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## RENAL FUNCTION, SODIUM AND WATER HOMEOSTASIS IN PATIENTS WITH IDIOPATHIC EXTRAHEPATIC PORTAL VEIN THROMBOSIS COMPARED WITH NORMAL HEALTHY CONTROLS

Brian L Rayner, Simon C Robson, Ralph E Kirsch, Michael Voigt

**Objectives.** To determine whether portal hypertension in the absence of liver disease contributes to changes in renal function and renal sodium and water handling.

**Methods.** Nine patients with extrahepatic portal vein thrombosis (PVT) with normal liver function and histology were compared with 9 matched healthy control subjects. All underwent standard measurements of glomerular filtration rate and effective renal blood flow using inulin and para-aminohippuric acid (PAH) clearances, respectively. Sodium excretion and renin and aldosterone levels were studied before, during and after an intravenous saline infusion.

**Results.** At baseline there were no differences in inulin clearance, PAH clearance, fractional excretion of sodium and free water excretion. During and after the saline infusion both groups showed a significant increase in sodium excretion with a reduction in water excretion, while the PAH and inulin clearances remained unchanged. Although aldosterone and renin levels both fell after the infusion, aldosterone levels were significantly lower in the PVT group. There were no other significant differences between the PVT and control groups.

**Conclusion.** Renal function and sodium and water handling were comparable in healthy controls and patients with PVT. It is unlikely that portal hypertension alone plays a significant role in the impaired ability to excrete sodium and water in patients with liver cirrhosis.

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Renal Unit, Department of Medicine, University of Cape Town

Brian L Rayner, MB ChB, FCP (SA), MMed

Medical Research Council Liver Research Centre, University of Cape Town

Simon C Robson, MB ChB, DCH, FRCP, FCP, PhD

Ralph E Kirsch, MB ChB, MD, DSc (Edin), FCP (SA)

Michael Voigt, MB ChB, MMed, FCP (SA)



Liver cirrhosis is associated with marked abnormalities in the systemic circulation and in renal function, which tend to increase with time.<sup>1,3</sup> In the pre-ascitic phase patients do not have abnormalities in renal function, but they may be unable to excrete a sodium load or escape the sodium retaining effects of mineralocorticoids.<sup>1,4,5</sup> In the ascitic phase there is sodium retention leading to cirrhosis and oedema.<sup>2</sup> As the cirrhosis advances the renal capacity to excrete sodium worsens, and there is renal vasoconstriction, which may culminate in the hepatorenal syndrome.<sup>1</sup> The most important initiating pathophysiological event appears to be peripheral arterial vasodilatation leading to maldistribution of the blood volume and a hyperdynamic circulation.<sup>6</sup> Nitric oxide, a potent endothelium-derived relaxing factor, may be a mediator of haemodynamic abnormalities and sodium and water retention in cirrhosis.<sup>7</sup>

Chronic portal hypertension results in increased portal pressure and reduced splanchnic vascular resistance leading to marked splanchnic hyperaemia.<sup>8</sup> In experiments using animals with surgically induced portal hypertension there is enhanced production of nitric oxide,<sup>9,11</sup> but this may be less than in cirrhotic rats.<sup>12</sup> Portal caval shunting may also be a factor as in experimental models using animals with surgically created portacaval shunting, there is hyperaldosteronuria and reduced ability to excrete a sodium load.<sup>13</sup> There are also changes in the production of prostaglandins, and a heightened sensitivity to the haemodynamic effects of endotoxin.<sup>14,15</sup> These animal experiments suggest a possible role for portal hypertension and portal caval shunting in haemodynamic changes, and sodium and water retention seen in cirrhotics. There are no human studies examining the effect of portal hypertension in the absence of liver disease in the genesis of systemic vasodilatation, and the resultant abnormalities in renal function and sodium excretion. Patients with idiopathic portal vein thrombosis (PVT) have portal hypertension and portal systemic shunting in the absence of liver disease. A local cohort of these patients has been previously described<sup>16</sup> and extensively studied, showing abnormalities in autonomic function, haemostasis and immunological function.<sup>17-19</sup> Detailed investigation of renal function, sodium and water handling have not been previously undertaken. This presented an ideal opportunity to test the hypothesis that portal hypertension in the absence of cirrhosis may play a role in the genesis of renal functional abnormalities and impaired ability to excrete salt and water.

## PATIENTS AND SUBJECTS

Nine patients with PVT were studied, all with a history of variceal bleeding. The patients had previously been extensively evaluated.<sup>16</sup> This included a liver biopsy, ultrasound and computed tomographic scanning, and angiography, which consisted of splenic and superior mesenteric artery and venous phase filling. The diagnosis of PVT was based on a normal

liver biopsy, normal liver function tests, and demonstration of obstruction of the portal vein. All patients were followed up regularly at the Liver Clinic for ongoing surveillance and obliteration of their oesophageal varices. Healthy sex- and age-matched volunteers were used as control subjects. Informed consent was obtained from all subjects and patients, and the study was approved by the University of Cape Town Research and Ethics Committee. Patients with PVT were excluded from the study if their oesophageal varices had not been successfully obliterated and/or they had had a variceal bleed in the past 6 months, or if they had any evidence of concomitant but unrelated renal disease.

## METHODS

Estimation of glomerular filtration rate (GFR) and effective renal blood flow (ERBF) was carried out as outlined by Duarte *et al.*<sup>20</sup> using inulin and para-aminohippuric acid (PAH) clearances. Inulin and PAH were supplied by Cypros Pharmaceuticals, USA and MSD, South Africa respectively. At 0 minutes the subjects and patients were given 700 ml of water of drink, and a loading dose of inulin (0.5 ml/kg, 10% solution) and PAH (0.05 ml/kg, 20% solution) in 50 ml saline was administered intravenously. This was followed by a continuous infusion of inulin and PAH to maintain stable plasma levels. Oral water intake was matched to the urine output until the saline infusion was commenced. No food intake was allowed for the duration of the study. At 45 minutes the bladder was completely emptied, and the estimation of GFR and ERBF was commenced under basal conditions. Blood and urine were taken at half-hourly intervals for inulin, PAH, sodium and creatinine until the completion of the study at 255 minutes. The collections were conveniently divided into two 30-minute collections before, during, and after the saline infusion. The urine volume osmolality was also measured, and the serum osmolality was estimated by doubling the serum sodium.

At 105 minutes blood specimens were taken for renin and aldosterone, and 1 litre of normal saline was infused intravenously and completed at 165 minutes. The inulin and PAH infusion was stopped at 225 minutes, and at 255 minutes the final urine and blood specimens (including renin and aldosterone) were taken.

For the purposes of easier analysis, the inulin and PAH clearances were averaged for the hour before the saline infusion, the hour during, and the hour after. Free water clearance was calculated using the formula:  $C_{\text{water}} = V(1 - U_{\text{osm}}/P_{\text{osm}})$ , where  $V$  is urine volume,  $U_{\text{osm}}$  and  $P_{\text{osm}}$  are the urine and plasma osmolality, and  $C_{\text{water}}$  is the free water clearance.

Inulin was assayed by hydrolysis to fructose, which was then reacted with indole-3-acetic acid to form a purple colour, and read photometrically. PAH was assayed following diazotisation with  $\text{HNO}_2$ . The excess  $\text{HNO}_2$  was removed with  $N$ -1-naphthyl-ethylenediamine. The mauve colour was read photometrically.



Aldosterone and renin were assayed using the Aldosterone Maia Kit and the GammaCoat<sup>125</sup>I Plasma Renin Activity Radioimmunoassay Kit respectively. Urine osmolality was determined by comparative measurements of freezing points of pure water and urine. Creatinine and sodium were measured using Synchron CX Systems.

Statistical analysis was done with Statistica using the repeated measures analysis of variance, with time and group allocation the independent variables.

**RESULTS**

Nine patients and 9 age- and sex-matched controls were studied. All patients in the PVT group were of mixed racial origin, while in the control group there were 3 whites, 3 blacks and 3 patients of mixed racial origin. There were 5 males and 4 females in each group. The 2 groups were well matched at baseline with no significant differences in GFR, ERBF, creatinine, aldosterone, renin, free water clearance fractional excretion of sodium and sodium excretion (Table I).

With the initiation of the saline infusion the GFR and ERBF were not significantly changed during or after completion of the infusion (Figs 1 and 2). The rate of urinary sodium increased significantly during and after the infusion, but again did not differ between the two groups (Fig. 3). Free water clearance decreased significantly after the saline infusion (Fig. 4). Serum sodium levels remained fairly constant in both the PVT and control groups (not shown). Not unexpectedly, both the aldosterone and renin levels declined appropriately before and after the saline infusion. In addition, while the renin levels were similar in the two groups, the aldosterone levels were significantly lower in the PVT group when compared with control equivalent time points (Figs 5 and 6).

**DISCUSSION**

The role of portal hypertension and portal systemic shunting in the genesis of sodium and water retention in chronic liver

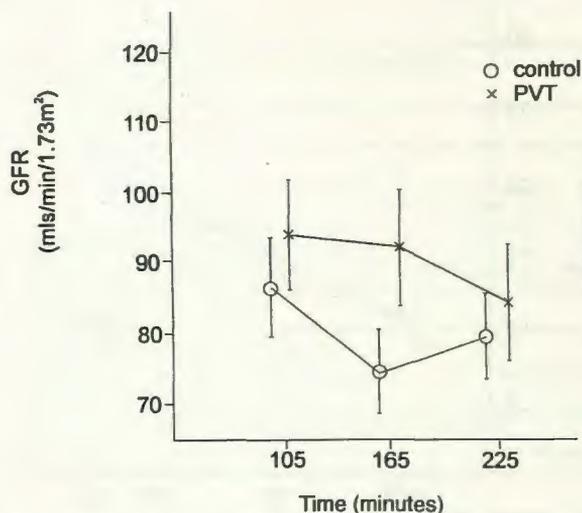


Fig. 1. Changes in mean GFR in the PVT and control groups over time. (Please note: In all figures the means of the control and PVT groups are separated slightly at the time points for ease of viewing.)

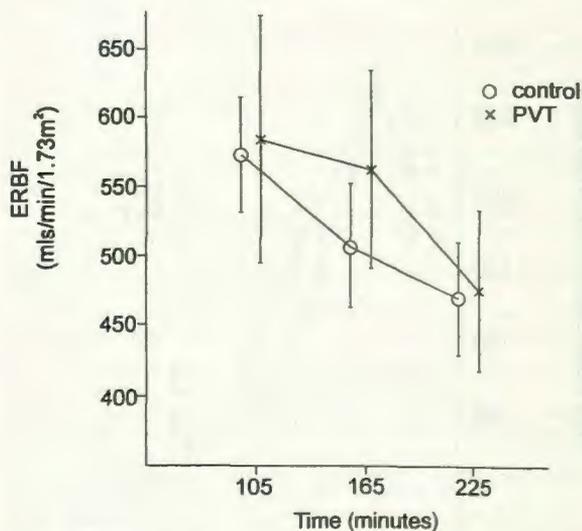


Fig. 2. Changes in mean ERBF in the PVT and control groups over time.

Table I. Mean baseline parameters and mean differences in the PVT and control groups

Parameter	Control (SEM)	PVT (SEM)	Differences (SEM)
Age (yrs)	35.4 (3.1)	35 (5.3)	0.44 (1.57)
Surface area (m²)	1.85 (0.1)	1.7 (0.16)	0.15 (0.09)
Sodium (mmol/l)	140.6 (0.79)	139.5 (0.83)	1.11 (1.05)
Creatinine (µmol/l)	77 (4.4)	69 (4.1)	10.7 (0.55)
GFR (ml/min/1.73 m²)	86.3 (6.83)	94.2 (8.1)	-7.11 (10.99)
ERBF (ml/min/1.73 m²)	572.6 (41.6)	583.6 (73)	-13.65 (67.16)
Renin (ng/ml/hr)	0.88 (0.250)	0.72 (0.18)	0.17 (0.38)
Aldosterone (pM)	252.2 (27.7)	214.3 (24.2)	37.88 (36.64)

SEM = standard error of mean; PVT = portal vein thrombosis; GFR = glomerular filtration rate; ERBF = effective renal blood flow.

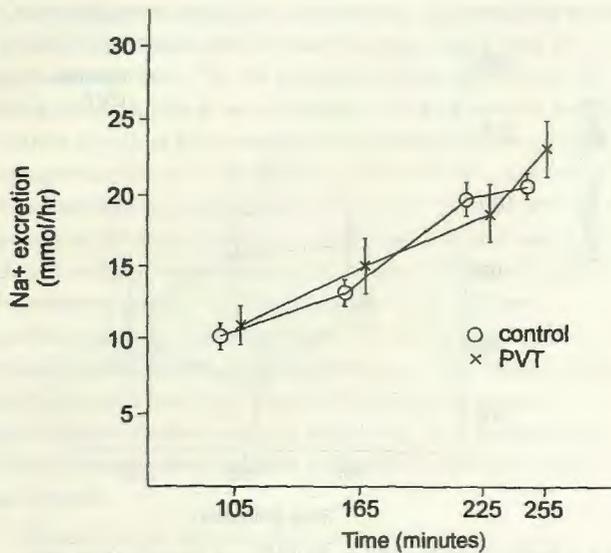


Fig. 3. Changes in mean sodium excretion in the PVT and control groups over time.

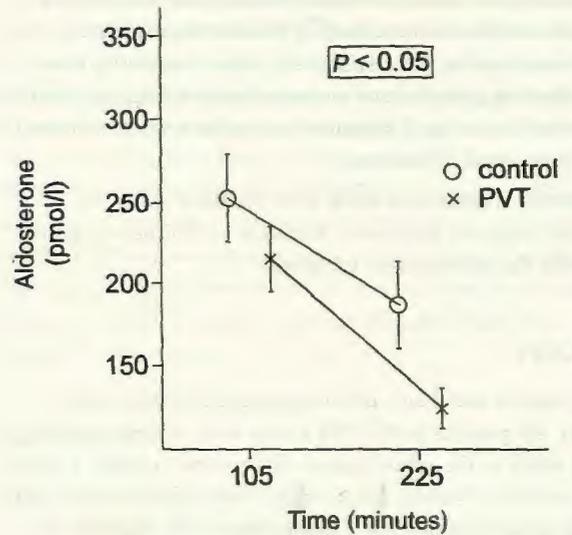


Fig. 5. Changes in mean aldosterone levels in the PVT and control groups over time.

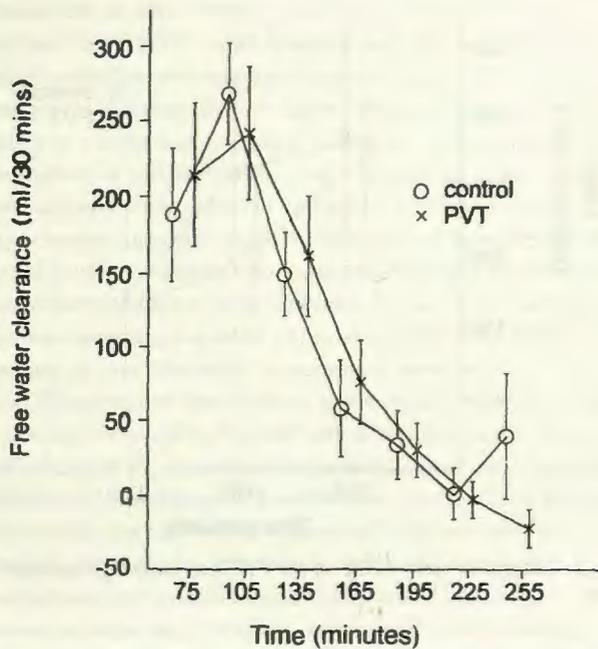


Fig. 4. Changes in mean free water clearance in the PVT and control groups over time.

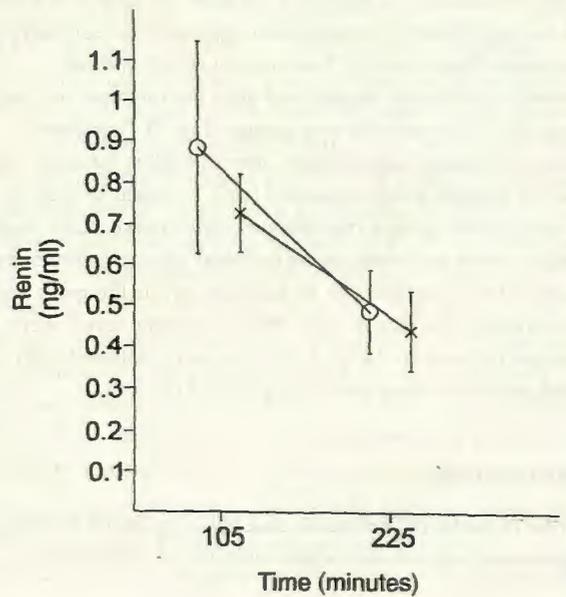


Fig. 6. Changes in mean renin levels in the PVT and control groups over time.

disease has never been fully resolved. Animal experiments have suggested a role. In animals with surgically induced portal hypertension there is enhanced production of nitric oxide,<sup>9,11</sup> it has been suggested that this plays an important pathophysiological role in animals and humans with cirrhosis.<sup>7</sup> In one comparative experiment the production of nitric oxide was greater in cirrhotic rats compared with those with portal hypertension alone, suggesting a less important role for portal hypertension.<sup>12</sup> In other experimental models using animals

with surgically created portacaval shunting there was hyperaldosteronuria and reduced ability to excrete a sodium load.<sup>13</sup> Changes in the production of prostaglandins, and a heightened sensitivity to the haemodynamic effects of endotoxin, have also been recorded.<sup>14,15</sup> In contrast, there have been no experiments in humans to address this issue, and our patients with PVT without liver disease presented an ideal opportunity to test the hypothesis.