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Renal prostacyclin influences renal function in non-azotemic cirrhotic patients treated with furosemide

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The influence of prostaglandins on renal function changes induced by furosemide was analyzed in 21 non-azotemic cirrhotic patients with ascites. Patients were studied in two periods of 120 min immediately before and after furosemide infusion (20 mg, ev). Furosemide caused an increase in creatinine clearance in 15 patients (group A: 99 ± 7 vs. 129 ± 5 ml/min; mean ± S.E.) and a reduction in the remaining six (group B: 102 ± 13 vs. 71 ± 9 ml/min). Parallel changes were observed in the urinary excretion of 6-Keto-prostaglandin-$F_{1\alpha}$ (metabolite of renal prostacyclin) which augmented after furosemide in 14 of the 15 patients from group A (478 ± 107 vs. 1034 ± 159 pg/min, $p < 0.001$) and decreased in all patients from group B (1032 ± 240 vs. 548 ± 136 pg/min, $p < 0.05$). In contrast, the urinary excretion of prostaglandin E_2 was stimulated by furosemide in all patients (group A, 92 ± 19 vs. 448 ± 60 pg/min, $p < 0.001$; and group B, 209 ± 63 vs. 361 ± 25 pg/min, $p < 0.05$). In all of the patients furosemide-induced changes (post- minus pre-furosemide values) in creatinine clearance were closely correlated in a direct and linear fashion with those in 6-Keto-prostaglandin-$F_{1\alpha}$ ($r = 0.74$; $p < 0.001$). These changes were associated with a higher furosemide-induced natriuresis in group A than in group B (641 ± 68 vs. 302 ± 46 μmol/min, $p < 0.001$). In the basal period urinary 6-Keto-prostaglandin-$F_{1\alpha}$ was significantly higher ($p < 0.05$) in group B than in group A, no differences being found in the remaining parameters, including plasma renin activity (group A, 9.7 ± 2.6 vs. group B, 12.0 ± 3.9 ng/ml per h) and urinary sodium output (group A, 30.1 ± 10.6 vs. group B, 11.8 ± 3.5 μmol/min). In summary, our results suggest that renal prostacyclin metabolism influences renal response to furosemide in cirrhotic patients.

The mechanisms underlying the development of azotemia in some cirrhotic patients with ascites undergoing sustained furosemide therapy have not been fully defined (1–6). Although furosemide induces volume depletion and angiotensin II generation that can justify azotemia in some cases (5,6), profound impairments in renal function and renal plasma flow have been demonstrated immediately after a single dose of furosemide in patients in which these two alterations were absent (17). These complications cannot be predicted from clinical or analytical data and they seem to be unrelated to the degree of hyperreninism or to the status of renal function before diuretic challenge (7). Furthermore, recent data indicate that prostaglandin- (PG) E_2 and thromboxane A_2 exert little or no influence on changes in renal function and renal hemodynamics observed in cirrhotics with ascites immediately after furosemide administration (7,8). However, furosemide-induced renal vasodilation is absolutely abolished by inhibitors of PG synthesis (9,10).

Prostacyclin is a powerful renal vasodilatory PG, which plays a crucial role in protecting renal function against vasopressor agents in ascitic patients (11). This substance,

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whose renal synthesis is increased by furosemide in patients with liver cirrhosis (8), has been found to be involved in the changes of glomerular function induced by this diuretic in healthy animals (12). In this study we analyzed whether renal prostacyclin influences the response of renal function to a single dose of i.v. furosemide in nonazotemic cirrhotics with ascites.

Patients and Methods

Twenty-one patients (18 men, three women) with cirrhosis, ascites and preserved renal function were studied. The diagnosis of cirrhosis was established by liver biopsy and/or laparoscopy, and the presence of ascites was proved by diagnostic paracentesis in all cases. Patients with gastrointestinal bleeding, hepatic encephalopathy, infection, past or present history of cardiovascular disease, diabetes mellitus, neoplasia, functional renal failure or clinical or analytical data of parenchymal renal disease were not included in the study.

Protocol of study

In the 4 days before the study, patients were given a diet containing 60 mmol/day of sodium and were maintained on bed rest, and therapy with diuretics, PG synthesis inhibitors, vasoactive substances or any other drug able to modify renal hemodynamics or function was withdrawn. Indeed, no patient taking spironolactone, glucocorticoids or non-steroidal antiinflammatory drugs in the preceding 7 days was included in the study.

After an overnight fast and bed rest, patients were studied in the morning of the fifth day. After bladder evacuation, 5 cc of water/kg of body weight were given orally at 8 a.m. to maintain urine flow. All urine was collected in two consecutive periods of 2 h immediately before (8–10 a.m.) and after (10–12 a.m.) the intravenous administration of 20 mg of furosemide (Seguril, Hoechst Iberica Labs., Spain). Blood samples obtained at 9 and 11 a.m., and urine aliquots of each period were used for analytical determinations. In all patients urinary volume (UV), urinary sodium excretion (UNaV), creatinine clearance (CCr), fractional sodium excretion (FENa), and the urinary excretion of PGE_2 ($UPGE_2$) and of 6-Keto-prostaglandin-$F_{1\alpha}$ (U-6-Keto-$PGF_{1\alpha}$), the stable urinary metabolite of renal prostacyclin, were determined in both periods of the study, while plasma renin activity (PRA) was measured only in the basal one.

Analytical determinations

Electrolytes and creatinine were measured in serum and urine by flame photometry and Jaffe's chromogen reaction, respectively. Liver function parameters were determined by standard methods. Blood for PRA was collected in EDTA, immediately processed at 4 °C and the sera stored at −40 °C. PRA was estimated by radioimmunoassay for angiotensin I (Cea Sorin, France). Urine samples for PG quantitation, were collected on ice in lysine-acetylsalicylate and frozen at −40 °C until use. To determine $UPGE_2$ and U-6-Keto-$PGF_{1\alpha}$, polar lipids were extracted from urine aliquots (10 ml) on disposable C-18 cartridges (Sep-Pak, Waters Assoc., Milford, MA, U.S.A.) (13), being both metabolites measured in the resultant eluates by specific radioimmunoassays as previously described (14). Mean recoveries for PGE_2 (82 ± 4%) and for 6-Keto-$PGF_{1\alpha}$ (79 ± 3%) were calculated by the addition of labelled PGE_2 and 6-Keto-$PGF_{1\alpha}$ to five urine aliquots before processing. These mean values were used for corrections in all samples. In 11 normal subjects under a similar protocol, mean values of U-6-Keto-$PGF_{1\alpha}$ and U-PGE_2 were 191.8 ± 28.4 and 272 ± 83.1 pg/min, respectively. The administration of indomethacin (100 mg twice the day before urine collection) to these controls significantly inhibited the urinary excretion of both metabolites (56.7 ± 5.2%, $p < 0.01$; and 63 ± 6.4%, $p < 0.01$, respectively). Tritiated 6-Keto-$PGF_{1\alpha}$ and PGE_2 (100 000 dpm) were used as standards. Antiserum against 6-Keto-$PGF_{1\alpha}$ was raised from rabbits in our laboratory by the method of Kirton et al. (15), with its binding characteristics and cross-reactivities as reported elsewhere (14). Antiserum for PGE_2 was obtained from the Pasteur Institute (France), and its cross-reactivities with other prostanoids were as follows: 0.11% with $PGF_{2\alpha}$; 0.01% with $PGF_{1\alpha}$; and less than 0.01% with TxB_2, PGD_2 and 6-Keto-$PGF_{1\alpha}$. All samples in a single batch were determined in duplicate to minimize errors due to interassay variation.

Statistical analysis

Results are expressed as mean ± S.E. Comparisons between groups were made by variance analysis. The Student *t*-test for paired data or the non-parametric Wilcoxon test were used for intragroup comparisons as indicated. Regression analysis was performed by the least-squares method.

Results

Patients were retrospectively divided into two groups according to the furosemide-induced change in CCr (post-minus pre-furosemide values). In 15 patients (group A), CCr increased in response to furosemide (mean change: 30.3 ± 5.6 ml/min; +30.6%), whereas in the remaining

TABLE 1

Characteristics of cirrhotic patients with ascites included in the study

	Age (years)	Sex (M/F)	Serum albumin (g/dl)	Serum bilirubin (mg/dl)	Prothrombin time (%)	Serum sodium (mmol/)	Plasma renin activity (ng/ml per h)	Mean arterial pressure (mm Hg)
Group A (n = 15)	59.3 ± 3.3	13/2	3.13 ± 0.13	2.58 ± 0.62	73.8 ± 5.2	132.9 ± 0.9	9.73 ± 2.55	81.4 ± 3.4
Group B (n = 6)	52.3 ± 3.8	5/1	3.10 ± 0.32	4.95 ± 1.14	67.5 ± 5.5	130.2 ± 0.9	12.01 ± 3.90	79.1 ± 3.6

Results are mean ± S.E. No significant differences were found between groups.

six (group B) changes of CCr were negative (mean change: −31.5 ± 6.3; ml/min; −30.8%).

Mean age (A, 59.3 ± 3.3; B, 52.3 ± 3.8 years; N.S.), male/female ratio (A, 13/2; B, 5/1), etiology of cirrhosis (A, 12 alcoholic, three post-necrotic; B, five alcoholic, one post-necrotic), mean arterial pressure (A, 81.4 ± 3.4; B, 79.1 ± 3.6 mm Hg; N.S.), as well as basic analytical parameters and PRA levels (Table 1) were similar in both groups.

Renal function parameters

Table 2 summarizes mean values of renal function parameters before and after furosemide in both groups.

Before furosemide no significant differences were found between groups in CCr, UNaV, UV nor FENa, although UNaV and FENa tended to be lower in group B than in group A. In the post-furosemide period, mean values of these parameters were significantly higher in group A than in group B, with the exception of FENa which was similar in both groups.

TABLE 2

Parameters of renal function before (pre-) and after (post-) furosemide administration in non-azotemic cirrhotic patients with ascites divided according to their positive (group A) or negative (group B) change in creatinine clearance in response to furosemide

		Group A (n = 15)	Group B (n = 6)
Creatinine clearance (ml/min)	pre-	99.9 ± 7.1	102.2 ± 13.3 (N.S.)
	post-	129.3 ± 5.3^{b}	70.7 ± 9.3^{a,**}
Urine volume (ml/min)	pre-	0.62 ± 0.14	0.91 ± 0.21 (N.S.)
	post-	6.34 ± 0.56^{b}	3.82 ± 0.51^{b,*}
Urine sodium excretion (μmol/min)	pre-	30.1 ± 10.6	11.8 ± 3.5 (N.S.)
	post-	670.9 ± 75.0^{b}	313.8 ± 48.1^{a,**}
Fractional sodium excretion (%)	pre-	0.20 ± 0.06	0.10 ± 0.03 (N.S.)
	post-	3.85 ± 0.33^{b}	3.50 ± 0.41^{b} (N.S.)

Results are mean ± S.E.
Intragroup comparisons (Student t-test for paired data):
$^{a}p < 0.01$, $^{b}p < 0.001$.
Group A vs. group B: $^{*}p < 0.05$; $^{**}p < 0.001$.
N.S., not significant.

Urinary excretion of renal PG metabolites

Individual values of U-6-Keto-$PGF_{1\alpha}$ and $UPGE_2$ in the two periods of the study are represented in Figs. 1 and 2, respectively.

In the basal period, U-6-Keto-$PGF_{1\alpha}$ was significantly lower in group A than in group B, whereas no significant differences were found in $UPGE_2$ levels, although it tended to be higher in group B. In response to furosemide, $UPGE_2$ increased in all patients, with post-furose-

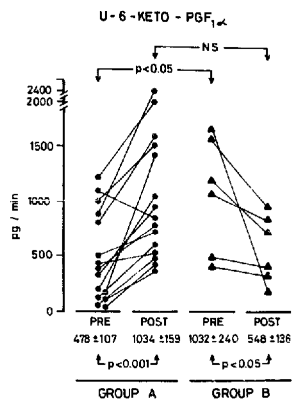

Fig. 1. Urinary excretion of 6-Keto-prostaglandin-$F_{1\alpha}$ (U-6-Keto-$PGF_{1\alpha}$) before and after furosemide administration (20 mg, ev) in non-azotemic cirrhotic patients with ascites, showing, respectively, an increase (group A) or decrease (group B) in creatinine clearance in response to furosemide.

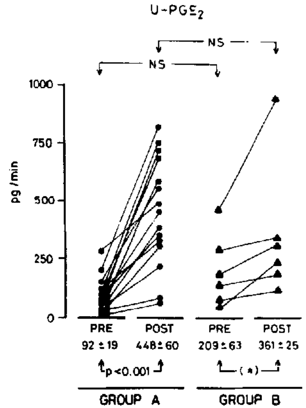

Fig. 2. Urinary excretion of prostaglandin E_2 before and after furosemide administration (20 mg, ev) in non-azotemic cirrhotic patients with ascites showing, respectively, an increase (group A) or decrease (group B) in creatinine clearance in response to furosemide. Comparisons between groups are in the figure. Intragroup comparisons (Student *t*-test for paired data): (a) $p < 0.001$, (•) $0.05 < p < 0.1$ and $p < 0.05$ with the non-parametric Wilcoxon test.

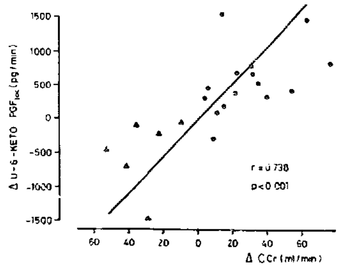

Fig. 3. Correlation between the furosemide-induced increases in creatinine clearance (Δ CCr) and in the urinary excretion of 6-Keto-Prostaglandin-$F_{1\alpha}$ (Δ-U-6-Keto-$PGF_{1\alpha}$) in non-azotemic cirrhotics with ascites. (●) and (▲) indicate, respectively, patients from groups A and B.

mide levels significantly higher than those in the basal period in both groups. However, U-6-Keto-$PGF_{1\alpha}$ was increased after furosemide in 14 patients, all of them from group A. In the remaining seven patients (one from group A and all from group B) this metabolite decreased after furosemide. As a result, as compared with baseline levels, mean values of U-6-Keto-$PGF_{1\alpha}$ were significantly increased and decreased in groups A and B, respectively, in response to furosemide.

The absolute furosemide-induced response (obtained by subtracting pre- from post-furosemide values in each patient) in the urinary excretion of PG as well as in renal function parameters is showed in Table 3.

Finally, when all patients were taken together, furosemide-induced changes in CCr were closely correlated with those in U-6-Keto-$PGF_{1\alpha}$ ($r = 0.75$; $p < 0.001$) (Fig. 3) and, to a lesser extent, with those in U-PGE_2 ($r = 0.51$; $p < 0.05$). In addition, the changes in each metabolite correlated among them in a linear and direct fashion ($r = 0.55$; $p < 0.05$). However, a multiple correlation obtained by plotting furosemide-induced changes in CCr against those in U-6-Keto-$PGF_{1\alpha}$ and $UPGE_2$, disclosed that only the levels of the former metabolite influenced significantly changes in CCr.

Discussion

This study was designed to evaluate whether the acute effects of furosemide on renal function in non-azotemic cirrhotics with ascites are influenced by renal prostacyclin. Renal prostacyclin synthesis was assessed through

TABLE 3

Furosemide-induced changes in parameters of renal function and urinary prostaglandin excretion in non-azotemic cirrhotic patients with ascites divided according to their positive (Group A) or negative (Group B) change in creatinine clearance

	Creatinine clearance (ml/min)	Urine volume (ml/min)	Urinary sodium (mmol/min)	Fractional sodium excretion (%)	$UPGE_2$ (pg/min)	U-6-Keto-$PGF_{1\alpha}$ (pg/min)
Group A ($n = 15$)	30.3 ± 5.6	5.72 ± 0.51	641 ± 68	3.65 ± 0.29	356 ± 55	556 ± 122
Group B ($n = 6$)	(−)31.5 ± 6.3(*) $p < 0.001$	2.90 ± 0.40 $p < 0.05$	302 ± 46 $p < 0.01$	3.40 ± 0.40 N.S.	152 ± 74 $0.05 < p < 0.1$	(−)484 ± 227 $p < 0.001$

Results (mean ± S.E.) were obtained by subtracting pre- from post-furosemide values in each patient. The Student *t*-test was used for comparisons. N.S., not significant.
(*) Classification criterium.

the measurement of U-6-Keto-$PGF_{1\alpha}$. Although a fraction of this urinary metabolite probably arises from prerenal sources, its quantitation is a widely accepted method for measuring the production of prostacyclin by the kidneys, since several studies (16–18), including recent data from cirrhotic patients (19), support a markedly predominant renal origin for the U-6-Keto-$PGF_{1\alpha}$ present in urine.

Present results confirm earlier observations and demonstrate an acute impairment of renal function in some cirrhotic patients with ascites following furosemide administration (7). Other studies have pointed out that the renovascular effects of furosemide are partially dependent on the stimulation of the renal synthesis of vasodilatory prostaglandins induced by this diuretic (9). Recently, no differences were observed in pre- or post-furosemide levels of $UPGE_2$ between cirrhotic patients showing increases or decreases of renal plasma flow after the diuretic. Thus, a primary role for PGE_2 in the hemodynamic effects of furosemide seems to be unlikely. In contrast, the parallel changes of CCr and U-6-Keto-$PGF_{1\alpha}$ observed after furosemide administration in this study, suggest that renal prostacyclin may modulate, at least in part, the acute glomerular effects of this diuretic in cirrhotic patients.

Associated decreases of renal plasma flow and glomerular filtration rate have been demonstrated in some cirrhotics with ascites immediately after furosemide administration (7). It is conceivable that the fall of CCr observed in patients from group B in this study is secondary to a decrease in renal blood flow. In cirrhotic patients with ascites renal blood flow and CCr depend on an equilibrium between vasoconstrictor and vasodilatory forces acting on the kidney (11). Vasoconstrictor agents were not measured after furosemide in our study. However, it may be reasonably assumed that group B patients were exposed to increased vasoconstrictor influences since they exhibited mean basal levels of plasma renin activity exceeding the upper normal limit by about 5 times, and furosemide has been shown to increase the release of pressor agents shortly after its administration (12). In such a situation, a drop in renal vasodilators should be expected to determine an impairment of both renal blood flow and renal function, as was found in patients from group B in which both CCr and U-6-Keto-$PGF_{1\alpha}$ were reduced in the post-furosemide period. On the other hand, in patients from group A, whose plasma renin activity levels were also supranormal before diuretic challenge, CCr was raised after furosemide, in association with a marked increase in U-6-Keto-$PGF_{1\alpha}$. Overall, these data are in agreement with the idea that renal vasodilatory prostaglandins contribute to maintain renal function in cirrhotic patients by counteracting the effects of pressor hormones (11).

Non-steroidal antiinflammatory drugs, whose primary action is the inhibition of prostaglandin synthesis, have been shown to impair renal function in cirrhotic patients with ascites and increased vasoconstrictor tone (11,20,21). Thus, our results suggest that the deterioration of CCr in patients from group B may reflect a shift in renal vasomotor equilibrium toward vasoconstriction, secondarily to the drop in renal prostacyclin synthesis.

Although unlikely, the possibility that changes in CCr might induce parallel modifications of renal prostacyclin synthesis or the urinary washout of U-6-Keto-$PGF_{1\alpha}$, cannot be excluded. Thus, this alternate explanation should be kept in mind to interpret findings in this study.

Increases of both $UPGE_2$ (all patients) and U-6-Keto-$PGF_{1\alpha}$ (group A) are consistent with the well-known stimulatory effect of furosemide on the cyclooxygenase pathway of arachidonic acid (10). The mechanisms leading to the isolated drop in U-6-Keto-$PGF_{1\alpha}$ levels in patients from group B cannot be ascertained from data in this study. These patients showed basal levels of U-6-Keto-$PGF_{1\alpha}$ significantly higher than those in group A. Whether this previous increase in activity of the prostacyclin synthesizing pathway may predispose it to failure after furosemide administration remains to be investigated.

On the other hand, mechanisms unrelated to renal prostaglandins might contribute, to some extent, to changes in CCr after furosemide. This drug inhibits the tubuloglomerular feedback mechanism which is involved in the maintenance of renal perfusion pressure during changes in arterial pressure (22). Early and transitory changes in arterial pressure have been observed after furosemide administration in patients with congestive cardiac failure (23). Although similar events remain to be verified in cirrhotic patients (24), it is possible that variations in arterial pressure in the post-furosemide period, might induce coupled changes in CCr in the presence of an impaired tubuloglomerular feedback mechanism (22).

In summary, this study suggests that renal prostacyclin may play a major role in mediating the glomerular effects of furosemide in cirrhotic patients with ascites and that a drop in its synthesis may contribute to the acute impairment of renal function occurring in some of these patients after furosemide administration.

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