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Absorption and Distribution of Ethanol during altered Portal Dynamics in the Dog* (33775)

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Many patients with Laennec's cirrhosis present with a long history of alcoholism. Although derangements in portal blood flow often develop during the course of the disease, information concerning the absorption and distribution of alcohol under these circumstances is limited. Therefore, portal blood flow was altered in dogs to simulate abnormalities in patients with hepatic cirrhosis and the absorption of ethyl alcohol and its transport in blood and thoracic duct lymph was studied and compared to control dogs.

Material and Methods. Nineteen healthy fasted mongrel dogs (8–22 kg) were studied under light general anesthesia (Myotal). The abdominal aorta, right atrium, and thoracic duct were cannulated with polyethylene tubing in 19 animals, and the portal vein was catheterized after splenectomy in 16 animals. In 12 dogs a single hepatic vein was catheterized via the right external jugular vein, and in three other dogs hepatic venous blood was sampled indirectly from the thoracic inferior vena cava just below a constricting ligature. In 16 dogs the thoracic duct was cannulated in the right chest and ventilation was controlled by a Harvard positive-pressure piston respirator. In three dogs the thoracic duct was cannulated in the neck, respiration was unassisted, and the chest and abdomen were not opened. Blood pressure was followed continuously on a direct writing polygraph (Sanborn) and venous pressures on the polygraph or by saline manometry. After control samples of blood and lymph were taken, and all fluid was carefully aspirated from the stomach, distilled absolute ethyl alcohol (Publiker Industries, Inc.) diluted with distilled water to a 75% solution (3 g/kg) was inserted into the stomach by tube gastrostomy (16 dogs) or through an oro-gastric tube (3 dogs). Simultaneous serial samples of blood and thoracic duct lymph were obtained at specific times after intragastric administration, and alcohol levels were determined in plasma and lymph by titration of free iodine with sodium thiosulfate after diffusion into potassium dichromate and liberation of iodine with excess potassium iodide (1). Lymph from the thoracic duct was allowed to flow by gravity drainage, and, except for small samples taken for determination of alcohol content, was returned to the bloodstream via the right atrial catheter. After 3 hr, gastric contents were aspirated and the remaining alcohol content in the stomach

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TABLE I. Alcohol Levels in Plasma and Thoracic Duct Lymph in Five Control Dogs after Intragastric Administration of 75% Ethyl Alcohol (3 g/kg).[a]

Time (min)	Plasma				Lymph thoracic duct
	Aorta	Hepatic vein	Portal vein	Right atrium	
5	87 ± 58	103 ± 66	389 ± 58	63 ± 38	37 ± 21
15	152 ± 42	153 ± 50	330 ± 46	125 ± 32	97 ± 69
30	197 ± 58	154 ± 68	346 ± 65	169 ± 40	166 ± 35
60	213 ± 69	225 ± 65	334 ± 39	173 ± 69	247 ± 66
120	237 ± 58	264 ± 59	396 ± 90	213 ± 67	324 ± 61
180	269 ± 64	267 ± 69	364 ± 55	253 ± 58	328 ± 62

[a] Data expressed as mean value with standard deviation of ethyl alcohol in mg/100 ml.

was determined (1). Four groups of dogs were studied.

Group 1, (8 dogs) in three dogs the thoracic duct was cannulated in the neck and alcohol absorption and transport were studied during spontaneous respiration. In five dogs with controlled respiration the thoracic duct was cannulated in the right chest in conjunction with catheterization of the portal and hepatic veins, aorta and right atrium.

Group II, in three dogs the thoracic inferior vena cava was constricted approximately 50% with umbilical tape and 1 week later experiments were performed. The thoracic duct, portal vein, right atrium, and aorta were sampled from indwelling catheters, but hepatic venous blood was obtained by aspirating blood from an indwelling catheter positioned just below the caval ligature.

Group III, in four dogs the portal vein was narrowed by silk ligature approximately 50% to raise mesenteric venous pressure to 20–25 cm saline, and 1 week later the dogs were restudied. Complete ligation of the portal vein above the entry of the gastroduodenal vein was performed prior to administration of alcohol.

Group IV, in four dogs an end-to-side portacaval shunt was performed and 1 week later alcohol was administered.

Results. Table I–V summarize data concerning the absorption and distribution of ethyl alcohol in blood and thoracic duct lymph in control dogs and in those with altered portal blood flow. Group I, ethyl alcohol was rapidly absorbed into the portal vein and then widely distributed throughout the intravascular compartment. In thoracic duct lymph a slower but steady rise in concentration occurred. After 2–3 hr the alcohol content in thoracic duct lymph usually was greater than in systemic plasma (Table I). Alcohol levels observed in systemic blood samples after 3 g/kg of 75% ethanol were comparable to those obtained with the same dosage of alcohol in lower concentration (2), and similarly, almost all gastric alcohol administered was absorbed within 3 hr (Fig. 1) (3). No major changes were observed in arterial, right atrial, portal, or hepatic venous pressures. In three dogs with spontaneous respiration similar findings were obtained (Table II).

Group II, in dogs with caval constriction, thoracic duct lymph flow was regularly elevated, ascitic fluid was present and the liver appeared congested. Alcohol entered thoracic duct lymph more rapidly and portal blood

TABLE II. Alcohol Levels in Plasma and Thoracic Duct Lymph in Three Control Dogs with Spontaneous Respiration after Intragastric Administration of 75% Ethyl Alcohol (3 g/kg).[a]

Time (min)	Plasma		Lymph thoracic duct
	Aorta	Right atrium	
5	114 ± 35	151 ± 86	62 ± 26
15	156 ± 67	229 ± 70	68 ± 43
30	167 ± 14	189 ± 34	146 ± 77
60	249 ± 17	230 ± 88	221 ± 16
120	211 ± 46	219 ± 46	282 ± 4
180	247 ± 26	211 ± 26	291 ± 33

[a] Data expressed as mean value with standard deviation of ethyl alcohol in mg/100 ml.

TABLE III. Alcohol Levels in Plasma and Thoracic Duct Lymph in Three Dogs with Constriction of the Thoracic Inferior Vena Cava after Intragastric Administration of 75% Ethyl Alcohol (3 g/kg).[a]

Time (min)	Plasma				Lymph thoracic duct
	Aorta	Hepatic veins[b]	Portal vein	Right atrium	
5	117 ± 40	143 ± 63	194 ± 73	106 ± 20	90 ± 64
15	168 ± 23	192 ± 32	267 ± 46	139 ± 16	174 ± 12
30	157 ± 6	222 ± 47	258 ± 37	205 ± 60	204 ± 37
60	280 ± 57	279 ± 71	305 ± 27	230 ± 62	304 ± 58
120	339 ± 82	245 ± 87	365 ± 74	259 ± 38	257 ± 38
180	280 ± 70	321 ± 43	321 ± 16	298 ± 71	321 ± 30

[a] Data expressed as mean value with standard deviation of ethyl alcohol in mg/100 ml.
[b] Represents indirect sampling from thoracic inferior vena cava below a constricting ligature.

more slowly than in controls, but after 1 hr the distribution was similar to control dogs (Table III). After 3 hr alcohol absorption from the stomach was essentially complete (Fig. 1).

pressure during these experiments was approximately 27 cm saline. Alcohol absorption was significantly delayed as alcohol levels remaining in the stomach after 3 hr averaged more than one-third of the original dose adminis-

TABLE IV. Alcohol Levels in Plasma and Thoracic Duct Lymph in Four Dogs with Two-Stage Ligation of the Portal Vein after Intragastric Administration of 75% Ethyl Alcohol (3 g/kg).[a]

Time (min)	Plasma				Lymph thoracic duct
	Aorta	Hepatic vein	Portal vein	Right atrium	
5	76 ± 39	67 ± 51	180 ± 25	113 ± 45	40 ± 36
15	144 ± 32	87 ± 41	189 ± 64	154 ± 70	110 ± 68
30	157 ± 47	78 ± 45	208 ± 68	174 ± 69	117 ± 64
60	166 ± 54	129 ± 58	191 ± 72	213 ± 51	143 ± 77
120	144 ± 40	160 ± 47	175 ± 43	187 ± 64	188 ± 62
180	147 ± 46	166 ± 41	190 ± 33	198 ± 57	153 ± 61

[a] Data expressed as mean value with standard deviation of ethyl alcohol in mg/100 ml.

Group III, two-stage portal vein ligation produced portal hypertension and mesenteric congestion but with little effect on arterial and systemic venous pressure. Mean portal

tered (Fig. 1). Concentrations reached in blood and thoracic duct lymph were only ½ to ⅔ of levels in control animals (Table IV). Liver blood flow in this model derived

TABLE V. Alcohol Levels in Plasma and Thoracic Duct Lymph in Four Dogs with End-to-Side Portacaval Shunt after Intragastric Administration of 75% Ethyl Alcohol (3 g/kg).[a]

Time (min)	Plasma				Lymph thoracic duct
	Aorta	Hepatic vein	Portal vein	Right atrium	
5	156 ± 22	111 ± 58	306 ± 42	162 ± 89	70 ± 55
15	156 ± 59	172 ± 24	304 ± 50	227 ± 72	118 ± 57
30	204 ± 68	240 ± 68	302 ± 40	241 ± 50	184 ± 44
60	248 ± 22	239 ± 56	286 ± 35	254 ± 64	240 ± 43
120	259 ± 19	221 ± 21	285 ± 33	243 ± 84	293 ± 46
180	251 ± 54	228 ± 25	286 ± 31	230 ± 38	250 ± 47

[a] Data expressed as mean value with standard deviation of ethyl alcohol in mg/100 ml.

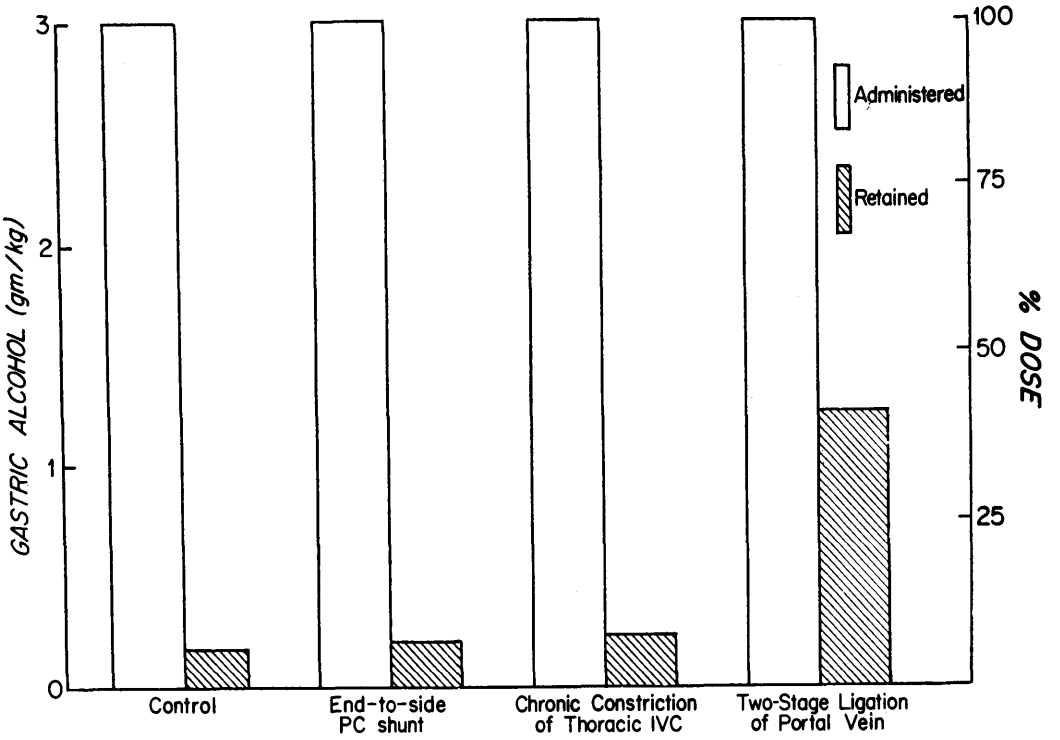

FIG. 1. Absorption in control dogs is almost complete 3 hr after intragastric instillation of ethanol, and is unaffected by complete diversion of portal blood into the vena cava or by hepatic venous outflow obstruction. Obstruction to portal blood flow with splanchnic congestion, however, significantly delays ethanol absorption ($p<0.05$); data represent mean values.

almost entirely from the hepatic artery and alcohol extraction by the liver (arterial–hepatic vein) was minimal (Fig. 2).

Group IV, after end-to-side portacaval shunt, absorption and distribution of alcohol was similar to control dogs (Table V) although extraction across the liver (arterial–hepatic vein) was low (Fig. 2). After 3 hr absorption of gastric alcohol was almost complete (Fig. 1).

Discussion. Ethyl alcohol is a hydrophilic, colorless liquid of low molecular weight that is absorbed from the gastrointestinal tract almost entirely by the portal circulation (3). It is rapidly distributed throughout the intravascular compartment (4) and eventually diffuses into interstitial fluid and lymph. Three hr after administration of a large intragastric dosage of alcohol, levels in thoracic duct lymph are consistent with distribution into total body water of the entire dose (5) except for a small amount oxidized by the liver.

However, when the portal circulation is deranged different patterns emerge. Obstruction to portal blood flow with extrahepatic portal hypertension and splanchnic congestion leads to delayed absorption of alcohol from the stomach and duodenum. Accordingly, alcohol levels in blood and thoracic duct lymph and probably in tissues are much lower. On the other hand, obstruction to hepatic venous outflow with intrahepatic portal hypertension and congestion of the liver leads to delayed absorption into the portal vein with higher initial levels in thoracic duct lymph. After 3 hr, however, alcohol levels in blood and thoracic duct lymph are similar to control dogs and total absorption is complete. After end-to-side portacaval shunt, absorption is rapid, but alcohol extraction across the liver is decreased as in dogs with portal vein

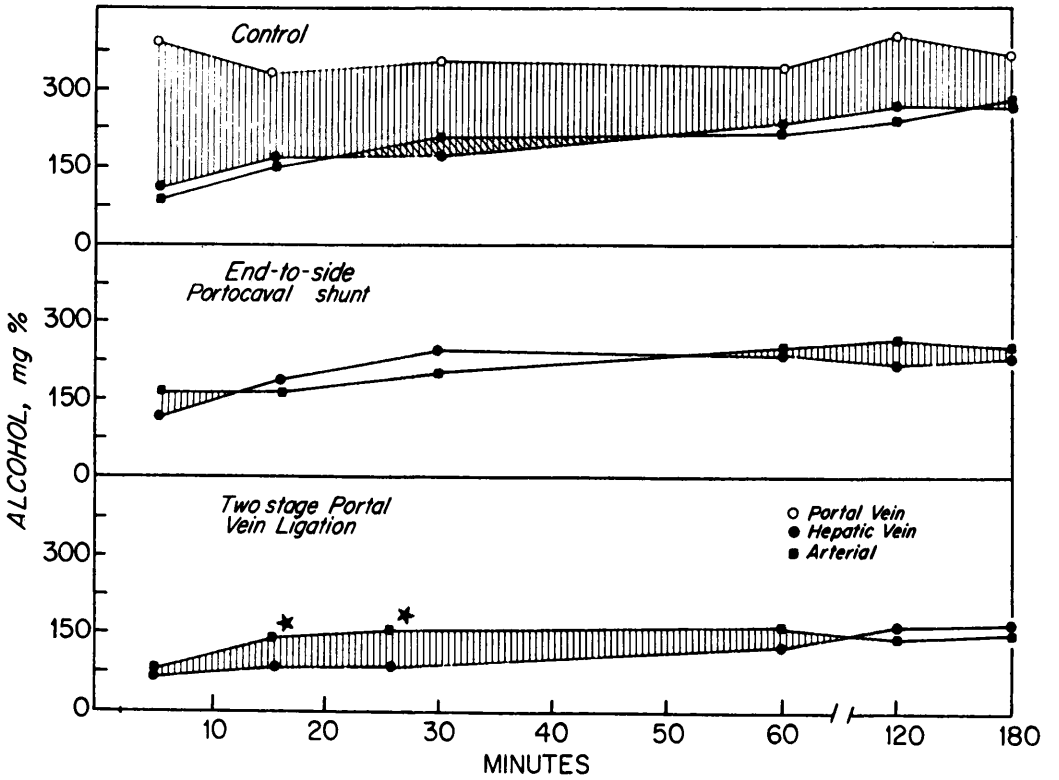

FIG. 2. Demonstration that diversion and/or obstruction to portal blood flow in dogs leads to marked reduction in hepatic extraction of ethyl alcohol: data shown as mean values. In control dogs where hepatic blood supply is derived from both portal vein and hepatic artery, alcohol uptake by the liver is reflected in the difference in alcohol concentration between portal and hepatic venous blood. In the experimental groups transhepatic portal venous flow is absent and alcohol uptake is determined by the difference in alcohol concentration between arterial and hepatic venous blood. There is no significant difference between arterial and hepatic venous concentrations of alcohol ($p>0.1$) except where designated with a star (✪) ($p<0.05$).

obstruction. This derangement is not reflected in altered blood and lymph levels of alcohol, as the administered dose is very large in comparison to the small amount oxidized (6) or excreted in 3 hr (2). It is possible, however, that impaired metabolism delays degradation of alcohol and prolongs its presence in the body. Enzymatic processes in the liver which oxidize ethanol to acetaldehyde may normally depend on portal blood flow for maximum efficiency and therefore may not proceed as well when the hepatic artery is the sole source of blood.

In patients with hepatic cirrhosis and marked portal congestion, absorption of *d*-xylose, urea, and ammonia is impaired (7, 8) and vastly improves after an effective portacaval shunt (7). These observations in dogs with deranged portal circulatory dynamics suggest that the absorption of alcohol follows a similar pattern. Perhaps "tolerance" or lower blood levels of alcohol observed in some "chronic drinkers" after ingestion of alcohol (9) is due to decreased absorption from the gastrointestinal tract and not necessarily induced enzyme activity in the liver. Moreover, some of the deleterious effects including bizarre behavior observed after portacaval shunt in patients with hepatic cirrhosis who continue to drink alcohol may paradoxically be related to postoperative improvement in alcohol absorption coupled with decreased alcohol extraction by the liver.

It is concluded that derangements in portal

blood flow influence the absorption and distribution of ethyl alcohol in the dog. These findings may apply to patients with hepatic cirrhosis with and without portacaval shunts who continue to drink large quantities of alcohol.

Summary. Absorption and distribution of ethyl alcohol was studied in dogs with altered portal blood flow and in control animals. Portal venous obstruction in association with extrahepatic portal hypertension retards absorption of alcohol from the gastrointestinal tract. Hepatic venous outflow obstruction in association with intrahepatic portal hypertension does not appreciably change absorption or distribution of alcohol. End-to-side portacaval shunt does not affect the rate of alcohol absorption but as in dogs with portal vein obstruction decreases extraction by the liver. These findings may be applicable to patients with hepatic cirrhosis who have ingested large quantities of ethanol and continue to do so after portacaval shunt.

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