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Renal function in fulminant hepatic failure: haemodynamics and renal prostaglandins

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SUMMARY Eighteen patients with fulminant liver failure were studied, 10 with normal renal function (group A) and eight with renal failure (group B , plasma creatinine >200 μmol/l). Renal function was assessed by standard clearance techniques and patients in group B had a marked reduction compared with group A in both renal plasma flow and glomerular filtration rate. Raised plasma renin activity was observed in both groups, but levels in group B were significantly higher than in group A. Renal prostacyclin production was estimated by radioimmunoassay (RIA) of 6-keto-prostaglandin $F_{1\alpha}$ in urine, and the excretion rate was markedly increased in group A as compared with nine healthy controls, but was low in group B. The plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 were similar in groups A and B and were both significantly higher than in controls. Haemodynamic measurements showed a high cardiac output with low vascular resistance and mean arterial pressure within normal limits in both groups. The pulse pressure, however, was significantly higher in group B than in group A. In conclusion, patients in FHF with renal failure have marked renal vasoconstriction with increased plasma renin activity and reduced renal prostaglandin excretion indicative of an imbalance between vasoactive forces.

Evidence accumulated during the past few years suggests that in decompensated cirrhosis, renal function is dependent on renal prostaglandin synthesis.[1] Inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs induces acute reversible reductions of renal blood flow and glomerular filtration rate.[2-4] Furthermore, it has been documented that renal synthesis of vasodilatory prostaglandins, such as prostaglandin (PG) E_2 and prostacyclin, is augmented in those patients with preserved renal function, while the spontaneous development of renal failure is accompanied by reductions in urinary prostaglandins.[4,5] Thus, derangements in renal prostaglandin production contribute to the development of the hepatorenal syndrome in patients with chronic liver disease.

Renal failure often complicates the clinical course of fulminant hepatic failure (FHF) and is associated with a poor prognosis. The aim of the present study was to investigate whether a similar relationship between renal function and prostaglandin synthesis occurs in patients with FHF, which has not been investigated previously. In contrast with cirrhosis, the onset of renal failure in this condition rapidly follows the massive liver necrosis. Hence this clinical condition provides a different situation in which to investigate the role of prostaglandins in combined liver and kidney dysfunction. Data on systemic haemodynamics obtained simultaneously in these patients are also included in the study.

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Methods

PATIENTS

The patients entering the study had been admitted to the Liver Failure Unit with FHF as a result of paracetamol overdose (eight cases), acute viral hepatitis (seven cases; four type B, two type A and one NANB), and one each of acute fatty liver of pregnancy, halothane hypersensitivity and shock liver. All patients were in either grade III or IV coma at the time of investigation, and presented with abnormal liver function tests including marked prolongation of the prothrombin time and raised serum bilirubin. The studies were started at least six hours after admission, central venous pressure being stable. Anuric patients were not included in the study. Patients undergoing charcoal haemoperfusion

or haemodialysis were investigated either before the extracorporeal support or at least 24 hours after. No patients had received vasoactive drugs, mannitol or sodium-containing infusions for at least six hours before the study.

The protocol included measurement of renal blood flow and glomerular filtration rate, haemodynamic monitoring and prostaglandin determinations in plasma and urine.

RENAL FUNCTION

Glomerular filtration rate and effective renal plasma flow were estimated by standard clearance techniques using ^{51}Cr-EDTA and ^{125}I-iodohippurate respectively (Amersham International, Amersham, UK). A priming bolus injection of the isotopes diluted in saline was given through a central line, followed by a constant infusion for three hours. After an equilibration period of one hour, the urine was collected through an indwelling bladder catheter for two hours. The urinary volume was measured and aliquots were separated to determine EDTA and iodohippurate levels, or stored with indomethacin (10μg/ml) at −20°C until prostaglandin assay. Before the infusion, blood samples were collected into ice cold EDTA tubes for plasma renin activity and into EDTA and indomethacin for prostaglandin assay. Plasma samples were also obtained for liver function tests, electrolytes, creatinine and determination of EDTA and iodohippurate, the last sample being taken in the middle of the urine collection period.

HAEMODYNAMICS

Haemodynamic measurements were obtained during the course of routine monitoring in the Liver Failure Unit. Cardiac output was estimated by thermodilution using a Swan-Ganz catheter (mean of three readings; Edwards Laboratories). Arterial blood pressure was measured after intra-arterial cannulation with the mean value derived electronically (Simonsen and Weel Ltd, series 9000; Ames transducer AE 840). From these data the derived value for total systemic vascular resistance was obtained.

ASSAYS

Plasma renin activity was determined by radioimmunoassay of angiotensin I generated in plasma (Clinical Assays, Cambridge, USA). Prostacyclin and thromboxane (TX) A_2 were estimated directly in plasma and urine by specific radioimmunoassay of their stable derivatives 6-keto-$PGF_{1\alpha}$ and TXB_2, respectively. Validations and technical data of the radioimmunassays are reported elsewhere.[5] Plasma and urine samples were also obtained from nine healthy subjects (five men and four women, age ranging from 21-40 years) on an unrestricted diet who were not taking any drugs in order to estimate control values for the prostaglandin and plasma renin activity determinations.

STATISTICAL ANALYSIS

Results are presented as mean ± SEM. Data on cardiac output, effective renal plasma flow and glomerular filtration rate were normalised for a body surface area of 1·7m^2. Statistical differences were tested using Student's *t* test or Mann-Whitney U-test as appropriate.

Results

CLASSIFICATION OF THE PATIENTS

Table 1 shows the clinical and laboratory data of the patients at the time of study. Renal failure was defined by plasma creatinine levels higher than 200 μmol/l, and accordingly patients were divided into two groups: group A consisted of 10 subjects with plasma creatinine within normal limits, and group B included eight patients with renal failure. All patients in group B had functional renal failure as defined by a urinary sodium of <20 mmol/l and a urine to plasma osmolality ratio >1·1:1. Five of the eight patients subsequently developed acute tubular necrosis with urinary sodium >40 mmol/l or anuria later in the course of their illness. As seen in Table I, sex distribution, age, liver function tests, grade of coma at time of study were similar in the two groups.

RENAL FUNCTION AND PROSTAGLANDIN LEVELS IN PLASMA AND URINE

Patients in group A had an effective renal plasma flow and glomerular filtration rate within the normal range. On the contrary, group B showed a marked reduction in both parameters (Fig. 1), revealing an intense renal vasoconstriction in these subjects. In fact, plasma renin activity was significantly higher

Table 1 *Clinical and laboratory data in the patients at the time of study*

	Group A	*Group B*
n	10	8
Sex (M/F)	5/5	4/4
Age range, (median)	16–49 (20)	14–47 (20)
Grade of coma (III/IV)	3/7	2/6
Plasma creatinine (μmol/l)	87±9	463±77*
Prothrombin time (sec)	63±13	57±8
Bilirubin (μmol/1)	185±64	272±46
Albumin (g/l)	31±2	33±1
Platelet count (×10^9/1)	128±21	130±35

*$p<0·01$, A *v* B.

($p<0.01$) in patients with renal failure (group B) than in the others, although both groups showed enhanced plasma renin activity when compared with controls (Fig. 2). As depicted in the figure, excretion of urinary 6-keto-$PGF_{1\alpha}$ was significantly increased in group A when compared with control subjects, while no significant differences in urine flow were observed (A: 1·15±0·20 ml/min; controls 0·85±0·10 ml/min). Patients in group B, however, showed similar 6-keto-$PGF_{1\alpha}$ excretion to controls; urine flow (0·45±0·15 ml/min, $p<0.05$) was lower but no differences were found in the urinary concentration of the prostanoid when compared with controls. Urinary TXB_2 was higher in group A (926±272 pg/min) than in group B (204±86 pg/min, $p<0.05$) or controls (318±17 pg/min, $p<0.05$).

Plasma 6-keto-$PGF_{1\alpha}$ was found to be substantially raised in both groups (A: 310±24 pg/ml, B: 272±26 pg/ml) because control values were undetectable (<50 pg/ml, $p<0.001$). Likewise, plasma TXB_2 concentrations were significantly increased in all the patients, unrelated to the presence of renal failure (A: 241±30 pg/ml; B: 259±68 pg/ml, and controls <50 pg/ml, $p<0.001$).

HAEMODYNAMIC MEASURMENTS

All patients had a high cardiac output and no differences were found between the two groups (Table 2). The increase in cardiac output was associated with reduced total peripheral vascular resistance and mean arterial pressure was maintained within normal limits in both groups studied. Of interest, patients in group B showed higher systolic blood pressure than group A, while diastolic pressure was similar in both groups. Thus, group B characteristically exhibited higher pulse pressure than group A.

Table 2 *Haemodynamic measurements in patients studied*

	Group A	*Group B*	*Normal range*
Cardiac output (l/min)	8.9±0·6	8·4±0·5	4–6
Total vascular resistance (dyne × sec × cm^{-5})	823±81	926±48	1100–1600
Mean arterial pressure (mm Hg)	91±5	100±5	85–105
Diastolic pressure (mm Hg)	70±6	65±4	60–90
Systolic pressure (mm Hg)	140±5	177±7*	110–150
Pulse pressure (mm Hg)	71±7	111±9*	30–80

*$p<0.01$, A *v* B.

Discussion

As previously shown by Wilkinson *et al*,[6] the occurrence of renal failure complicating fulminant hepatic failure (FHF) is not related to the severity

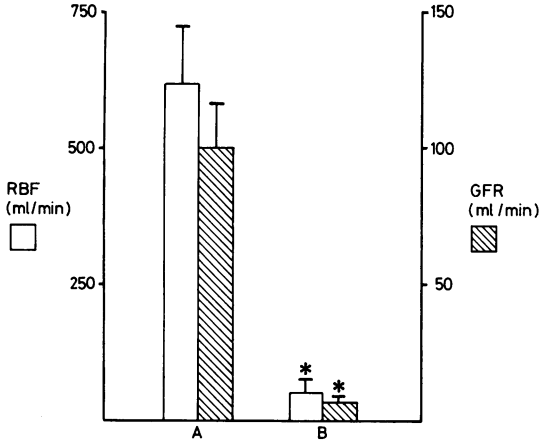

Fig. 1 *Effective renal plasma flow (RBF) determined from the clearance of ^{125}I-iodohippurate was significantly reduced in patients with renal failure (group B: 52±28 ml/min) as compared with those with preserved renal function (group A:610±122). Likewise, glomerular filtration rate (GFR) determined from the clearance of ^{51}Cr-EDTA was significantly lower in group B (7±3 ml/min) than in group A (97±17). *$p<0.001$ compared with respective parameter in group A.*

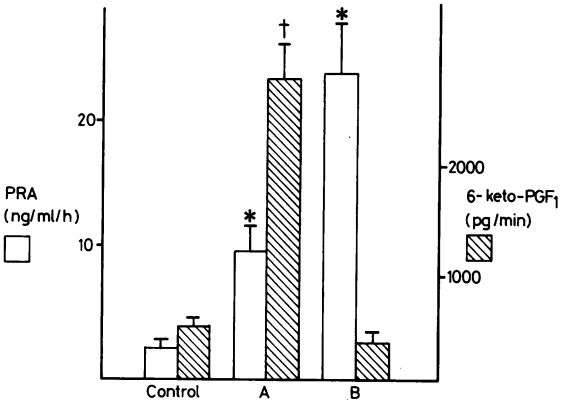

Fig. 2 *Plasma renin activity (PRA), determined by RIA of angiotensin I generated in plasma, was significantly higher in both patients with preserved renal function (group A:10·1±1·9 ng/ml/h) and patients in renal failure (group B:24·9±4·4) as compared with controls (1·8±0·3). Urinary excretion of 6-keto-$PGF_{1\alpha}$ determined by radioimmunoassay was significantly increased in group A (2928±778 pg/min) when compared with controls (525±24), but was unchanged in group B (389±183). *$p<0.001$ compared with control for plasma renin activity. † indicates $p<0.01$ compared with control for urinary excretion of 6-keto-$PGF_{1\alpha}$.*

of hepatic necrosis. In our study, patients with functional renal failure had similar abnormalities in liver function tests and clinical features to the patients with preserved renal function. Major differences were observed in renal haemodynamics as patients in renal failure showed a marked reduction of renal plasma flow and glomerular filtration rate. Thus, constriction of renal vessels seems to play an important role in the development of renal failure.[7]

Prostacyclin is a potent vasodilator able to modulate vascular reactivity to pressor hormones.[8] After its local synthesis, prostacyclin is readily hydrolysed to 6-keto-$PGF_{1\alpha}$ and then enzymatically transformed to several metabolites. Urinary 6-keto-$PGF_{1\alpha}$ is believed to be mainly of renal origin while further metabolic products would reflect systemic prostacyclin synthesis.[9] We found that the excretion rate of urinary 6-keto-$PGF_{1\alpha}$ is highly stimulated in FHF without renal failure, but not in patients with renal failure. On the other hand, plasma renin activity was increased in all patients,[10] with those in renal failure showing highest levels. These findings suggest that enhanced renal prostacyclin synthesis in FHF would counteract vasoconstrictor forces in an attempt to maintain renal function within normal limits.

The fact that urinary 6-keto-$PGF_{1\alpha}$ is reduced in patients with renal failure may be interpreted either as a decrease in renal prostacyclin synthesis or as an impairment of its excretion because of a reduced glomerular filtration rate. The possible contribution of preglomerular sources to urinary 6-keto-$PGF_{1\alpha}$ is not well established. Nevertheless, studies have shown that sulindac inhibits systemic prostacyclin synthesis without changing urinary 6-keto-$PGF_{1\alpha}$,[11] while frusemide increases urinary excretion without systemic changes,[12] suggesting that urinary 6-keto-$PGF_{1\alpha}$ mainly derives from intrarenal sources. On the other hand, prostacyclin was shown to represent the major arachidonic acid product synthesised by medullary microsomes of human kidney and, in addition, biosynthetic capacity is five to 20 times higher in medulla than in cortex.[13] These data would suggest that prostacyclin production is comparatively higher within the tubules than in preglomerular vessels. Assuming that factors stimulating cortical prostacyclin synthesis would also stimulate production within the tubules, it may be concluded that patients in renal failure showed the highest constrictor stimuli without an appropriate response in renal prostacyclin synthesis. An imbalance between vasoactive forces would lead to renal failure, as previously suggested in patients with decompensated cirrhosis.[4]

Urinary excretion of TXB_2 also varied in the groups studied with a similar pattern to that of 6-keto-$PGF_{1\alpha}$, although stimulation in group A was less marked. This finding may be dependent on the renal activation of the arachidonic acid metabolic cascade yielding different products. The present results differ from those observed in cirrhosis with renal failure, where raised urinary TXB_2 excretion was observed.[5,14] This may be related to a more severe reduction of renal plasma flow and glomerular filtration rate in patients with FHF compared to those with cirrhosis.

The plasma concentrations of both 6-keto-$PGF_{1\alpha}$ and TXB_2 were similarly increased in the two groups of patients studied, irrespective of their renal function. This suggests the ability to synthesise prostaglandins in peripheral vessels is not impaired in patients with renal failure. Increased plasma prostaglandin metabolites may be the result of an enhanced platelet wall interaction in FHF, consistent with the altered platelet aggregation and adhesiveness in this condition.[15,16] Reduced renal prostaglandin synthesis is thus more likely to depend on local causes acting within the kidney.

Finally, both groups of patients exhibited a hyperdynamic circulation with high cardiac output and low systemic vascular resistance, as previously observed.[17,18] Hyper-reninism is probably a homeostatic response to reverse a decrease in peripheral vascular resistance.[10,19] Regional distribution of cardiac output was different between the two groups at least in regard to renal blood flow, which was markedly reduced in patients with renal failure. Such a reduction in the presence of a high cardiac output would suggest the existence of areas of very low vascular resistance that would not occur to the same extent in patients with preserved renal function. In addition, in this study, renal failure was associated with a wide pulse pressure as a result of raised systolic pressure. This finding suggests there is a low arterial elasticity probably caused by raised vascular tone and, in fact, these patients showed highest plasma renin activity. Taken together, these data might indicate the existence of areas of arteriovenous shunt in patients with renal failure and, additionally, a generalised stimulation of vasoconstrictor systems as a homeostatic response.

In summary, patients with FHF who developed renal failure showed marked renal vasoconstriction and reduced renal synthesis of prostacyclin. As plasma renin activity was highest in these patients, an imbalance between vasoactive factors may be involved in the pathogenesis of renal failure.

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