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Influence of converting enzyme inhibition on glomerular filtration rate and proteinuria

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The progression of chronic renal failure is facilitated by the presence of arterial hypertension. Antihypertensive therapy has been shown to effectively protect the kidney from continuous functional derangement [1, 2]. The degree of proteinuria has also been shown to be a prognostic factor for the progression of chronic renal insufficiency [3, 4].

Recently, experimental [5, 6] and preliminary clinical data [7] have shown that converting enzyme inhibitors are effective in slowing the progression of chronic renal failure. These drugs also have the capacity to reduce glomerular proteinuria [8, 9], and through this mechanism they also have the ability to change the rate of progression of chronic renal failure.

On the other hand, the measurement of the progression of chronic renal failure remains as a matter of debate [10, 11]. The usefulness of the slopes of the reciprocal of serum creatinine has been questioned [10–12] and there seems to be general agreement in the sense that sequential measurements of isotope glomerular filtration rate or inulin clearance are the most reliable methods to determine the rate of progression of chronic renal failure.

This paper contains our experience on long-term effects of the therapy with the angiotensin converting enzyme, captopril, on the glomerular filtration rate and on the rate of progression of renal insufficiency of patients with chronic renal failure and arterial hypertension. Two previous publications of our group [7, 9] contain the initial results of this study obtained during the first year of follow-up in Group 1 and the first six months in Group 2. Before switching their therapy to captopril, patients were divided in two groups: Group 1, patients with primary non-glomerular disease who exhibited a progressive decline in renal function; their blood pressure was adequately controlled by means of standard triple therapy. They were initially classified by the finding of a negative and significant slope of the reciprocal of serum creatinine. Group 2 were patients diagnosed by a renal biopsy as having a primary glomerular disease with chronic renal failure, who presented with an adequate control of their arterial hypertension with one or two standard drugs. The long-term comparison of captopril versus standard therapy on the progression of renal failure and on non-diabetic glomerular proteinuria, as well as an evaluation of the different methods employed to evaluate glomerular filtration rate are presented.

Methods

Group 1 comprised 10 patients, aged 46 to 60 years, five males and five females, with histologically-proven chronic interstitial nephropathy in five, chronic renal failure of unknown etiology with small-sized kidneys, low range proteinuria and without microhematuria in four, and adult polycystic kidney disease in one.

All of them had been followed for at least 12 months period during which they exhibited a progressive decline in the slope of reciprocal of serum creatinine, an adequate control of blood pressure with standard triple therapy (furosemide 40 to 180 mg/day, propranolol 120 to 300 mg/day, and hydralazine 50 to 200 mg/day) and had not changed their dietary habits for at least eight months.

The Group 2 included 20 patients, aged between 20 and 61 years, 14 males and 6 females, who had been diagnosed by renal biopsy as having primary glomerular disease (IgA nephropathy in 8, focal and segmental glomerulosclerosis in 7, mesangiocapillary glomerulonephritis in 2, membranous nephropathy in 2, and rapidly progressive glomerulonephritis in 1). All were being treated with one or two antihypertensive drugs (furosemide 40 to 120 mg/day, propranolol 120 to 200 mg/day). The patients were divided for analysis of the data in two subgroups according to the presence of a daily proteinuria in excess (Group 2a) or below (Group 2b) 3 g. Patients were encouraged to continue with their previous dietary habits. After obtaining baseline clinical and laboratory data the patients were switched to the CEI captopril, in doses adequate to control hypertension to levels similar to those while on standard therapy. After 48 to 72 hours of discontinuation of the standard therapy, captopril was initiated at a dose of 25 mg twice daily. The dose of captopril was titrated weekly thereafter.

The effect of captopril on renal hemodynamics was determined by measuring the C_{In} and C_{PAH} at baseline, and after 3 months and every 6 months during the therapy with captopril. In addition the estimated slope of $1/C_r$ plotted versus time was obtained and calculated in Group 1 for the 12 months before initiation of captopril and yearly thereafter. The values of serum creatinine and creatinine clearance were obtained monthly during all the follow-ups in every patient, together with the variations of blood pressure (BP), body weight and other laboratory parameters. Plasma renin activity (PRA) and plasma aldosterone (PA) values were estimated with the same frequency as inulin and PAH clearances. BP was measured by two trained observers with a standard mercury sphygmomanome-

ter. Systolic (first phase) and diastolic (fifth phase) BP were measured in the sitting position in an out-patient clinic.

The methods utilized for the measurement of C_{In}, C_{PAH}, PRA and PA, and the other biochemical parameters have been previously described [7, 9].

All data were analyzed by repeated measure analysis of variance (ANOVA) followed by a Dunnett test and by regression analysis using standard formulae. Statistical significance was defined as $P < 0.05$.

Results

Group 1

As can be seen in Figure 1, the control of blood pressure was similar when values from standard triple therapy were compared with those obtained with captopril alone. Meanwhile, inulin and para-aminohippurate clearances increased significantly during the first three months. This was probably attributable to the withdrawal of triple therapy, although a beneficial effect of captopril cannot be excluded. The initial improvement remained throughout 18 months, and values similar to those obtained at the baseline were found thereafter.

The variations of PRA and PA were as expected: an increase of the first and a fall of the second. Plasma potassium and the urinary excretion of urea persisted within similar levels, indicating that the renal handling of potassium remained within acceptable limits and that the protein intake in the diet was stable. Table 1 shows the evolution of the reciprocal of serum creatinine plotted versus time during follow-up before and after the change to the ACE inhibitor. The slope changed significantly during the first year and was less negative during the second and third years.

A positive correlation was found between 1/Crs and C_{In}, C_{Cr} and C_{PAH}. C_{In} also correlated with C_{Cr} and C_{PAH} (Table 2).

Group 2

Figure 2 and Figure 3 show the data obtained in patients included in Group 2 divided according to the level of 24-hour proteinuria as previously stated. An increase in C_{In} and C_{PAH} was observed in both subgroups of patients after three months of captopril therapy. The improvement was maintained only in those patients exhibiting initial proteinuria levels below the nephrotic range. Serum albumin increased and serum cholesterol decreased in subgroup 2a but not in Group 2b. PRA, PA and potassium and urine urea excretion exhibited changes similar to those observed in Group 1.

Proteinuria decreased significantly in Group 2a after the first month of therapy and remained within similar levels during the two years of follow-up. In subgroup 2b the level of proteinuria fell significantly only during the second year of follow-up (Fig. 4).

A positive correlation was also found between the values of 1/Crs and C_{In}, C_{Cr} and C_{PAH} in both groups of patients. C_{In} correlated with C_{Cr} and C_{PAH} (Table 3). A negative and significant correlation ($r = -0.250$, $P < 0.01$) was found between 1/Crs and proteinuria in those patients with baseline proteinuria above 3 g/24 hr but not in the others. On the other hand, proteinuria did not correlate with C_{Cr} or C_{In}.

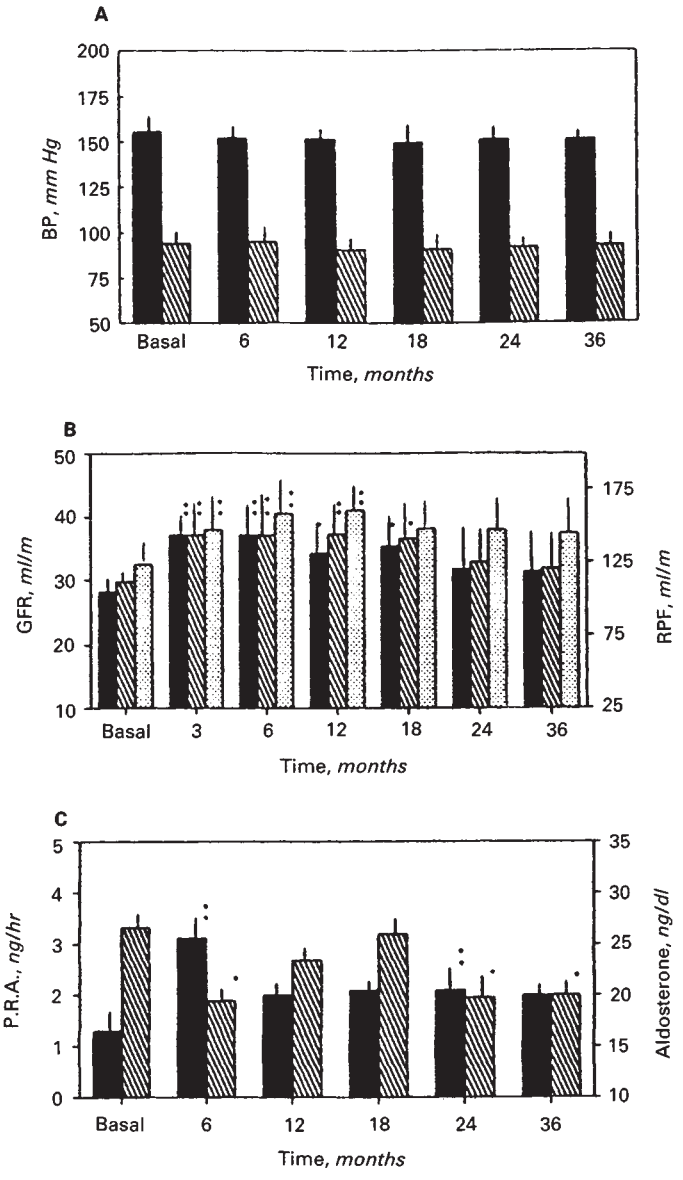

Fig. 1. *Values (SEM and* P*) of BP, GFR, RPF, PRA and PA during standard therapy (Basal) and after captopril therapy in patients of Group 1.* Symbols are: **A**: (■) SBP; (▨) DBP; P = NS; **B**: (■) C_{In}, (▨) C_{Cr}, (□) C_{PAH}; $^{**}P < 0.01$, $^{*}P < 0.05$; C: (■) PRA; (▨) aldosterone; $^{**}P < 0.01$, $^{*}P < 0.05$.

Discussion

Comparison of captopril with standard triple therapy

The group of ten patients whose arterial hypertension was controlled with triple drug therapy exhibited an increase of C_{In} and C_{PAH} by approximately 24% to 30% during the first three months of captopril therapy. This change took place despite similar degrees of BP control by both therapeutic regimes. Subsequently both parameters remained significantly elevated until the eighteenth month of captopril therapy, and were not different from baseline values thereafter. Although the initial changes could be ascribed to the withdrawal of standard therapy [13, 14], the sustained beneficial effect on renal hemody-

Table 1. Slope of the linear regression between the reciprocal of serum creatinine versus time in patients of Group 1

	Standard therapy (basal) 12 months	Captopril therapy 12 months	24 months	36 months
Mean	−0.0067	+0.003[a]	−0.0015	−0.0011
SEM	0.0013	0.001	0.0134	0.0034

[a] $P < 0.01$

Table 2. Correlation between different parameters of renal function in patients of Group 1

Correlation	r	P	N
1/Crs − C_{In}	0.827	<0.01	80
1/Crs − C_{Cr}	0.828	<0.01	360
1/Crs − C_{PAH}	0.742	<0.01	80
C_{In} − C_{Cr}	0.935	<0.01	80
C_{In} − C_{PAH}	0.931	<0.01	80

namics probably depends on the hemodynamic effect of captopril [15]. Other non-hemodinamically mediated factors could also have participated in the improvement of renal function [16].

Our results are in accordance with the statement that inulin clearance is the most adequate method, together with isotopic methods, to estimate the rate of progression of renal failure [10, 11]. Creatinine measurements in plasma and urine have been considered as misleading in evaluating progression [11]. Nevertheless, in our experience the measurement of serum creatinine and its renal clearance seems to be adequate to estimate the rate of progression, at least, if the conditions in which our study was performed are provided. It is at present unclear whether changes in 1/Crs over time represent a precise and consistent method of measurement, particularly when patients are subjected to dietary maneuvers that can influence creatinine production [10, 11]. In our patients, the urinary urea excretion did not change during the follow-up, indicating that roughly their protein intake remained stable. This fact, together with the good correlation of 1/Crs with inulin clearance permits a consideration that ACE inhibition arrested the progression of renal failure during the period of the study.

Effect on proteinuria

ACE inhibitors have been shown to reduce diabetic [17] and nondiabetic [8, 9] glomerular proteinuria. Proteinuria is a factor that indicates a poor prognosis for the progression of renal failure [3, 4]. The diminution of the rate of protein excretion in urine could be a contributing factor in slowing the progression of renal failure. In fact, the reduction of microalbuminuria has been accompanied by an improvement in renal function in diabetic patients [18–20].

We have found that captopril therapy was able to improve renal function and decrease proteinuria in patients with primary renal disease. Nevertheless, no clear correlation was found between proteinuria and glomerular filtration rate measured either by creatinine or inulin clearances. The improvement in renal function remained longer in those patients exhibiting the lower baseline values of proteinuria. This seems to be in accordance with the poorer prognosis of those patients exhibiting higher levels of urinary protein excretion [3, 4].

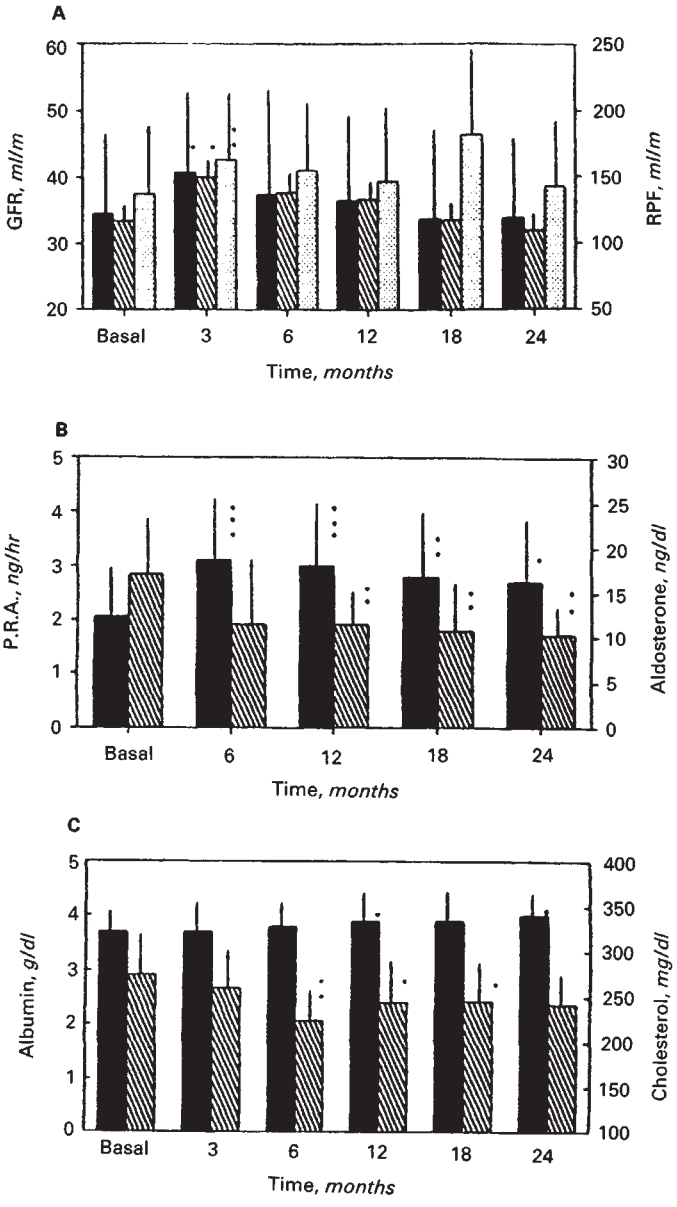

Fig. 2. *Values (SEM and P) of GFR, RPF, PRA, PA, serum albumin and serum cholesterol during standard therapy (Basal) and after captopril therapy in patients of Group 2a.* Symbols are: **A**: (■) C_{In}, (▨) C_{Cr}; (▩) C_{PAH}, $^{**}P < 0.01$, $^{*}P < 0.05$; **B** (■) PRA, (▨) aldosterone, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$; **C** (■) albumin, (▨) cholesterol, $^{**}P < 0.01$, $^{*}P < 0.05$.

In glomerular patient group the measurement of inulin clearance also seemed to be the most adequate method for evaluating renal function, although creatinine clearance behaved in a quite similar fashion.

In summary, in our experience, provided that protein intake remains roughly unchanged, and patients are maintained at equal levels of blood pressure control, converting enzyme inhibition seems to have advantages over standard therapy to

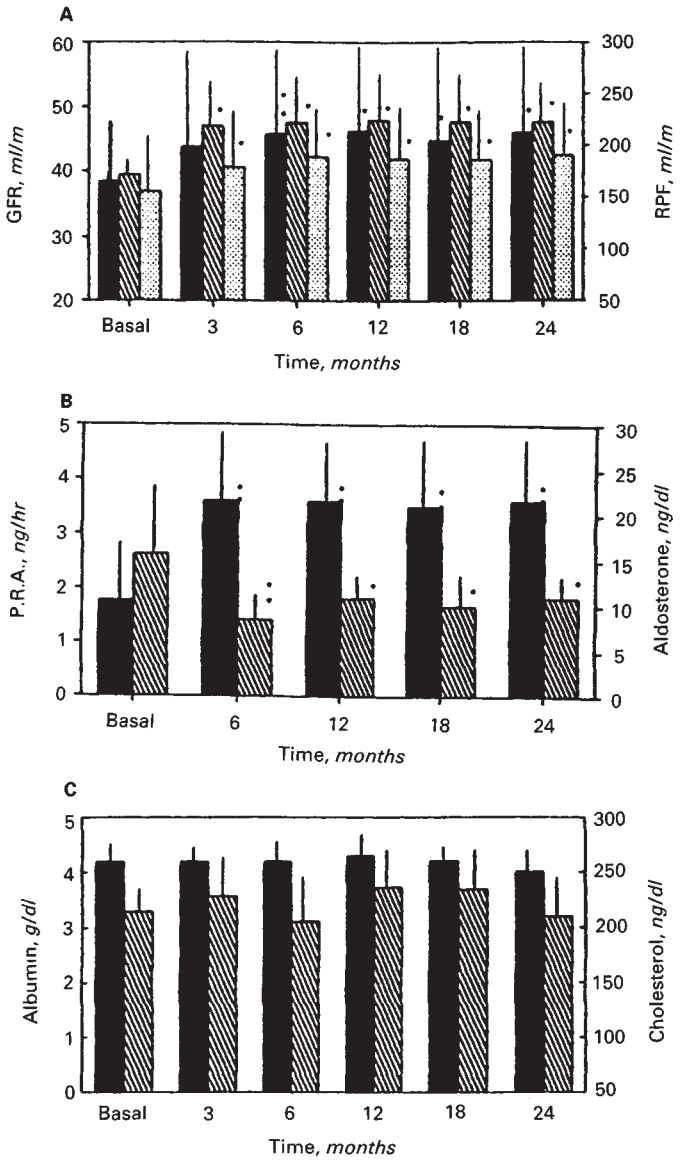

Fig. 3. *Values (SEM and P) of GFR, RPF, PRA, PA, serum albumin and serum cholesterol during standard therapy (Basal) and after captopril therapy in patients of Group 2b.* Symbols are: **A**: (■) C_{In}, (▨) C_{Cr}, (□) C_{PAH}, $^{**}P < 0.01$, $^{*}P < 0.05$; **B**: (■) PRA; (▨) aldosterone, $^{**}P < 0.01$; $P < 0.05$; **C**: (■) albumin, (▨) cholesterol.

arrest the rate of progression of chronic renal failure by increasing or maintaining glomerular filtration rate. This therapeutic modality also reduces non-diabetic glomerular proteinuria.

Inulin clearance is the most appropriate method to measure glomerular filtration rate in chronic renal failure. Reciprocal of serum creatinine and creatinine clearance can be useful in clinical studies followed-up during long periods of time.

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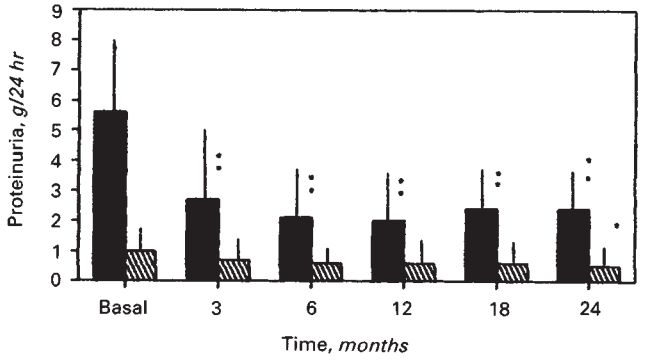

Fig. 4. *Twenty-four hour protein excretion during standard therapy (Basal) and after captopril therapy in patients of Groups 2a and 2b.* Symbols are: (■) Group 2A; (▨) Group 2b; $^{**}P < 0.001$; $^{*}P < 0.05$.

Table 3. Correlations between different parameters of renal function in patients of Group 2

	Group 2a			Group 2b		
Correlation	*r*	*P*	*N*	*r*	*P*	*N*
1/Crs – C_{In}	0.906	<0.01	72	0.863	<0.01	42
1/Crs – C_{Cr}	0.901	<0.01	307	0.830	<0.01	144
1/Cr – C_{PAH}	0.895	<0.01	72	0.886	<0.01	42
C_{In} – C_{Cr}	0.980	<0.01	72	NS	NS	NS
C_{In} – C_{PAH}	0.937	<0.01	72	0.959	<0.01	42

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