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# PARTICIPATION OF RENAL PROSTAGLANDINS IN THE NEPHROTIC SYNDROME

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## Summary

The participation of renal prostaglandins in the nephrotic syndrome has been investigated by the measurement of the urinary excretion of prostaglandin $E_2$ ($PGE_2$), renal function and the renin-angiotensin-aldosterone system before, during and after the administration of indomethacin in a group of patients diagnosed as having chronic idiopathic glomerulonephritis with and without nephrotic syndrome. Our results indicate increased renal production of $PGE_2$ in nephrotic patients. This contributes to the maintenance of renal function, probably by counteracting an activated renin-angiotensin system and could be accompanied by a simultaneous and deleterious enhancement of the degree of proteinuria. Nevertheless, the participation of angiotensin II in this last event cannot be excluded.

## Introduction

The nephrotic syndrome is frequently characterised by the co-existence of a preserved renal plasma flow and glomerular filtration rate together with factors such as an increased production of angiotensin II capable of reducing them [1,2]. The renal prostaglandins participate in the control of renal haemodynamics [3] and could contribute, at least partly, to the explanation of this paradoxical situation. Recently, our group has described the finding of high urinary excretion of $PGE_2$ in patients with nephrotic syndrome [4]. This prompted us to investigate the participation of renal prostaglandins in the maintenance of renal function in the nephrotic syndrome through a study of the effects of indomethacin administration.

## Material and methods

Twenty-one patients (8 male, 13 female, 17–52 years old), diagnosed as having chronic idiopathic glomerulonephritis and a control group (CG) of 27 normo-

tensive volunteers (16 male, 11 female, 21–36 years old) were studied. The patients were normotensive, in nine a moderate degree of renal insufficiency was present (creatinine clearance 43–76ml/min) and in 12 a nephrotic syndrome (24-hour proteinuria in excess of 3.5g) was diagnosed. After the withdrawal of all medication for at least two weeks the patients were admitted to the hospital. Both patients and CG were studied while taking an 'ad libitum' sodium diet for at least six days. Body weight, blood pressure, creatinine clearance, plasma renin activity (PRA), plasma aldosterone and the 24-hour urinary excretion of sodium, protein and $PGE_2$ were measured. The same parameters were determined again in 16 patients (9 with and 7 without nephrotic syndrome) on the third day of indomethacin administration (2mg/kg/day) and three days after stopping indomethacin. The levels of PRA were measured following the method of Haber et al [5] modified as described by Epstein et al [6]. Plasma aldosterone by the method of Sancho and Haber [7] and urinary $PGE_2$ by a technique described elsewhere [8]. Statistical analysis of the data was performed by means of the paired Student's t test, the Wilcoxon test for unpaired data and linear regression analysis.

## Results

### *Results of the initial study*

TABLE I. Values obtained in the initial study of 21 patients with chronic idiopathic glomerulonephritis and in 27 normotensive volunteers (CG)

| | CG | GN without NS | GN with NS |
|---|---|---|---|
| (n) | 27 | 9 | 12 |
| BW(kg) | 64.5 ± 5.2 | 62.7 ± 11.9 | 61.0 ± 11.6 |
| SBP (mmHg) | 116 ± 11 | 115 ± 12 | 121 ± 17 |
| DBP (mmHg) | 75 ± 8 | 74 ± 10 | 79 ± 10 |
| CC (ml/min) | 120 ± 15 | 72 ± 30* | 75 ± 23 |
| Proteinuria (g/24h) | – | 0.83 ± 0.50 | 6.16 ± 3.90 |
| $U_{Na}$ (mEq/24h) | 233 ± 70 | 140 ± 33* | 82 ± 44† |
| PRA[1] (ng/ml/h) | 0.9 ± 0.5 | 1.2 ± 0.7 | 3.3 ± 2.4† |
| PRA[2] (ng/ml/h) | 4.2 ± 1.9 | 4.3 ± 2.5 | 10.7 ± 6.9† |
| PA[1] (ng/dl) | 4.2 ± 2.1 | 3.1 ± 1.0 | 8.0 ± 5.7† |
| PA[2] (ng/dl) | 11.9 ± 6.1 | 13.0 ± 7.0 | 22.8 ± 15.2† |
| $PGE_2$ (μg/24h) | 1.3 ± 0.5 | 1.1 ± 0.4 | 2.5 ± 1.4† |

Values expressed as $\bar{X}$ ± SD

* $p<0.01$ vs CG; † $p<0.01$ vs CG and GN without NS

GN = glomerulonephritis; NS = nephrotic syndrome; SBP = systolic blood pressure; DBP = diastolic blood pressure; CC = creatinine clearance; $U_{Na}$ = natriuresis; PRA = plasma renin activity; PA = plasma aldosterone; [1] = after overnight recumbency; [2] = after 3 hour upright posture

Table I contains the values obtained in CG and in glomerular disease with and without nephrotic syndrome. The creatinine clearance was similar in the two groups of patients although lower than CG ($p<0.01$). The 24-hour natriuresis was lower when the nephrotic syndrome was present together with clearly increased values of PRA, plasma aldosterone and urinary $PGE_2$ ($p<0.01$).

*Effect of indomethacin administration*

In patients with nephrotic syndrome indomethacin induced an increase in body

TABLE II. Values obtained in the initial study (A), after three days of indomethacin administration (B), and three days after indomethacin withdrawal (C) in 16 patients (9 with, 7 without NS)

| | PATIENTS WITH NS | | |
|---|---|---|---|
| | A | B | C |
| BW (kg) | 60.5 ± 13.5 | 61.3 ± 13.2* | 60.2 ± 12.6 |
| SBP (mmHg) | 121 ± 17 | 121 ± 13 | 115 ± 12 |
| DBP (mmHg) | 79 ± 15 | 78 ± 9 | 79 ± 12 |
| CC (ml/min) | 82 ± 20 | 61 ± 15** | 86 ± 13 |
| $U_{Na}$ (mEq/24h) | 90 ± 47 | 62 ± 66† | 112 ± 54 |
| PRA[1] (ng/ml/h) | 3.7 ± 2.6 | 2.2 ± 2.0†† | 3.7 ± 2.4 |
| PRA[2] (ng/ml/h) | 9.9 ± 5.7 | 5.3 ± 2.5†† | 10.1 ± 5.6 |
| PA[1] (ng/dl) | 8.5 ± 6.0 | 4.8 ± 4.0†† | 8.5 ± 5.9 |
| PA[2] (ng/dl) | 22.9 ± 14.0 | 12.5 ± 7.5†† | 24.3 ± 15.1 |
| Proteinuria (g/24h) | 7.0 ± 4.0 | 2.9 ± 1.6†† | 9.6 ± 6.1 |
| $PGE_2$ (μg/24h) | 2.6 ± 1.1 | 0.5 ± 0.5†† | 2.5 ± 0.9 |
| | PATIENTS WITHOUT NS | | |
| | A | B | C |
| BW (kg) | 63.5 ± 13.4 | 63.6 ± 13.1 | 63.1 ± 12.5 |
| SBP (mmHg) | 115 ± 12 | 121 ± 6 | 118 ± 7 |
| DBP (mmHg) | 74 ± 10 | 78 ± 14 | 75 ± 8 |
| CC (ml/min) | 75 ± 30 | 74 ± 32 | 69 ± 31 |
| $U_{Na}$ (mEq/24h) | 116 ± 63 | 117 ± 50 | 119 ± 58 |
| PRA[1] (ng/ml/h) | 1.2 ± 0.6 | 0.7 ± 0.4† | 1.3 ± 0.4 |
| PRA[2] (ng/ml/h) | 3.8 ± 1.5 | 1.7 ± 1.0†† | 3.7 ± 1.1 |
| PA[1] (ng/dl) | 2.9 ± 1.1 | 2.1 ± 0.9 | 2.8 ± 1.1 |
| PA[2] (ng/dl) | 11.2 ± 4.6 | 6.0 ± 2.0†† | 11.8 ± 3.9 |
| Proteinuria (g/24h) | 0.7 ± 0.5 | 0.2 ± 0.3†† | 0.8 ± 0.4 |
| $PGE_2$ (μg/24h) | 1.0 ± 0.4 | 0.4 ± 0.2†† | 1.0 ± 0.4 |

Values expressed as $\bar{X}$ ± SD

†$p<0.05$ vs A; *$p<0.025$ vs A; **$p<0.01$ vs A; ††$p<0.005$ vs A

See Table I for abbreviations

weight ($p<0.025$) and a diminution of creatinine clearance ($p<0.01$), proteinuria ($p<0.005$), natriuresis ($p<0.05$), PRA ($p<0.005$), plasma aldosterone ($p<0.005$) and urinary $PGE_2$ ($p<0.005$). In the absence of nephrotic syndrome similar changes were observed for PRA, plasma aldosterone, urinary $PGE_2$ and proteinuria ($p<0.05$–$0.005$) but the remaining parameters did not change. After stopping indomethacin the values returned to previous levels in both groups of patients (Table II).

*Relationship between the changes of the different parameters measured in the nephrotic syndrome group*

No correlation was found between the percent changes of creatinine clearance and proteinuria (Figure 1). The percent changes of glomerular filtration rate correlated with the initial values of urinary $PGE_2$ ($r=0.637$, $p<0.05$). The percent changes of proteinuria correlated both with those of $PGE_2$ ($r=0.765$, $p<0.01$) and those of PRA ($r=0.738$, $p<0.01$).

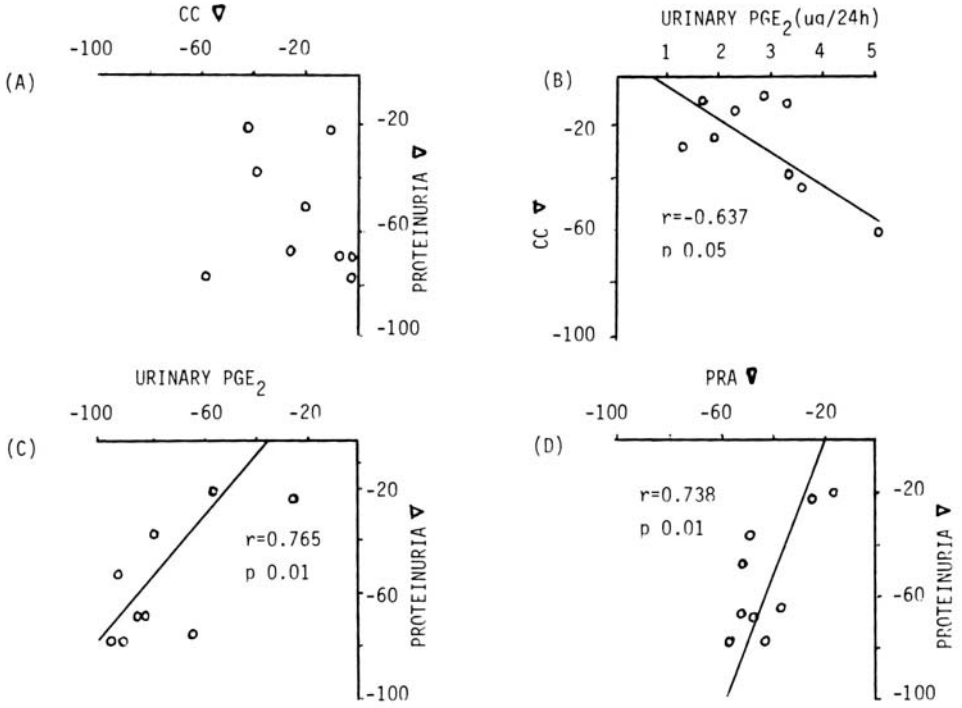


Figure 1. Correlations after indomethacin administration: (A) percent changes of creatinine clearance (CC) and proteinuria; (B) initial value of urinary $PGE_2$ and percent changes of CC; (C) percent changes of urinary $PGE_2$ and proteinuria; (D) percent changes of PRA and proteinuria

## Discussion

The present data confirm the existence of an activated renin-angiotensin-aldosterone system as well as an increased urinary excretion of $PGE_2$ in the nephrotic

syndrome. The renal prostaglandins participate in the normal regulation of renal haemodynamics and in the renal handling of sodium and water [3,9] and they are able to counteract the effects of pressor hormones [10]. Our group of nephrotic patients presented with a lower urinary excretion of sodium and with higher values of PRA and aldosterone supporting the existence of a diminished effective plasma volume. In this situation an increase in the renal vascular resistances and a diminution of renal plasma flow can be expected [1,2]. The simultaneous increase of urinary $PGE_2$ probably represents an attempt to overcome those effects to maintain renal function. The effects of indomethacin, especially the correlation between urinary $PGE_2$ and the fall of glomerular filtration rate, seem to confirm this theory.

In all the patients studied, the administration of indomethacin was followed by a decrease in urinary protein excretion which returned to previous values promptly after stopping the drug. This finding suggests by its rapidity that the changes in proteinuria are mainly mediated by renal functional changes. Nevertheless, other factors mediate this effect because the proteinuria also diminishes in the absence of nephrotic syndrome where indomethacin does not change renal function. The modifications of proteinuria are not related to changes in the rate of protein filtered by the glomeruli [11]. The diminution in proteinuria correlated with those of PRA and urinary $PGE_2$. It has been shown in animals, as in man, that angiotensin II can provoke the appearance of proteinuria even to the nephrotic range [12,13]. The reduction of proteinuria induced by indomethacin could then be secondary to a reduction of angiotensin II. The participation of renal $PGE_2$ in the degree of proteinuria is supported by its vasodilatory effects upon previously damaged juxtamedullary nephrons, thereby increasing proteinuria [14]. The effect of indomethacin seems to confirm this theory. Nevertheless the close relationship that exists between $PGE_2$ and the renin-angiotensin system renders the interpretation of these results difficult [4,9].

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**Open Discussion**

DAL CANTON (Naples) Micropuncture studies have clearly shown that prostaglandins reduce glomerular capillary ultrafiltration coefficient, thus it is not apparent how PG may increase proteinuria unless there is an increase in GFR.

RUILOPE Yes, in some way prostaglandins could modify the quantity of proteinuria through their vasodilatory action acting upon the juxtamedullary nephrons. Nevertheless, as you know, $PGE_2$ and renin run together and it is difficult to separate the effect of their decrease. Perhaps what we have seen is merely the consequence of angiotensin II inhibition. As you know angiotensin II can induce the appearance of proteinuria in the nephrotic range.

GABRIEL (London) May I ask please, in men how much of the urinary prostaglandin comes from prostate gland? Therefore how many of your patients were men and how could this have confounded your conclusions?

RUILOPE The extrarenal origin of $PGE_2$ in the urine of male people has been demonstrated and in our experience in normal people the values of urinary $PGE_2$ are higher in male than in female. The ratio male/female was lower in our group of nephrotic patients than in our control group. Nevertheless the level of urinary $PGE_2$ excretion was higher in the group of patients confirming our statement.