Effect of Acute Portal Hypertension on Hepatosplanchnic Hemodynamics and Liver Function

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Acute prehepatic portal hypertension was mechanically induced in Göttingen mini-pigs. A 125% increase in portal pressure resulted in a significant decrease in estimated hepatic blood flow. The decrease in blood flow was accompanied by a 25% reduction in the 'true' clearance of indocyanine green and an 18% decrease in splanchnic oxygen consumption. Judged from the splanchnic elimination rate of galactose, the functional liver cell mass was not altered by portal banding, and an unaltered lactate to pyruvate ratio in hepatic venous blood indicated that no functional parts of the liver became severely hypoxic.

Key words: Galactose elimination; hepatic blood flow; indocyanine green; liver metabolism; pigs; portal hypertension

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Hemodynamic studies in rats have demonstrated that chronic prehepatic portal hypertension (1, 2) and cirrhosis (3) are accompanied by an increase in splanchnic blood flow and a decrease in splanchnic arteriolar resistance. These findings have contributed to the hyperdynamic flow theory, which suggests that increased splanchnic blood flow may be of importance for consistent portal hypertension.

Little is known about the possible relationships between hepatosplanchnic hemodynamics and liver metabolism after chronic portal-vein banding (4, 5), and we have found no reports on these factors after acute portal-vein banding.

A series of experiments on Göttingen mini-pigs has been planned for the purpose of studying the development and successive treatment of esophageal varices produced by portal-vein banding.

It was therefore thought of relevance to examine a possible effect of induced changes in splanchnic hemodynamics on liver metabolism, and in the present report the acute effect of banding of the portal vein is described.

MATERIALS AND METHODS

Twenty mini-pigs (Göttingen) with a mean weight (±SEM) of 16.6 ± 0.4 kg were fasted for 24 h, but with free access to water. They were premedicated with ketamine (100 mg/10 kg body weight intramuscularly) and anesthetized with halothane (0.75%) and O_2 under spontaneous breathing. The abdomen was opened through a midline incision, and the portal vein exposed and mobilized from the entry of the splenic vein to the bifurcation. A loose ASD band (3-mm-wide teflon (Bard)) was placed around the main portal trunk close to the bifurcation. The spleen was then exposed, and the splenic vein catheterized with a polyethylene catheter (inside diameter, 1.02 mm; outside diameter, 2.79 mm). The tip of the catheter was placed in the main portal trunk below the ASD band.

A liver vein was catheterized via the right jugular vein and the right atrium. The catheter (Intravenous cannula 5 FG, 30 cm long, without side holes) was guided into the hepatic vein, and the position ascertained from the appearance of an anemic spot after rapid infusion of saline. The catheter was then withdrawn 1–2 cm to prevent wedging. The spleen was replaced and the wound mended with metallic clips.

A femoral vein was catheterized for infusion and a femoral artery for blood sampling. Portal-vein pressure (PP) and arterial blood pressure were measured at 5- to 10-min intervals by means of a strain-gauge transducer (Siemens no. 746).

After a recovery period of 45 min indocyanine green (ICG) (Hynson, Westcott & Dunning) was given as a priming dose of 300 μg/kg followed by continuous infusion of 5 μg/kg/min. In 14 of the animals galactose (Kabi) was also infused continuously (30 μmol/kg/min) after a priming dose of 0.5 mmol/kg, resulting in arterial concentrations at which the elimination capacity of galactose was saturated. The elimination rate was then a zero-order process (6–8).

An equilibration period of 20 min was followed by a control period of 30 min. Arterial and hepatic venous blood samples were drawn at 10-min intervals for determination of concentrations of ICG, galactose, lactate, and pyruvate and every 15 min for determination of the oxygen saturation.

After the control period a catheter (outside diameter, 3 mm) was placed alongside the length of the portal vein, and the ASD band was tied around both the catheter and the portal vein. The catheter was then removed and the portal vein allowed to reexpand. The variables were then studied for another 50-min experimental period.

The blood glucose level was also studied both before and after banding.

Analytical procedures and calculations. ICG, galactose, lactate, and pyruvate were determined by conventional methods (9–11) and glucose by the glucose peroxidase technique (GLOX). Oxygen saturation was measured spectrophotometrically.

The estimated hepatic blood flow (EHBF) was calculated by the method of Bradley et al. (12), using the Fick principle.

The splanchnic elimination rate of galactose and consumption of oxygen were calculated by multiplying the arteriohepatic venous differences by the EHBF. The oxygen content in arterial and hepatic venous blood was calculated from the oxygen saturation of hemoglobin and physically dissolved oxygen.

Liver function was also studied by determining the 'true' clearance of ICG (13, 14), calculated as i/c, where i is the amount of ICG infused (corrected for the amount retained in plasma) and c is $Ca - Cv/\ln(Ca/Cv)$ (Ca = arterial concentration of ICG, Cv = hepatic venous concentration of ICG).

The splanchnic vascular resistance (SVR) was calculated as mean arterial blood pressure divided by the EHBF.

Statistical procedure. All results are given as the mean ± SEM or median and range. The effect of portal banding was tested by the methods of paired comparison using Student's *t* test or, for variables not normally distributed (true clearance of ICG, SVR, and lactate/pyruvate), using the Wilcoxon rank test.

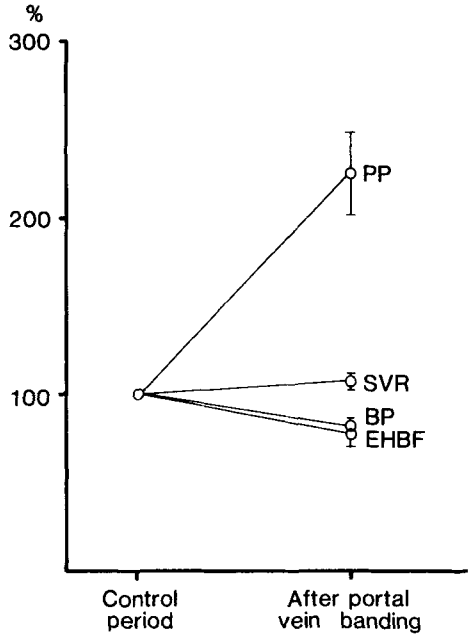

Fig. 1. The effect of portal-vein banding on portal pressure (PP), mean arterial blood pressure (BP), total splanchnic vascular resistance (SVR), and estimated hepatic blood flow (EHBF).

Table I. The effect of portal-vein banding on estimated hepatic blood flow (EHBF), hepatic galactose elimination (mean ± SEM), and 'true' clearance of indocyanine green (ICG) (median and range)

	EHBF (ml/kg/min) ($n = 20$)	Hepatic galactose elimination (μmol/kg/min) ($n = 14$)	'True' clearance of ICG (ml/kg/min) ($n = 20$)
Control	30.4 ± 2.2	15.1 ± 1.9	8.3 (2.7–16.5)
After banding	23.0 ± 2.4 ($p < 0.01$)	16.2 ± 1.6 NS	5.2 (2.0–9.0) ($p < 0.01$)

RESULTS

The hemodynamic changes caused by portal-vein banding are illustrated in Fig. 1. Portal pressure increased from 8.6 ± 1.0 mm Hg to 17.3 ± 1.3 mm Hg ($p < 0.0001$). The mean arterial blood pressure decreased immediately after banding from 85 ± 5.5 mm Hg to 6.5 ± 4.2 mm Hg ($p < 0.001$). After 10 min arterial blood pressure increased to a constant level of 71 ± 5.6 mm Hg, which was maintained for the last 30 min of the experimental period. This value is still significantly lower ($p < 0.001$) than the control value. The decrease in EHBF was significant (Table I). No change was observed in splanchnic vascular resistance.

A typical effect of portal-vein banding on the

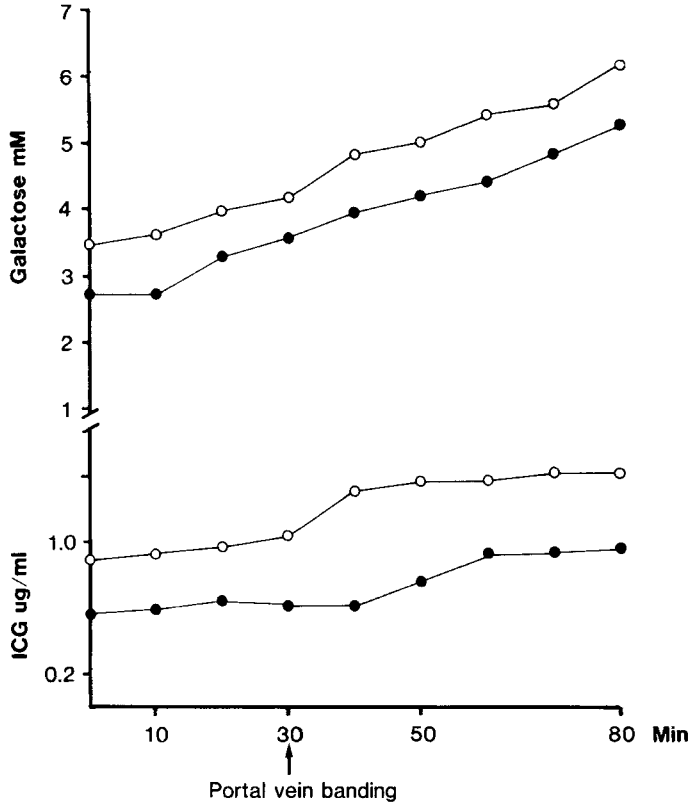

Fig. 2. The effect of portal-vein banding on the arterial (○) and hepatic venous (●) plasma concentrations of indocyanine green (ICG) and galactose.

elimination curves of galactose and ICG is shown in Fig. 2. The slight increase in the arteriohepatic venous galactose difference corresponds to the decrease in EHBF, leaving the splanchnic elimination rate of galactose unchanged (Table I). The 'true' clearance of ICG decreased by 25% after banding (Table I).

There was a slight increase in the blood glucose level from 3.5 ± 0.4 mmol/l in the recovery period to 4.3 ± 0.4 mmol/l in the experimental period.

The splanchnic oxygen consumption (Table II) decreased 18% after portal-vein banding, and splanchnic oxygen extraction increased 6%. There was no change in the lactate to pyruvate ratio of the hepatic venous blood.

DISCUSSION

The Göttingen mini-pig was chosen for the experiments for several reasons. In many respects, including splanchnic hemodynamics and liver metabolism, it resembles the human organism (15). Furthermore, it has a suitable size, and preliminary studies have shown that it tolerates portal banding for at least 6 months, a period considered to be necessary for a planned study of acute and chronic effects of induced portal hypertension.

Electromagnetic blood flow measurements were initially attempted but had to be abandoned because banding interfered with the portal-vein diameter and made calibration impossible. The banding procedure also influenced the position of the arterial flow probe and made arterial flow measurements unreliable. The splanchnic blood flow, therefore, had to be determined indirectly, and the indocyanine green method was chosen for this purpose. The hepatic blood flow estimated in this manner appeared to be in accordance with the results of others (16).

Steady-state levels in the variables studied were obtained in the control period, and about 10 min after banding new steady levels were found. It was therefore unnecessary to extend the experimental period further than the 50 min.

Banding of the portal vein caused an immediate fall in EHBF, which stabilized after about 10 min. This may be explained by a fall in both portal venous and hepatic arterial blood flow caused by pooling of blood in the prehepatic splanchnic area and a subsequent fall in circulating blood volume in agreement with the concomitant fall in blood flow and blood pressure. It is well known that a fall in portal venous flow is often accompanied by a decrease in hepatic arterial resistance, but quantitative compensation of flow is usually not achieved (17) and would certainly not be expected in the present experiments, in which banding caused a fall in blood pressure and splanchnic blood flow without any change in SVR.

Banding also caused an 18% fall in splanchnic oxygen consumption, which cannot simply be a consequence of the fall in EHBF and thus the oxygen supply of the liver. The latter would be accompanied by an almost complete desaturation of the hepatic venous blood (18), whereas only a slight fall in desaturation was observed. Moreover, the lactate to pyruvate ratio in hepatic venous blood did not change on banding, which indicates that no functioning part of the liver became severely anoxic.

It might be thought that banding could have induced maldistribution of intrahepatic blood

Table II. The effect of portal-vein banding on splanchnic oxygen consumption and extraction (mean ± SEM) in 9 pigs and the lactate to pyruvate ratio in hepatic venous blood (medium and range) in 18 pigs

	Splanchnic oxygen consumption (μmol/kg/min)	Splanchnic oxygen extraction (%)	Lactate to pyruvate ratio
Control	50.3 ± 2.5	20.8 ± 1.5	35.1 (17.8–177.0)
After banding	41.2 ± 2.3 ($p < 0.02$)	26.9 ± 2.7 NS	36.6 (15.5–143.0) NS

flow with exclusion of liver tissue from the circulation and a fall in oxygen consumption as a result. This would be expected to depress the hepatic true clearance of ICG, as observed. In previous experiments in cats, however, the true clearance also seemed to be flow-dependent (19), and the existence of maldistribution is not supported by the hepatic elimination rate of galactose, which was unaffected by banding. At the present arterial concentrations of galactose, the galactose elimination system is saturated, and the unaltered elimination rate implies that the number of functioning liver cells is not reduced (13).

The results, therefore, indicate that banding does not affect the hepatic oxygen uptake to any great extent, and the observed fall in splanchnic oxygen consumption must, therefore, be located in the prehepatic splanchnic area, which accounts for approximately a third of the total splanchnic oxygen consumption (18). The cause of this reduction in oxygen consumption is not evident but could be secondary to the splanchnic pooling of blood, which may change the microcirculation and thereby the oxygen supply to the tissue.

It is concluded that acute prehepatic portal hypertension, in contrast to results found in chronic hypertension (1, 2), is accompanied by a decrease in splanchnic blood flow without any changes in the functional capacity of the liver.

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