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Angiotensin converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy

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Angiotensin converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. Clearances of uncharged dextrans of broad size distribution were used to evaluate the effects of a 30 day course of enalapril on glomerular barrier function in 10 patients with IgA nephropathy and proteinuria (from 1.4 to 5.6 g/day). Dextran clearance experiments were repeated three times: before enalapril therapy, after 30 days of enalapril and again 30 days after enalapril withdrawal. GFR, but not RPF, was significantly reduced by enalapril (basal 38.3 ± 11.9, enalapril 30.2 ± 12.6 ml/min/1.73 m^2) and returned to basal values after enalapril withdrawal. Urinary protein excretion and fractional clearance of albumin were both significantly reduced by enalapril (basal 2.3 ± 1.1 g/day and 102 ± 90 × 10^{-5}, enalapril 1.2 ± 0.6 g/day and 51 ± 23 × 10^{-5}, respectively) and returned to basal values after enalapril withdrawal. Transglomerular passage of large dextrans (radii 54 to 62 Å), but not of lower size (26 to 42 Å) were significantly lowered by enalapril. When enalapril was withdrawn the dextran-sieving profile returned comparable to the baseline levels. A theoretical analysis of dextran-sieving profiles indicated that enalapril lowered the radius of largest membrane pores. This effect was independent from glomerular hemodynamic changes. We conclude that angiotensin converting enzyme inhibitors (CEI) in humans with IgA nephropathy reduces urinary protein excretion by a primary action on the intrinsic glomerular membrane properties enhancing barrier size-selective function. The hypofiltration associated with enalapril therapy in these patients, which was eliminated by its withdrawal, has to be taken into account as a possible undesired effect of CEI in long-term treatment.

Angiotensin-converting enzyme inhibitors (CEI) reduce proteinuria in various experimental and human glomerular diseases. Data are conflicting on the extent of this effect and on whether it applies to all forms of glomerular injury involving increased glomerular permeability to proteins. Data on the favorable effects of CEI on proteinuria have mainly been obtained in rats with reduction of renal mass and streptozotocin diabetes [1, 2] and in diabetes mellitus in humans [3–5]. Of interest in both laboratory and human studies the reduction of glomerular permeability to proteins induced by CEI is associated with an enhancement of glomerular barrier size-selectivity [5, 6]. However, so far no controlled information is available on the effect of CEI on other forms of glomerular damage, particularly in proliferative glomerulonephritis.

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One of the most widespread forms of human proliferative glomerulonephritis is IgA nephritis, a disease of recurrent hematuria and glomerular deposits of immunoglobulin and complement in the mesangial region. Most of these patients have proteinuria, and recently a subset of patients has been identified in which the disease may rapidly progress to terminal renal failure [7]. Since the most proteinuric forms of IgA glomerulonephritis tend to have a severely progressive course, any attempt to reduce proteinuria is of primary clinical relevance.

The present study was designed to explore the effects of CEI on glomerular function and size-selective properties in patients with IgA glomerulonephritis. Glomerular function and size-selectivity were explored by a solute clearance technique. Renal clearance studies were done before and after one month of treatment with CEI, and were repeated in all patients one month after withdrawal of CEI therapy.

Methods

Patient population

Ten male patients with biopsy-proven IgA mesangial nephropathy were studied. Admission criteria to the study were: clinical proteinuria (>1 g/day) on three consecutive occasions in the last two months before entry into the study; normal or moderately reduced renal function (creatinine clearance >30 ml/min); no previous or concomitant immunosuppressive treatment; no treatment with NSAID or CEI in the three months before selection. Informed consent was obtained before entry into the study.

The patients' average age was 34 years (range 25 to 58). At admission four patients were normotensive, blood pressure (BP) less than 140/85 mm Hg, five patients were on antihypertensive treatment with beta blocker (atenolol < 100 mg/day), one patient was on calcium antagonist (nifedipine 20 mg/day) therapy plus diuretic (furosemide 25 mg/day). Patients on antihypertensive therapy had BP values less than 150/95 mm Hg.

Study protocol

The effect of a CEI, enalapril (Merk Sharp & Dome Italia, Rome, Italy), on glomerular function was evaluated using a sequential study protocol. A first evaluation of glomerular function was done before enalapril treatment by measurement

of inulin, para-aminohippurate (PAH) and neutral dextran clearance. Starting right after the basal evaluation patients received enalapril for one month, at the end of which the clearance study was repeated. A third clearance study was done one month after enalapril withdrawal. These three clearance studies are referred to as basal, enalapril and enalapril withdrawal, respectively.

Enalapril therapy was started at a dose of 5 mg/day, increased if necessary to a maximum of 15 mg/day over the next few days to maintain systolic BP between 100 and 150 mm Hg and diastolic BP between 70 and 95 mm Hg. During treatment with CEI other antihypertensive drugs were discontinued. When CEI treatment was completed patients were returned to their original antihypertensive therapy if previously adopted.

Clearance studies

Inulin, PAH and neutral dextran clearances were measured as previously described [8] under a steady state of diuresis induced by oral water loading; exactly the same procedure was followed for each patient during the three clearance studies. A priming infusion containing 10% inulin, 20% PAH and 10% Dextran 40 (Rheomacrodex, Pharmacia, Uppsala, Sweden, 130 mg/kg) was infused, followed by continuous administration of inulin and PAH to maintain constant plasma concentrations of approximately 15 and 1.5 mg/dl, respectively.

After an equilibration period of about 60 minutes, three exactly-timed urine collections of about 30 minutes were made by spontaneous voiding. Blood was sampled at the beginning and end of each clearance period for assays of inulin and PAH. From urine and plasma samples obtained during the first clearance period the concentrations of neutral dextrans of graded sizes and albumin were also determined. Fractional clearance of these test macromolecules was computed as: $(U/P)_m/(U/P)_{IN}$, where $(U/P)_m$ and $(U/P)_{IN}$ are the urine to plasma concentration ratios of the test macromolecule and inulin, respectively.

GFR and RPF were calculated respectively as the average inulin and PAH clearance for the three timed collection periods, corrected for body surface area. For RPF calculation an assumed PAH extraction ratio of 0.7 was also adopted to account for the depression of renal PAH extraction observed in patients with proteinuric glomerular disease and reduced GFR [9].

Laboratory methods

Inulin and PAH concentrations in plasma and urine samples were determined using methods previously described [10, 11]. Graded size dextran molecules and inulin in the same samples were separated by gel permeation chromatography on a Ultrogel AcA 44 column (1.6 × 95 cm, LKB, Uppsala, Sweden). Column calibration was performed periodically using dextran fractions of known molecular weight (Dextran T10, T40 and T70, Pharmacia, Uppsala, Sweden) and inulin. Effective molecular radius, r, for dextran molecules in eluted fractions was calculated from the following linear relationship [12, 13] as a function of molecular weight (MW):

$$r = 0.33 \times (MW)^{0.463}$$

Dextran and inulin were assayed in the eluted fractions using the anthrone method of Scott and Melvin [14], with slight modifications. Urine-to-plasma concentration ratios for inulin were calculated from inulin concentrations in eluted fractions. Albumin concentrations in plasma and urine samples were determined using a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, California, USA). Protein concentration in urine samples was determined by the Coomassie blue-g dye binding method [15]. Other laboratory tests were done with routine laboratory methods.

Theoretical analysis of glomerular ultrafiltration and solute transport

To detect changes in membrane permeability properties induced by the drug treatment we analyzed experimental observations of fractional clearance of test macromolecules using a mathematical model of glomerular size-selectivity described in detail previously [16, 17]. This model permits a differentiation between the effects of membrane permeability changes and glomerular hemodynamic alterations on glomerular filtration of neutral macromolecules. It considers the glomerular membrane as perforated by cylindrical pores having a lognormal distribution of radii given by the following equation:

$$g(r) = \frac{1}{\sqrt{2\pi}\, r\, \ln(s)} \exp\left[-\frac{1}{2}\left(\frac{\ln(r) - \ln(u)}{\ln(s)}\right)^2 \right]$$

This function is characterized by two parameters, u and s. According to this distribution the mean value of ln(r) is ln(u), and s is a measure of the spread of the distribution.

Beside these two pore-size distribution parameters the model is based on another freely adjustable parameter, the ultrafiltration coefficient (K_f), which is the product of the hydraulic membrane permeability and glomerular filtering surface area. Assuming that the glomerular population is uniform in function, K_f was calculated as extended to all glomeruli in both kidneys by using a model of glomerular ultrafiltration [16, 18]. The intrinsic membrane permeability parameters were calculated by non-linear regression fitting of experimental data obtained in single patients during the three clearance studies [17].

Statistical analysis

All results are expressed as mean ± standard deviation (SD). All data were subjected to one-way analysis of variance and statistical significance of differences between measurements in the three studies was assessed using the Tukey-Cicchetti test for multiple comparisons. Urinary protein excretion rates and albumin fractional clearances were log-transformed before statistical analysis. Statistical significance was defined as $P < 0.05$.

Results

Blood pressure

Mean systolic and diastolic BP recorded during the clearance studies are reported in Table 1. Systolic and diastolic BP were both slightly but significantly lower at the end of enalapril treatment than during basal evaluation; after enalapril withdrawal both systolic and diastolic BP returned to pre-CEI values.

Table 1. Clinical findings

	Basal	Enalapril	Enalapril withdrawal
Systolic BP *mm Hg*	143 ± 12	132 ± 13[a]	140 ± 9
Diastolic BP *mm Hg*	87 ± 8	77 ± 10[b]	85 ± 6[c]
Serum creatinine *mg/dl*	1.4 ± 0.3	1.5 ± 0.4	1.5 ± 0.3
Serum proteins *g/dl*	5.3 ± 0.4	5.4 ± 0.3	5.4 ± 0.4

Values are mean ± SD. Abbreviation is: BP, blood pressure.
[a] $P < 0.05$
[b] $P < 0.01$ vs. Basal
[c] $P < 0.01$ vs. Enalapril

Renal function

No significant difference was observed in mean serum creatinine levels and in total serum proteins during the three clearance studies (Table 1). The results of the renal hemodynamic studies are represented in Figure 1. Basal GFR averaged 38.3 ± 11.9 ml/min/1.73 m^2; by the end of enalapril treatment in all patients but one, GFR showed a tendency to decline, averaging 30.2 ± 12.6 ml/min/1.73 m^2 ($P < 0.01$). When enalapril treatment was withdrawn GFR rose again in all patients, returning toward basal values averaging 37.8 ± 11.2 ml/min/1.73 m^2 ($P < 0.01$ vs. enalapril). Enalapril had no effect on RPF, averaging 501 ± 129, 500 ± 154 and 487 ± 167 ml/min/1.73 m^2, respectively before, after CEI treatment, and one month after CEI withdrawal. Thus the reduction in GFR observed after enalapril treatment, with constant RPF, resulted in a slight but significant reduction in filtration fraction (Fig. 1).

Values of 24-hour urinary protein excretion, measured before each clearance study, and albumin fractional clearance are reported in Figure 2. Both parameters decreased significantly ($P < 0.01$) with enalapril treatment, as compared to pre-CEI values, and returned to basal values after withdrawal of the drug. Sieving coefficients of neutral dextran molecules of graded sizes (from 26 to 62 Å) measured in basal conditions and at the end of enalapril treatment are reported in Table 2 and in Figure 3. Fractional clearance of small dextran molecules (< 42 Å) was not significantly affected by the drug treatment. Sieving coefficients of larger dextran molecules (radii from 44 to 50 Å, and from 54 to 62 Å) were significantly lower after CEI treatment (Fig. 3). Figure 4 compares fractional dextran clearance values at the end of enalapril therapy with values one month after enalapril withdrawal. Withdrawal of the CEI was associated with significant elevation of sieving coefficients for dextrans larger than 54 Å returning almost to pre-treatment values (Fig. 4, Table 2).

Theoretical analysis of glomerular dextran transport

Dextran sieving coefficients and renal hemodynamic parameters were used for the theoretical analysis of glomerular size-selective function. This theoretical approach requires the assumption of the value of Dp, the hydraulic pressure gradient across the glomerular membrane, that can not be measured in humans. To overcome this limitation, and in accordance with previous studies [5, 12], several values of Dp below and above

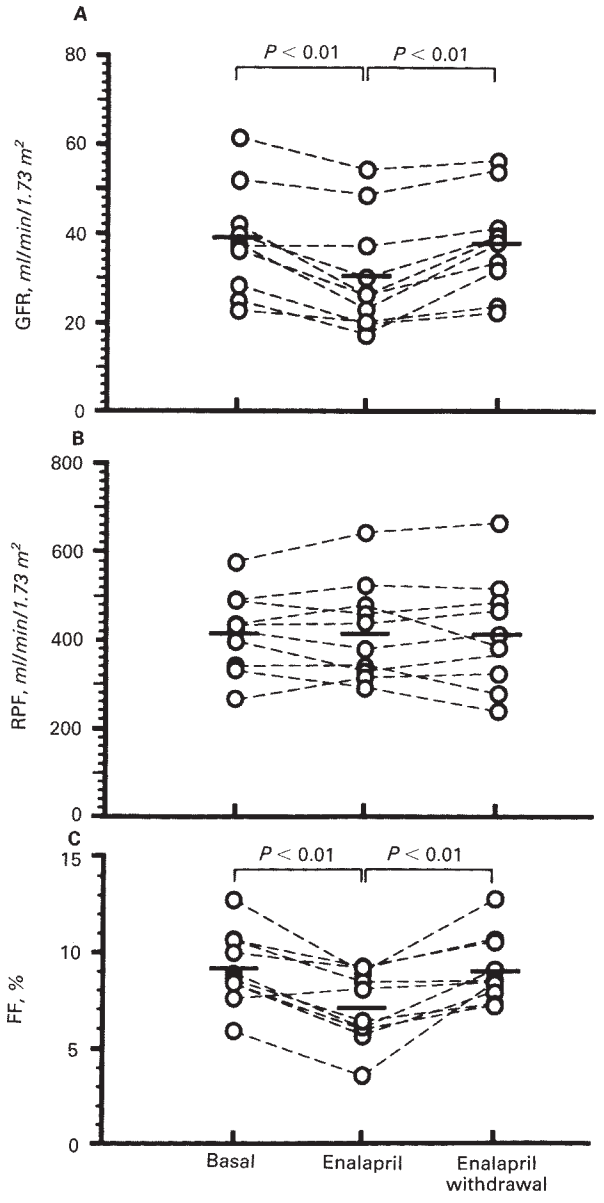

Fig. 1. *Renal functional parameters measured before (basal), after enalapril treatment (enalapril), and one month after enalapril withdrawal (enalapril withdrawal).* Abbreviations are: GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction.

35 mm Hg have been assumed, that is, the values believed to represent normal Dp in humans. In particular, since experimental studies indicate that Dp may be increased in some glomerular disease models and that enalapril decreases Dp in this conditions [1, 2, 19], values of Dp were assumed ranging from 30 to 45 mm Hg, to take into account these possibilities.

The results of the theoretical analysis are reported in Table 3. Estimation of the ultrafiltration coefficient (K_f) showed that when Dp was assumed to be lowered by enalapril (by about 5 mm Hg), K_f remained comparable for the three sequential studies. On the other hand, when Dp was assumed to be unaffected by the drug treatment calculated, K_f was significantly lower after enalapril treatment as compared to basal and

Table 2. Fractional clearance of neutral dextrans

Molecular radius (A)	26	28	30	32	34	36	38	40	42	44
Basal	0.773 ±0.086	0.673 ±0.076	0.544 ±0.091	0.435 ±0.084	0.333 ±0.080	0.245 ±0.058	0.181 ±0.046	0.13 ±0.036	0.09 ±0.028	0.066 ±0.023
Enalapril	0.808 ±0.151	0.656 ±0.130	0.522 ±0.113	0.391 ±0.075	0.287 ±0.050	0.207 ±0.040	0.148 ±0.032	0.104 ±0.022	0.071 ±0.016	0.048 ±0.012
P vs. Basal	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.05
Enalapril withdrawal	0.844 ±0.130	0.701 ±0.130	0.571 ±0.131	0.438 ±0.114	0.331 ±0.104	0.244 ±0.080	0.176 ±0.055	0.124 ±0.040	0.085 ±0.027	0.059 ±0.016
P vs. Enalapril	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Values are mean ± SD. Abbreviation NS is not significant.

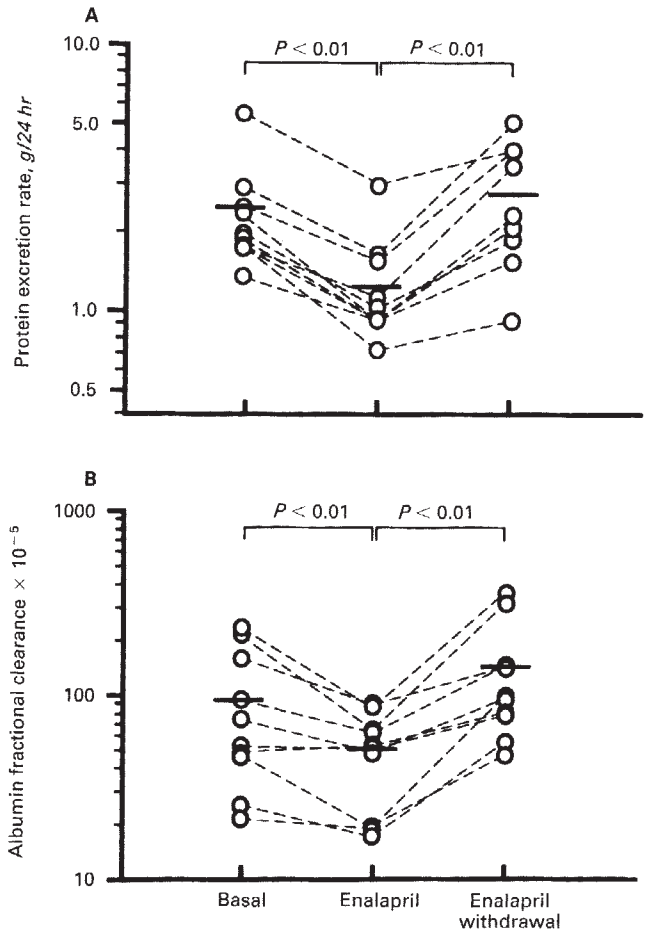

Fig. 2. *Urinary protein excretion and fractional clearance of albumin and IgG measured before (basal), after enalapril treatment (enalapril) and one month after enalapril withdrawal (enalapril withdrawal).*

enalapril withdrawal values. As mentioned previously, technical limitations make it impossible to further investigate which of these two parameters is reduced by the CEI and is indeed responsible for the reduced GFR.

Considering the calculated membrane pore parameters previously defined, it appeared that both parameters u and s, respectively a measure of the mean and the spread of the pore radii distribution, were not sensitive to changes of assumed Dp values. That membrane pore parameters are not importantly affected by the value of Dp is in line with previous observations [16]. Statistical comparison of the average values of u and s, calculated for the three clearance studies, indicated that both parameters were not significantly affected by the drug treatment. This is consistent with the experimental finding that filtration of small dextrans (radii ranging from 26 to 42 Å) were not affected by the CEI therapy, since these molecules can pass the glomerular membrane through pores whose radii are similar to the average membrane pore size. The experimental observation that largest dextran molecules (radii ranging from 56 to 62 Å) were significantly affected by the drug treatment suggests that enalapril may induce changes in the dimension of few large membrane pores. We therefore calculated the membrane pore parameter r*(1%), as described in detail previously [17], that is, the pore radius at which 1% of the filtrate volume is filtered by pores with radii greater than r*(1%). As reported in Table 3, r*(1%), independently of the Dp value adopted for the calculation, was significantly and uniformly reduced by enalapril treatment of about 4 Å. After enalapril withdrawal r*(1%) rose again significantly, reaching values comparable to the basal evaluation. Thus CEI therapy seems mainly to have modified the radius of the largest membrane pores leaving the selective small pores unaffected. This effect is independent of changes in GFR determinants (Dp and/or K_f) but is intrinsic to the membrane's permeability properties to macromolecules.

Discussion

In patients with IgA nephropathy participating in the present study, enalapril slightly but significantly reduced systolic and diastolic BP compared to pre-enalapril values or to values recorded in the same patients one month after enalapril withdrawal. Renal function changes associated with enalapril therapy involved a statistically significant reduction in GFR (21% on average) without significant changes in RPF.

Little data is available so far on the possibility that enalapril selectively induces glomerular hypofiltration in humans. Previous studies in animals and humans did not show significant GFR reduction associated with CEI treatment [1, 2, 5]. The fact that in the present study enalapril therapy was associated with a reduction in GFR but not in RPF suggests that the renal hypofiltration was a consequence of changes in other determinants of GFR. Beside RPF, GFR is regulated by the colloid osmotic pressure in glomerular capillaries due to circulating plasma proteins, by the transmembrane hydraulic pressure difference (Dp) and by the ultrafiltration coefficient (K_f). Since no significant differences were recorded in protein concentrations in arterial plasma during the study, the fall in GFR must depend upon changes in either Dp or K_f, or both. Direct

Table 2. *Continued*

46	48	50	52	54	56	58	60	62
0.045	0.032	0.022	0.015	0.012	0.010	0.008	0.006	0.004
±0.014	±0.009	±0.005	±0.004	±0.003	±0.004	±0.003	±0.003	±0.003
0.032	0.022	0.016	0.011	0.008	0.006	0.004	0.003	0.002
±0.009	±0.006	±0.006	±0.004	±0.004	±0.003	±0.002	±0.001	±0.001
0.01	0.01	0.05	NS	0.05	0.05	0.01	0.01	NS
0.04	0.027	0.019	0.015	0.012	0.010	0.007	0.006	0.006
±0.010	±0.007	±0.005	±0.004	±0.003	±0.003	±0.002	±0.002	±0.003
NS	0.05	NS	NS	0.05	0.05	0.01	0.01	0.01

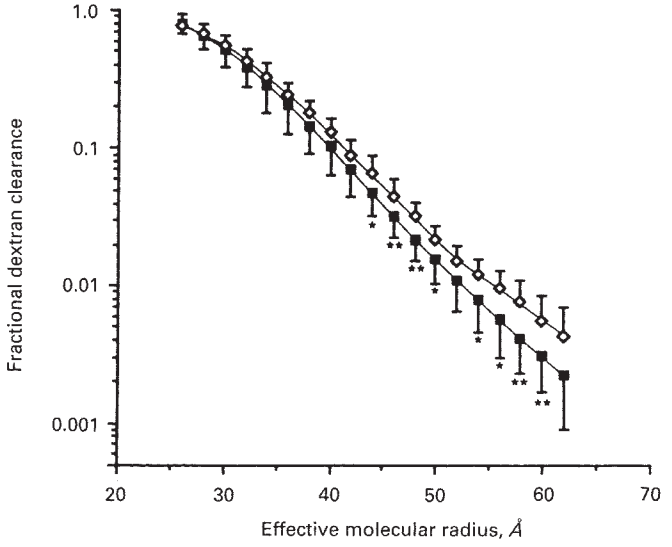

Fig. 3. *Fractional clearance of neutral dextran molecules of graded molecular size, measured before (□) and after enalapril treatment (■).* * $P < 0.05$, ** $P < 0.01$ as compared to Basal.

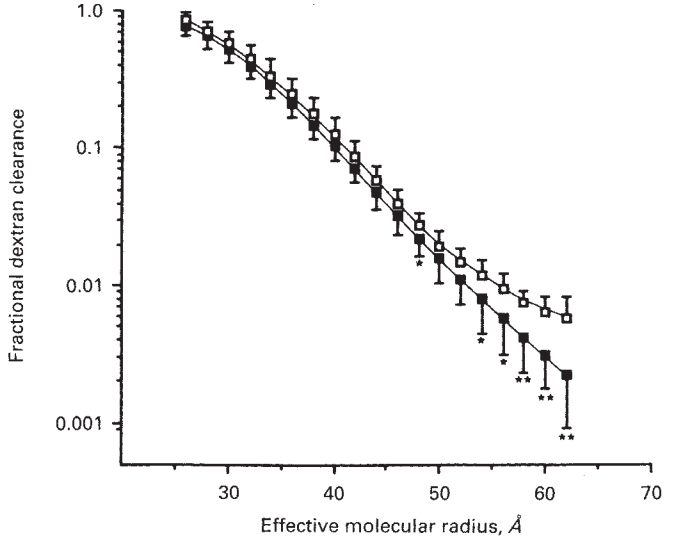

Fig. 4. *Fractional clearance of neutral dextran molecules of graded molecular size, measured after enalapril treatment (■) and one month after enalapril withdrawal (□).* * $P < 0.05$, ** $P < 0.01$ as compared to enalapril withdrawal.

measurement of Dp and consequent calculation of K_f is not possible in humans, so all information available so far are necessarily derived from experimental work.

That Dp may be reduced by CEI has been extensively documented experimentally [2, 5, 19]. In such studies CEI therapy always reduced Dp while it tended to increase K_f. On the basis of these experimental evidences the reduction in GFR observed in our patients is likely a consequence of an effect of enalapril of reducing Dp rather than K_f.

That enalapril could have lowered GFR by reducing glomerular capillary pressure is also suggested by the observed reduction in mean systolic and diastolic BP of about 10 mm Hg. This decrease in BP could account for a reduction of 5 mm Hg for hydraulic pressure in glomerular capillaries induced by the CEI. Moreover, according to the theoretical analysis, and considering an hypothetical reduction in Dp associated with enalapril therapy equal to 5 mm Hg (approximately 50% of the observed reduction in mean arterial pressure), mean calculated K_f did not change significantly during the three studies (Table 3). This would reinforce the concept that the fall in GFR induced by enalapril in IgA nephropathy could result from a selective reduction in glomerular capillary pressure.

This would be consistent with previous findings [20] that in patients with unilateral renal artery stenosis CEI reduced the tone of postglomerular arterioles, leading to a reduction in Dp. On the same line, enalapril treatment in patients with renovascular hypertension [21] has been reported to be associated with loss of intrinsic glomerular vasoregulatory capacity with relatively greater preservation of renal blood flow, while GFR fell markedly both acutely and in the long term.

A second finding of the present study is that CEI therapy was associated with a significant reduction in 24-hour urinary protein excretion, compared to the basal values, and that urinary protein excretion rose back toward the baseline after enalapril withdrawal. Consistent with the reduction in total urinary protein excretion were data on albumin fractional clearance, which was significantly reduced by enalapril and returned to basal values after drug withdrawal.

To investigate whether this reduction in protein excretion was related to an improvement of glomerular barrier function induced by the drug, and not a consequence of changes in tubular handling of filtered proteins, we measured the fractional clearance of neutral dextrans of graded sizes. Enalapril did not affect the sieving coefficient of small, relatively permeant dextran molecules (< 42 Å), but significantly reduced that of large dextran macromolecules with radii from 56 to 62 Å. This

Table 3. Computed membrane parameters

	Dp *mm Hg*	Basal	Enalapril	Enalapril withdrawal
K_f	30		2.65 ± 1.39	
ml/min/mm Hg/1.73m²	35	2.33 ± 0.97	1.84 ± 0.90[a]	2.41 ± 1.04
	40	1.78 ± 0.69	1.41 ± 0.66	1.82 ± 0.71
	45	1.44 ± 0.53		1.46 ± 0.5
u (Å)	30		46.7 ± 2.9	
	35	48.6 ± 3.7	47.1 ± 2.8	46.7 ± 3.5
	40	48.8 ± 3.6	47.3 ± 2.7	46.9 ± 3.4
	45	48.8 ± 3.4		47.0 ± 3.2
s	30		1.17 ± 0.03	
	35	1.17 ± 0.04	1.17 ± 0.03	1.19 ± 0.03
	40	1.17 ± 0.04	1.17 ± 0.03	1.19 ± 0.02
	45	1.17 ± 0.03		1.19 ± 0.02
r*(1%) (Å)	30		74.6 ± 3.3[b]	
	35	78.2 ± 4.3	74.4 ± 3.2[b]	78.8 ± 1.8
	40	78.1 ± 4.3	74.4 ± 3.2[b]	78.7 ± 1.7
	45	78.1 ± 4.3		78.6 ± 1.6

Values are mean ± SD. Abbreviations are: Dp, transmembrane pressure difference; K_f, ultrafiltration coefficient; u and s, a measure of the mean and spread of pore radii distribution, respectively; r*, calculated membrane pore parameter.

[a] $P < 0.01$ vs. Basal and vs. Enalapril withdrawal, for the same Dp value

[b] $P < 0.05$ vs. Basal and $P < 0.01$ vs. Enalapril withdrawal, for all Dp values

amelioration of the size-selective function can be responsible for the reduction in glomerular filtration of circulating proteins and in final urinary excretion.

Transglomerular passage of circulating macromolecules depends on the intrinsic properties of the glomerular membrane and on convective and diffusive forces resulting from glomerular hemodynamics [22]. To further investigate whether the reduced fractional clearance of large dextran molecules was induced by a real improvement in glomerular membrane selective properties or by changes in glomerular hemodynamics, we adopted a theoretical model of glomerular size-selective function that separates the effects of hemodynamic changes and changes in intrinsic membrane permeability, on the filtration of test macromolecules [16, 17]. This model represents the glomerular membrane as perforated by cylindrical pores having a lognormal probability distribution of their radii. Enalapril treatment had little effect on the mean (u) and the distribution (s) of membrane pore radii, but significantly reduced the size of the largest pores (Table 3). The radius of these non-restrictive pores, which are responsible for the passage of circulating macromolecules into the urinary space, was significantly reduced, as indicated by the calculated parameter r*(1%) (Table 3). Of note is the fact that the calculated change in membrane pore radius associated with the CEI is unrelated to the assumed value of Dp; thus, on a theoretical basis, the reduced filtration of circulating test macromolecules could not result from an hypothetical reduction in glomerular capillary pressure, associated with CEI treatment, but must derive from changes in intrinsic membrane permselective properties.

The parallelism between changes in largest membrane pores dimensions and mean fractional albumin clearance would suggest that the two phenomena are related. Albumin is a protein with a gel chromatographic radius of 36 Å but, for its molecular configuration and charge, albumin filtration seems to take place only through largest membrane pores [23]. The fact that after enalapril therapy fractional clearance of largest dextran molecules (that is, 60 Å, Table 2) and albumin (Fig. 2) were both reduced to approximately 50% of basal values, and that a comparable percentage increase was measured in these two parameters after enalapril withdrawal, would suggest that the observed size-selective changes can be sufficient to explain the magnitude of changes in albumin fractional clearance. This would suggest that CEI therapy has negligible influence on charge selective properties of the glomerular membrane.

That in patients with IgA nephropathy enalapril directly influences glomerular membrane functional properties is in keeping with our previous experimental observation in MWF/Ztm rats, a strain that spontaneously develops proteinuria and glomerular structural damage [6]. Long-term enalapril therapy protected these animals against the development of proteinuria and an improvement was seen in glomerular size-selective properties. The present results thus further demonstrate in humans that the beneficial effect of enalapril on urinary protein loss derives from a restoration of glomerular size-selectivity. That enalapril has this particular action of restoring size-selective properties of the glomerular barrier was recently suggested by Morelli et al [5], who showed that in patients with insulin-dependent diabetes mellitus enalapril therapy lowered the transglomerular passage of neutral dextrans of graded sizes.

Beside the fact that enalapril improves glomerular size-selectivity both in IgA nephropathy and in diabetic nephropathy, it is of interest that this effect differs qualitatively in the two conditions. In IgA nephropathy only the size of largest non-selective pores is reduced, whereas in diabetes both small and large pores became smaller. Thus enalapril may have different effects on glomerular barrier size-selectivity in different diseases.

The mechanism(s) by which enalapril reduced the mean size of the largest non-selective membrane pores in IgA nephropathy must at the moment remain speculative. Since angiotensin II increases the transglomerular passage of large neutral dextrans, as documented by studies in which it was infused to rats and humans [12, 24], it can be postulated that in IgA nephropathy enalapril may improve glomerular barrier size-selectivity by preventing angiotensin II formation [25].

Regardless of its mechanisms, the beneficial effect of enalapril on glomerular barrier size-selectivity observed in this study may open important perspective for preventing the progression of IgA nephropathy to end-stage renal failure. The increased traffic of plasma proteins across the glomerular capillary wall may be one factor responsible for the long-term deterioration of glomerular structure that eventually leads to glomerulosclerosis [26]. Consistent with this are experimental findings that in various models of renal disease progression, enalapril not only lowers urinary protein excretion but also preserves the structure of the glomerulus and prevent the development of glomerulosclerosis [1, 2, 6, 19]. Whether in humans with IgA nephropathy the long-term treatment with enalapril to reduce proteinuria will also protect glomerular structural damage and retard the progressive nature of the disease is a possibility that merits an appropriate controlled trial.

Our data also suggest that CEI may lower GFR in these patients. Whether this also apply to other categories of renal

disease or to patients treated with CEI for cardiac failure or hypertension merits further investigation.

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References

1. ANDERSON S, RENNKE HG, BRENNER BM: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77:1993–2000, 1986
2. ZATZ R, DUNN BR, MEYER TW, ANDERSON S, RENNKE HG, BRENNER BM: Prevention of diabetic glomerulopathy by pharmacologic amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
3. HOMMEL E, PARVING HH, MATHIESEN E, EDSBERG B, DAMKJAER M, GIESE J: Effect of captopril on kidney function in insulin-dependent diabetic patients with nephropathy. *Br Med J* 293:467–470, 1986
4. PARVING HH, HOMMEL E, SMIDT UM: Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *Br Med J* 297:1086–1091, 1988
5. MORELLI E, LOON N, MEYER TW, PETERS W, MYERS BD: Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes* 39:76–82, 1990
6. REMUZZI A, PUNTORIERI S, BATTAGLIA C, BERTANI T, REMUZZI G: Angiothensin converting enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. *J Clin Invest* 85:541–549, 1990
7. LEVY M, GONZALES-BURCHARD G, BROYER M, DOMMERGUE JP, FOULARD M, SOREZ JP, HABIB R: Berger's disease in children. Natural history and outcome. *Medicine* 64:157–180, 1985
8. REMUZZI A, SCHIEPPATI A, BATTAGLIA C, REMUZZI G: Angiotensin-converting enzyme inhibition ameliorates the defect in glomerular size selectivity in hyponatremic hypertensive syndrome. *Am J Kid Dis* 14:170–177, 1989
9. MYERS BD, PETERSON C, MOLINA CR, TOMLANOVICH SJ, NEWTON LD, NITKIN R, SANDLER H, MURAD F: Role of cardiac atria in the human renal response to changing plasma volume. *Am J Physiol* 254:F562–F573, 1988
10. HIGHASHI A, PETERS L: A rapid colorimetric method for the determination of inulin in plasma and urine. *J Lab Clin Med* 35:475–480, 1950
11. SMITH HW, FINKELSTERIN N, ALIMINOSA L, CRAWFORD B: The renal clearance of substituted hippuric acid derivatives and other aromatic acid in dog and man. *J Clin Invest* 24:388–104, 1945
12. LOON N, SHEMESH O, MORELLI E, MYERS BD: Effect of angiotensin II infusion on the human glomerular filtration barrier. *Am J Physiol* 257:F608–F614, 1989
13. GRANATH KA, KVIST BE: Molecular weight distribution analysis by gel chromatography on sephadex. *J Chromatogr* 28:69–91, 1967
14. SCOTT TA, MELVIN EH: Determination of dextran with anthrone. *Anal Chem* 25:1656–1661, 1953
15. READ SM, NORTHCOTE DH: Minimization of variations in the response to different proteins of the Coomassie blue G dye-binding assay for protein. *Anal Biochem* 116:53–64, 1981
16. DEEN WM, BRIDGES CR, BRENNER BM, MYERS BD: Heteroporous model of glomerular size selectivity: Application to normal and nephrotic humans. *Am J Physiol* 249:F374–F389, 1985
17. REMUZZI A, BATTAGLIA C, ROSSI L, ZOJA C, REMUZZI G: Glomerular size selectivity in nephrotic rats exposed to diets with different protein content. *Am J Physiol* 253:F318–F327, 1987
18. DEEN WM, ROBERTSON CR, BRENNER BM: A model of glomerular ultrafiltration in the rat. *Am J Physiol* 223:1178–1183, 1972
19. YOSHIDA Y, KAWAMURA T, IKOMA M, FOGO A, ICHIKAWA I: Effects of antihypertensive drugs on glomerular morphology. *Kidney Int* 36:626–635, 1989
20. WENTING GJ, TAN-TJIONG HL, DERKX FHM, DE BRUYN JHB, MAN IN'T VELD AJ, SCHALEKAMP MADH: Split renal function after captopril in unilateral renal artery stenosis. *Br Med J* 288:886–890, 1984
21. BENDER W, LA FRANCE N, WALKER WG: Mechanism of deterioration of in renal function in patients with renovascular hypertension treated with enalapril. *Hypertension* 6(Suppl I):I-193–I-197, 1984
22. CHANG RLS, UEKI IF, TROY JL, DEEN WM, ROBERTSON CR, BRENNER BM: Permselectivity of the glomerular capillary wall to macromolecules. I. Theoretical considerations. *Biophys J* 15:887–895, 1975
23. GOLBETZ H, BLACK V, SHEMESH O, MYERS BD: Mechanism of the antiproteinuric effect of indomethacin in nephrotic humans. *Am J Physiol* 256:F44–F51, 1989
24. BOHRER MP, DEEN WM, ROBERTSON CR, BRENNER BM: Mechanism of angiotensin II-induced proteinuria in the rat. *Am J Physiol* 233:F13–F21, 1977
25. YOSHIOKA T, MITRARAI T, KON V, DEEN WM, RENNKE HG, ICHIKAWA I: Role for angiotensin II in overt functional proteinuria. *Kidney Int* 30:538–545, 1986
26. REMUZZI G, BERTANI T: Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? *Kidney Int* 38:384–394, 1990