

Effect of portal-systemic anastomosis on renal haemodynamics in cirrhosis

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SUMMARY In 12 patients with portal hypertension and repeated bleedings from oesophageal varices the central haemodynamics, portal pressure, and mean renal blood flow (RBF) were investigated immediately before and two to seven months after portal-systemic shunt. Cardiac output increased significantly, whereas arterial pressure was unchanged after operation. RBF, which was initially less than in controls, did not change. As portal pressure decreased significantly, a direct portal-renal, neural, or humoral reflex mechanism does not explain the subnormal RBF in cirrhosis. As plasma volume was large and unchanged after operation a 'diminished circulating plasma volume' is an unlikely explanation. Therefore, on the basis of the present observations, previously postulated causes of renal hypoperfusion in cirrhosis need revision.

The fundamental pathophysiological factor in functional renal failure in the late stage of cirrhosis (Kew, 1972) is renal vasoconstriction causing a decreased renal blood flow (Schroeder *et al.*, 1967; Barnardo *et al.*, 1970; Cohn *et al.*, 1970; Epstein *et al.*, 1970). However, a diminished renal blood flow may be present even before there is clinical and laboratory evidence of impaired renal function (Kew *et al.*, 1971). The pathogenesis of the renal hypoperfusion in cirrhosis has remained an enigma. Decreased renal blood flow has been demonstrated in patients with extrahepatic and presinusoidal portal hypertension and normal liver function (Kew *et al.*, 1972). This, and several animal studies of experimental portal hypertension showing a decrease in the renal blood flow (Onnis *et al.*, 1962; Onesti, 1971; Newsome *et al.*, 1971; Kilcoyne *et al.*, 1971; Gordon *et al.*, 1973; Levy, 1974a, b), has drawn attention towards portal hypertension as a possible pathogenetic factor. The hypothesis is that either a direct portal-renal reflex, or splanchnic pooling, resulting in a decreased 'effective circulating plasma volume', may be the cause of the reduced renal blood flow. As the animal studies of experimental portal hypertension have all been in a non-steady state, and, as studies of the effect of portal decompression upon the renal circulation have not been performed in cirrhotic patients, the purpose of the present study

was to evaluate the effect on renal haemodynamics in cirrhosis of normalising the portal pressure.

Methods

PATIENTS

Eleven patients with advanced cirrhosis of different aetiology and one patient with presinusoidal portal hypertension of unknown aetiology (possibly caused by arsenic medication) were examined immediately before and from two to seven months (mean 3.5 months) after a portal-systemic shunt was carried out. The interval allowed a new haemodynamic steady state to be established. Table 1 presents clinical and laboratory data on the patients, four females and eight males with a mean age of 50 years. The diagnoses were verified by liver biopsy. In all patients oesophageal varices were observed either by radiography or by oesophagoscopy, and the patients had experienced repeating bleeding episodes that were sufficiently severe to demand transfusions. Emergency operations were not performed. The patients were without clinical and electroencephalographic signs of hepatic encephalopathy at the time of investigation. Ascites and peripheral oedema were not present, but four patients received diuretics at the time of the first examination, and seven patients had been treated with diuretics at some time before the actual admission. Renal, cardiac, or hypertensive diseases were excluded by history,

Table 1 Biochemical variables in 12 patients before and after portal-systemic shunt

No.	Init.	Sex	Age (yr)	Diagnosis	Serum bilirubin (< 17 μ mol/l)	Serum albumin (532-813 μ mol/l)	Prothrombin time (85-115)	Galactose elimination (1.38-3.50 mmol/min)	Serum creatinine (< 0.13 mmol/l)
1	EA	F	56	AC	11.57	347-366	41-27	1.48—	0.08-0.08
2	GB	F	59	IC	55-59	420-307	60-39	1.28-1.03	0.08-0.06
3	KO	F	28	PPH	16-35	508-452	59-48	1.68-1.38	0.08-0.08
4	PL	M	57	AC	10-10	473-446	68-71	3.06-2.54	0.08-0.07
5	LH	F	57	IC	16-24	390-377	69-62	2.11-1.21	0.08-0.09
6	BS	M	37	AC	43-22	462-446	83-78	1.11-1.16	0.12-0.09
7	SE	M	53	AC	16-22	489-500	74-73	1.12-1.07	0.11-0.12
8	WH	M	51	AC	31-19	418-445	57-65	1.73-1.74	0.09-0.08
9	KK	M	47	AC	5-8	535-407	87-62	1.75-1.65	0.11-0.08
10	JP	M	72	IC	14-71	530-393	72-50	1.21-1.03	0.10-0.08
11	KE	M	42	AC	6-6	436-440	99-76	2.32-2.17	0.06-0.08
12	KH	M	43	AC	14-20	463-421	65-57	1.66-1.49	0.09-0.08
Mean			50		19-29	455-416	69-59	1.62-1.49	0.09-0.08
					P > 0.05	P < 0.05	P < 0.01	P < 0.02	P > 0.05

AC: alcoholic cirrhosis. IC: idiopathic cirrhosis. PPH: presinusoidal portal hypertension.

physical examination, and laboratory findings. At the time of the investigation the patients' hydration was normal and there were no abnormalities in their electrolyte status.

In two patients (cases 1 and 7) a splenorenal shunt, and in two patients (cases 2 and 11) a side-to-side portacaval shunt was performed. The rest of the patients had an end-to-side portacaval shunt. In two cases complications occurred. In case 7 a thrombosis of the shunt necessitated a splenorenal shunt nine days after the first operation. Normal function of this shunt was verified by coeliac angiography. Case 8 went into hepatic coma (grade II-III) after surgery. Later, sepsis with *Escherichia coli* occurred, during which the patient had gastrointestinal bleeding from a duodenal ulcer (seen at gastroscopy). The sepsis was treated with antibiotics, and the ulcer was treated conservatively. Both complications were eventually overcome.

A decrease in intrasplenic pressure or a radiographically open shunt was observed in all cases. However, in three cases a discrepancy between intrasplenic pressure decrease and radiographical findings was found. In case 4 a moderately increased intrasplenic pressure remained unchanged after surgery (23 to 22 mm Hg) despite a radiographically open shunt. In case 5 the intrasplenic pressure fell considerably, but not to normal levels (37 to 28 mm Hg). On the splenoportogram the shunt appeared open, but minimal oesophageal varices were still present. In case 11 the intrasplenic pressure fell to normal, but an open shunt was not visualised at the splenoportogram. None of the patients experienced bleeding from oesophageal varices during the interval between surgery and follow-up examination.

TECHNIQUES

The following programme was carried out before

and after shunt operation. After fasting for eight hours the patients were premedicated with diazepam 10 mg. A right-sided cardiac catheterisation was performed, and subsequently the hepatic veins were catheterised in order to measure the wedged hepatic venous pressure. Then an Ödman catheter no. 6 was introduced percutaneously under local anaesthesia into a femoral artery, and under fluoroscopic control the tip was placed in the renal artery. Catheter position and possible reflux during injection was checked by injecting 5-10 ml 30% Urografin. Renal blood flow was measured at least 10 minutes after Urografin was injected (Caldicott *et al.*, 1970). The catheter was also used to sample arterial blood.

The cardiac output was measured according to the principle of Fick while the venous catheter was placed in the pulmonary artery.

Plasma and erythrocyte volume were measured with the Evans-Blue technique and 51-Cr tagged erythrocytes according to method A as recommended by the International Committee for Standardization in Hematology (1971). Hepatic function was estimated by measuring galactose elimination capacity (Tygstrup *et al.*, 1963).

Renal blood flow (RBF) was measured by the $^{133}\text{Xenon}$ washout method, as described by Ladefoged (1966). A bolus injection of 1.0-2.0 mCi $^{133}\text{Xenon}$ (Amersham-XAS-11-P) dissolved in isotonic saline solution was injected into the renal artery, and the washout curve was followed with a scintillation detector placed below the kidney. The curve was registered through a Selektrolik pulse-height analyser model 45-22 with an optimal 'window' for $^{133}\text{Xenon}$. Peak count was more than 3000 c/s and time constant 1 s. Two washout curves were performed and the mean RBF was calculated from the average of the two initial slopes in a semi-logarithmic plot. The diffusion constant was corrected for

haematocrit according to Ladefoged (1966).

Control values for RBF were obtained in eight patients, four males and four females, aged 23 to 44 years, who were undergoing cardiac catheterisation for suspected but unconfirmed cardiac disease.

In all patients a splenoportogram with measurement of the intrasplenic pressure was performed. Unless otherwise stated, statistical analysis of observations before and after shunt operation was done by the method of paired comparison.

Results

As shown in the Figure the RBF was significantly lower in the patients with portal hypertension than in the controls, 1.95 ml/g/min and 3.50 ml/g/min, respectively ($P < 0.01$), (rank sum test, Mann-Whitney),

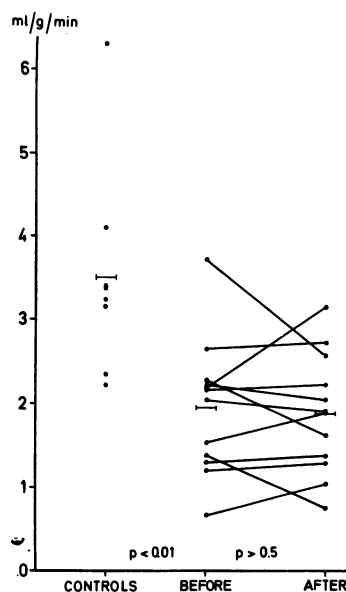


Figure Mean renal blood flow in eight controls and in 12 patients with portal hypertension before and after decompression operation.

even when the age difference between the two groups was considered (Hollenberg *et al.*, 1974). After the portal-systemic shunt operation the mean RBF was 1.88 ml/g/min and thus unchanged. The haemodynamic consequences of portal-systemic shunting were independent of shunt type or the aetiology of portal hypertension.

Some of the haemodynamic variables found before and after portal-systemic shunt are shown in Table 2. The plasma volume and, to a lesser extent, the blood volume were significantly greater before the shunt than could be predicted from age, sex, and weight (*Documenta Geigy, Scientific Tables*, 1968), mean 3.93 l (59.5 ml/kg or 2.19 l/m²), predicted 2.85 l ($P < 0.01$) and 5.68 l (84.5 ml/kg or 3.17 l/m²) predicted 4.84 l ($P < 0.05$). No significant change was seen after shunt operation ($P > 0.05$).

The cardiac output increased significantly from a mean value 5.68 l/min (3.09 l/min/m²) to 6.76 l/min (3.80 l/min/m²) ($P < 0.01$). This was exclusively due to an increase in the stroke volume from 72 to 92 ml.

The mean arterial blood pressure decreased from 87 to 82 mm Hg ($P > 0.05$), while the total peripheral resistance fell significantly from a mean of 1390 to 1048 dyne s cm⁻⁵ ($P < 0.05$).

After shunt surgery the intrasplenic pressure fell significantly from an average of 29 to 18 mm Hg ($P < 0.001$). The wedged hepatic venous pressure in the patients with cirrhosis receiving an end-to-side portacaval shunt is shown in Table 2. The pressure fell from 24.3 to 20.5 mm Hg ($P < 0.001$). In the two patients receiving a side-to-side shunt the wedged hepatic venous pressure fell from 23 to 14 and 22 to 14 mm Hg respectively; thus in both cases this pressure became practically normal. Pressure in one patient with a splenorenal shunt fell from 27 to 21 mm Hg.

As can be seen in Table 1 the shunting caused a minor but significant decrease in liver function as evaluated by galactose elimination capacity ($P < 0.02$), while all patients had normal renal function before and after shunt as judged by the serum creatinine level.

Table 2 Effect of portal-systemic shunt on haemodynamic parameters

	Before shunt			After shunt			P	n
	Mean	± SEM	Range	Mean	± SEM	Range		
Plasma volume (l)	3.93	0.23	2.83-5.58	4.01	0.18	3.10-5.12	> 0.5	11
Blood volume (l)	5.68	0.36	4.01-8.20	5.68	0.25	4.43-7.40	> 0.5	11
Cardiac output (l/min)	5.56	0.36	3.40-8.00	6.76	0.42	4.50-8.74	< 0.01	12
Stroke volume (ml)	72	5	38-92	92	7	49-121	< 0.01	11
Mean arterial blood pressure (mm Hg)	87	3	73-106	82	4	62-100	> 0.05	12
Intrasplenic pressure (mm Hg)	29	1	23-37	17	1	10-28	< 0.001	10
Wedged hepatic venous pressure (mm Hg)	24.3	2.0	32-16	20.5	2.0	28-15	< 0.001	6

Discussion

A decrease in portal pressure and a more hyperkinetic systemic circulation was the result of shunt operation, while changes in an initially low renal perfusion failed to appear.

The high plasma and blood volume and larger than normal cardiac output before shunt surgery are in agreement with previous studies (Murray *et al.*, 1958; Mashford *et al.*, 1962; Lieberman *et al.*, 1967).

Earlier studies have disclosed an increase in cardiac output and an unchanged or slightly decreased plasma volume after shunt operation. Foda *et al.* (1974) observed an increase in cardiac index from 4.78 to 6.76 l/min/m², and Gordon and Del Guercio (1972) found a parallel increase in cardiac index after shunt surgery in an initially normodynamic group of patients, while in an initially hyperdynamic group such an increase was absent. This difference does not appear in our material. Like us, Foda *et al.* (1964) found no changes in plasma volume or blood volume, whereas Lieberman and Reynolds (1967) found a decrease in these variables after shunting.

The mean RBF in the eight controls of this study corresponds well with the findings of Hollenberg *et al.* (1974) for this age group. The subnormal mean RBF in cirrhotic patients without signs of renal failure is similar to the results found by Kew and coworkers (1971) using the same method for determining the RBF in a comparable sample of patients.

A decreased RBF in cirrhosis as observed in the present material is caused by renal vasoconstriction (Barnardo *et al.*, 1970), but how this is initiated has not yet been established. The hypothesis that a raised portal pressure *per se* causes renal hypoperfusion is supported from animal studies (Onnis *et al.*, 1962; Hanback, 1970; Onesti 1971; Newsome *et al.*, 1971; Kilcoyne *et al.*, 1971; Gordon *et al.*, 1973; Levy, 1974a). However, in these studies the experimental increase in portal pressure has been acute, so that it was not possible for a new circulatory steady state to take place. On the other hand, the observation that RBF is reduced in patients with extrahepatic portal hypertension in a steady state situation supported this view (Kew *et al.*, 1972). However, the present study does not establish a relationship between portal decompression and recovery of renal perfusion. In studying the effect of blocking hepatic venous outflow by histamine injection, Levy found a decrease of renal blood flow which could not be produced by a similar rise of portal venous pressure by portal vein constriction. He therefore postulated that the rise not in portal but in intrahepatic pressure caused renal hypo-

perfusion (Levy, 1974b). That a reduction in RBF in cirrhotic patients is caused by an increase in intrahepatic rather than in portal pressure is a possibility. However, unchanged low RBF in two patients receiving side-to-side portacaval shunt, which also normalised the raised sinusoidal pressure does not support this view.

It has been suggested that a low 'effective circulating plasma volume' caused by splanchnic pooling is responsible for the low RBF seen in cirrhosis (Vlahcevic *et al.*, 1965; Tristani and Cohn, 1967). The reports on the effect of portacaval anastomosis on functional renal failure in cirrhosis are conflicting, ranging from claims of direct improvement (Schroeder *et al.*, 1970) to claims of initiation of the syndrome (Cohn, 1964; Garrett *et al.*, 1970), although RBF has not been measured in these cases. Schroeder suggested, after observing improvement in diuresis and creatinine clearance in one patient with functional renal failure who received a shunt, that this caused a redistribution in plasma volume, so normalising the 'effective circulating plasma volume' and leading to improved renal function. The portal-systemic shunt should be capable of relieving the splanchnic pooling. If a decreased 'effective circulating plasma volume' is a reality, it may be speculated that a fraction of the plasma volume before shunt surgery is trapped in the splanchnic area, and after surgery runs idle in the shunt and in this way is equally ineffective in the circulation.

Vasoactive amines have been incriminated in the pathogenesis of the reduction of RBF in cirrhosis (Epstein *et al.*, 1970; Fischer and Baldessarini, 1971). Speculation has been concentrated on the idea that such vasoactive agents are produced in, or not activated in, the sick liver. Correlation between endotoxins and renal impairment in acute liver failure has been recorded (Wilkinson *et al.*, 1974). Epstein and his colleagues found irregularities in their ¹³³Xenon washout curves which they attributed to circulating vasoactive amines. Since these vasoactive agents are thought to originate from the gut, a direct bypass *via* a portal-systemic shunt probably makes them more accessible to the target organ(s). The fact that, in the present study, the reduction in RBF did not decrease further in spite of unimproved or decreased liver function from first to second examination, seems to contradict this hypothesis, unless maximal detoxification is already taking place in the liver. However, vasoactive agents originating elsewhere—for example, *via* incomplete hormone catabolism, perhaps in the liver itself—are more likely to be responsible for the renal hypoperfusion.

On the basis of the present results, previously suggested causes for renal hypoperfusion in cirrhosis must be revised. A direct portal-renal, neural or

humoral, reflex mechanism seems absent. A diminished 'effective circulating plasma volume' is unlikely. Vasoactive amines or endotoxins from the intestines seem less probable, while agents with similar effect originated elsewhere, perhaps in the poorly functioning liver itself, are a possibility.

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