td>
<td>( \bar{x} ) 155 ± 40 0.99 ± 0.17</td>
<td>103 ± 23 1.28 ± 0.41</td>
<td>137 ± 33 0.98 ± 0.27</td>
<td>81 ± 23 1.98 ± 0.71</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ethanol 1.5 g/kg</td>
<td>( \bar{x} ) 108 ± 34 1.73 ± 0.31</td>
<td>82 ± 18 1.83 ± 0.61</td>
<td>79 ± 3 1.82 ± 0.47</td>
<td>64 ± 27 2.42 ± 0.54</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean (\( \bar{x} \)) and standard errors (±) for pancreatic flow and resistance. NS = P > 0.05; n = number of subjects. Rest value is obtained immediately prior to ethanol infusions and after drug pretreatment, if given.
values and post-ethanol resistances but not between the control and values after both ethanol and mannitol. Mannitol had no significant effect on flows in the other abdominal organs studied. Therefore, we concluded that mannitol partially reverses ethanol-induced elevation in pancreatic vascular resistance. Since mannitol is not metabolized, this is presumptive evidence that fluid shifts from cells into extracellular fluid can reverse the ethanol-induced rise in pancreatic vascular resistance.

Discussion

Although it has been known that ethanol induces vasodilation in the coronary circulation and in some cutaneous vessels, there has been little information about its influence on vascular resistance in other organs. In this study of regional flow in abdominal organs, we found that high concentrations of ethanol caused diminished blood flow in the pancreas. This did not reflect a generalized response in the splanchnic bed, since perfusion in other abdominal organs, such as the stomach and intestines, was not altered. It would appear that, in conscious dogs, the pancreas is unique among abdominal organs in its tendency to exhibit an elevated vascular resistance with exposure to high levels of ethanol.

We considered several possible mechanisms for the pancreatic blood flow changes during ethanol exposure. It has been reported that ethanol causes release of endogenous catecholamines (Nakano et al., 1974) and can potentiate catecholamine effects in aortic smooth muscle strips (Kalsner, 1970; Altura et al., 1976). Since catecholamine-mediated vasoconstriction would be most likely to occur by means of stimulation of α-adrenergic receptors, we pretreated a group of dogs with phenoxybenzamine, an α-receptor antagonist, prior to ethanol administration. Effective blocking doses of phenoxybenzamine did not prevent or attenuate the ethanol-induced elevation in pancreatic resistance. In two dogs, β-adrenergic receptors were blocked with propranolol and, again, a rise in pancreatic resistance occurred with ethanol infusion.

Because stimulation of prostaglandin release and potentiation of prostaglandin-induced pulmonary vasoconstriction with exposure to ethanol have been reported (Collier et al., 1975, Doekel et al., 1978), we also assessed the effects of pretreatment with high doses of meclofenamate, a prostaglandin synthetase inhibitor. Elevations in pancreatic resistance occurred with ethanol despite prior meclofenamate administration in five of six dogs tested. Although, in a previous study, direct administration of histamine did not appreciably alter pancreatic blood flow (Delaney and Grim, 1966), since ethanol administration can directly or indirectly result in
decreased histamine-mediated activity, including gastric hypersecretion which influences pancreatic function, we studied the effects of cimetidine, a histamine H2 receptor blocker, on pancreatic flow during ethanol exposure. Again, pancreatic vascular resistance rose with high-dose ethanol infusions in most dogs. Therefore, it is unlikely that pancreatic flow and resistance changes due to ethanol are mediated by the sympathetic nervous system, prostaglandins, or histamine H2 receptors.

We did note a substantial improvement in pancreatic blood flow previously reduced by ethanol when we infused hypertonic mannitol. The most likely mechanism by which a small increase in osmolality partially reversed the ethanol-induced increase in pancreatic resistance is by reduction of edema in perivascular cells, as has been described during severe ischemia in the kidney, brain, or heart (Ames et al., 1968; Flores et al., 1972; Willerson et al., 1972). In this context, it is more likely that the effect of ethanol is directly on pancreatic cells rather than on vascular control mechanisms determining arterial smooth muscle tone. Impaired metabolism in pancreatic parenchymal or perivascular cells may reduce energy production to levels insufficient for the active extrusion of sodium (Ames et al., 1968; Flores et al., 1972; Willerson et al., 1972). Accumulation of sodium intracellularly would cause water to passively diffuse into these cells (Ames et al., 1968; Flores et al., 1972) making them edematous. The swollen endothelial and interstitial cells may then compress capillaries and small arterioles, increasing pancreatic vascular resistance. Hypertonic mannitol, which enters the extracellular space but does not enter cells, presumably increased osmotic pressure, and water was passively drawn out of the cells, partially correcting the vascular compression. Although ethanol infusion itself elevated blood osmolality slightly, since this substance, unlike mannitol, diffuses readily into cells where osmotic pressure could also have been altered, this change may not have influenced the interchange of fluid across the cell membranes. The dosage of mannitol in our experiments was deliberately designed to be below levels which increase venous return to the heart or tend to trigger centrally mediated reflex mechanisms (Atkins et al., 1973) but sufficient to induce discernible osmotic effects (Atkins et al., 1973; Willerson et al., 1975).

By our formulation, the reduction of impaired pancreatic flow with infusion of a high dose of ethanol is likely to be the result of direct effects of ethanol on pancreatic cells. This is speculative, since there is very little information on effects of ethanol on pancreatic cell function. It is of interest that Deloire and Lowy (1963) reported that acute exposure of rats to toxic doses of ethanol resulted in a decrease in pancreatic cytoplasmic phosphate compounds, including adenosine monophosphate. Histopathological findings after acute administration of ethanol to animals have generally been limited to “venous congestion” without obvious cellular damage (Saries et al., 1971), although Tremoliers et al. (1963) reported acute lesions after administration of ethanol with gavage. A possible mechanism for pancreatic cell damage with ethanol exposure is through stimulation of hypersecretion which can lead to extravasation of proteolytic enzymes as described by Steer et al., (1979), who studied effects of ethanol on the in vitro rabbit pancreas.

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