Studies in Experimental Canine Cirrhosis:

Hemodynamic Alterations with Emphasis on Degree of Spontaneous Porto-Systemic Shunting

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EXPERIMENTAL STUDIES concerning the hemodynamic modifications occurring in hepatic cirrhosis have been limited in the past by the lack of a suitable animal model simulating human Laennec's cirrhosis. The canine model of experimental cirrhosis described by Madden and co-workers[5] appears to resemble the human state of Laennec's cirrhosis more closely than any previously described preparation. This animal model is produced by the oral feeding of the specific hepatotoxin, dimethylnitrosamine, over such a time period that the damaged hepatic cells are gradually replaced by fibrous tissue and an histologic picture resembling that of Laennec's cirrhosis results. The study here reported was designed to seek answers to the following specific questions:

1. Does the hyperdynamic state with increased cardiac output appear regularly as part of the picture of experimental canine cirrhosis?
2. To what extent is the hepatic blood flow altered by the experimental cirrhosis?
3. In what direction is the total splanchnic inflow modified in experimental cirrhosis?

Materials and Methods

Nine adult mongrel dogs of either sex, weighing between 18.6 and 24.5 Kg. (average 21.2 Kg.) were administered dimethylnitrosamine in sugar filled capsules orally twice a week for 3 weeks in a dosage of 2 microliters/Kg./body weight. Thereafter they received one capsule weekly for a total of 12-13 weeks from the onset of the dimethylnitrosamine (DMNA) administration for a total cumulative dose of 30 microliters/Kg./body weight.

Four to five weeks after discontinuing the medication, the animals had a series of hemodynamic studies carried out under intravenous pentobarbital anesthesia and artificial ventilation with room air. Through a left thoracotomy, a non-cannulating electromagnetic flow probe* was placed on the ascending aorta. The thoractomy was then closed leaving the probe *in situ*.

The thoracic aorta was cannulated via a femoral artery for central aortic pressure recording.

With the animal in the supine position, a midline celiotomy was performed and the celiac axis, superior and inferior mesenteric arteries, common hepatic artery and portal vein exposed. Suitably sized electromagnetic flow probes were placed about each of these vessels and a nylon occluding sling positioned distal to each probe to make possible recordings of occlusion zeros. All probes were connected to square wave electromagnetic flowmeters** and pressure and flow signals recorded on a multi-channel direct writing recorder. All flow probes had been previously calibrated either *in vivo* or *in vitro*.

Results

One animal died 8 weeks following the beginning of the DMNA administration of massive gastrointestinal

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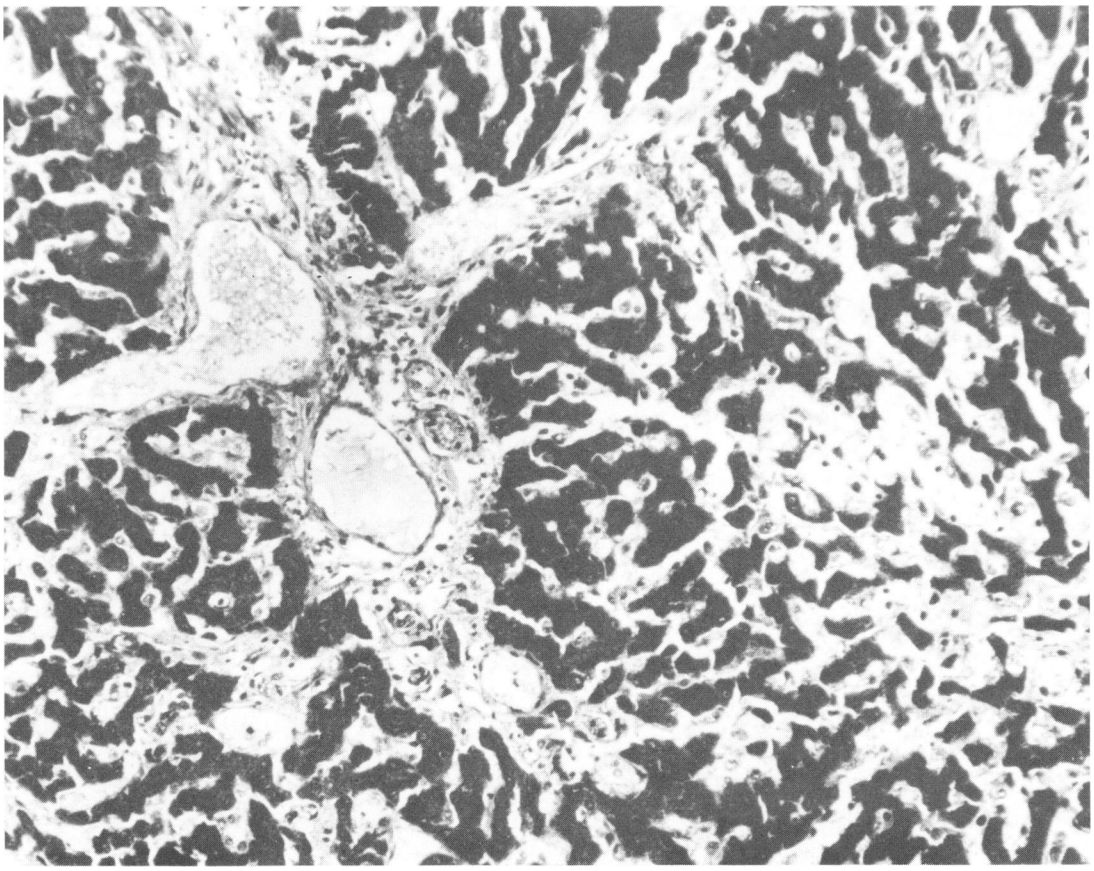

FIG. 1. Histological liver specimen of cirrhosis classification 2+ to 3+.

bleeding from extensive gastric mucosal ulceration. A second animal died 3 weeks following the discontinuation of the DMNA administration as a result of bleeding from the site of a transcutaneous needle liver biopsy. Seven animals remained therefore and were available for the hemodynamic studies. The results in these animals were compared to seven apparently normal animals having hemodynamic studies carried out on a random basis with the cirrhotic animals to secure control data.

TABLE 1

	Control	Cirrhosis	
	relative flow (ml./Kg./min.) mean ± SEM # % of cardiac output	relative flow (ml./Kg./min.) mean ± SEM # % of cardiac output	change
Cardiac output	127.1 ± 4.19 100%	145.3 ± 4.0 100%	14.3%↑ $p < 0.01$
Splanchnic inflow	30.0 ± 1.94 23.6%	37.7 ± 2.59 25.9%	25.7%↑ $p < 0.05$
Portal vein flow	27.6 ± 1.73 21.7%	23.9 ± 1.31 16.4%	13.6%↓ n.s.
Hepatic art. flow	9.6 ± 0.63 7.6%	10.16 ± 0.54 7.0%	5.5%↑ n.s.

At laparotomy, gross findings consistent with portal cirrhosis were encountered including ascites, enlarged portosystemic venous collateral communications and enlarged hepato-duodenal lymphatics.

Histologic examination of liver biopsies obtained at the time of the hemodynamic study revealed all animals having changes in the 2+ to 3+ classification as described by Madden[5] (Fig. 1).

The blood flow data are summarized in Table 1. Cardiac output was increased 14% above the control animals in the cirrhotic dogs. Total calculated peripheral resistance, however, was not significantly changed (Fig. 2).

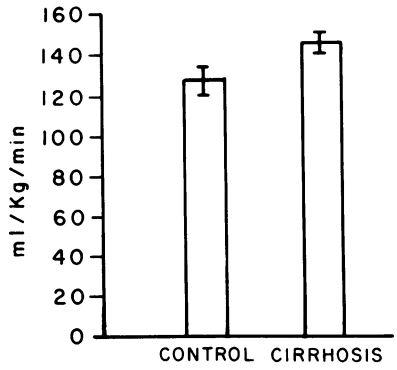

FIG. 2. Cardiac output in cirrhotic animals in ml./kg./min. as compared to controls.

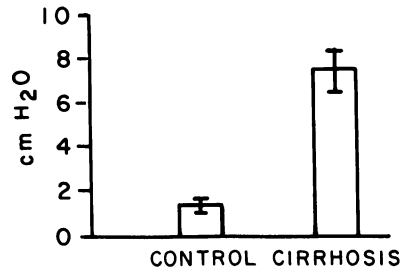

FIG. 3. Corrected portal vein pressure (difference between inferior vena cava pressure and portal vein pressure) in cirrhosis compared to controls in cm H_2O.

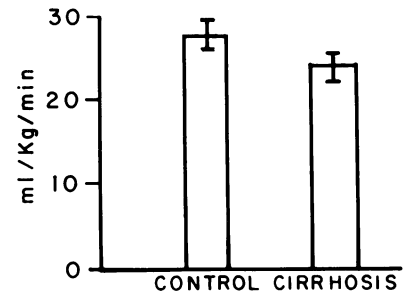

FIG. 4. Portal vein flow in cirrhotic animals in ml./Kg./min. as compared to controls.

The corrected portal pressure (difference between the portal vein and vena caval pressure at the same level) was increased in all cirrhotic animals to values between 6 and 14 cm. of water as compared with the control animals which in all cases showed readings less than 2 cm. of water (Fig. 3).

The portal vein flow was reduced approximately 14%. However this change was of questionable significance (Fig. 4).

Total splanchnic inflow, that is the total of celiac axis, superior and inferior and mesenteric artery flows minus hepatic artery flow, was increased 26% in the cirrhotic animals as compared with the control group (Fig. 5). using this figure for total splanchnic inflow, a calculation of portosystemic shunting was made as shown in Table 2. From this table it will be noted that approximately 8% of the splanchnic inflow in the control animals did not return via the portal vein. On the other hand, approximately 37% of the splanchnic inflow in the cirrhotic animals was not returned via the portal vein. These findings are demonstrated graphically in Figure 6.

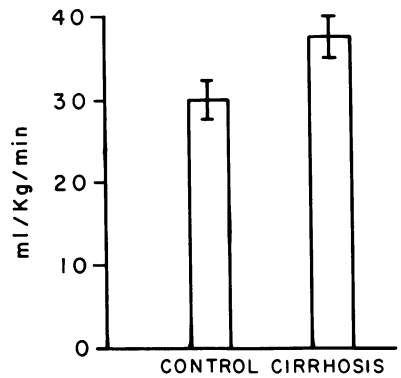

FIG. 5. Total splanchnic inflow (total flow of celiac axis, superior and inferior mesenteric artery minus hepatic artery flow) in ml./Kg./min.

TABLE 2.

	Control	Cirrhosis	
shunting volume ml./Kg./min. mean ± SEM	2.35 ± 0.37	13.84 ± 1.44	$p < 0.001$
% of splanchnic inflow	7.82%	36.65%	

Calculation of total hepatic inflow as a percent of cardiac output is shown in Table 3. The hepatic artery flow in the cirrhotic animals was essentially the same as in the controls. A 6% reduction in the percentage of cardiac output reaching the liver occurred in the cirrhotic animals and the hepatic artery to portal vein ratio was changed (Fig. 7).

Discussion

From the findings of this study, it is apparent that this canine experimental model of cirrhosis produces a hyperdynamic state with increased cardiac output resembling that seen in human Laennec's cirrhosis.[1,2,3,4,6] An absolute increase in total splanchnic inflow was seen but this increase was not adequate to fully account for the increase in cardiac output. This finding supports the clinical impression in patients with Laennec's cirrhosis that increased peripheral blood flow is also part of the picture.

To our knowledge the figures contained herein show the first quantitative assessment of the degree of portosystemic shunting in the control animal as compared with a cirrhotic and reveal that the normal small (8%) portosystemic shunting) is increased to approximately 37% portosystemic shunting in the cirrhotic animal.

Summary and Conclusions

1. A canine animal model resembling early human Laennec's cirrhosis was produced by the administration of the specific hepatotoxin, dimethylnitrosamine, as described by Madden and co-workers.

TABLE 3.

	Control	Cirrhosis
Hepatic inflow (hep. artery plus portal vein flow)	37.8 ± 2.1	34.0 ± 1.5
% of cardiac output	29.3%	23.4%
Hep. artery: portal vein ratio	1:2.94	1:2.36

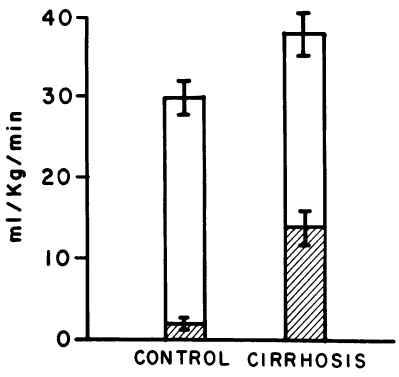

FIG. 6. Porto-systemic shunting calculated as difference between total splanchnic inflow (total column height) minus portal vein flow (shaded column) in ml./Kg./min.

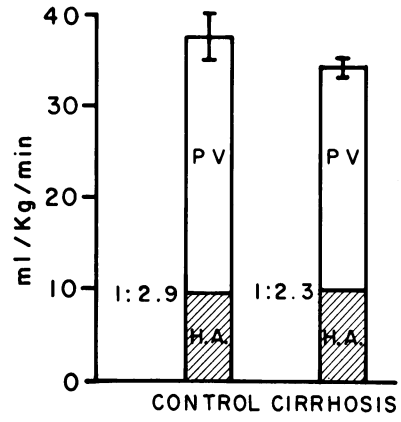

FIG. 7. Total liver blood flow in early cirrhosis in ml./Kg./min. as compared to controls.

2. The dogs so treated developed portal hypertension and an histologic picture resembling early Laennec's cirrhosis in approximately 12 weeks following the drug administration.
3. A hyperdynamic state with an increased cardiac output resulted.
4. Total hepatic blood inflow was reduced numerically but these findings were of questionable significance.
5. Total splanchnic inflow of blood was significantly increased.
6. Portosystemic shunting was increased from approximately 8% of the splanchnic inflow in the control animals to 37% of the splanchnic inflow in the cirrhotic animals.

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