Blood pressure reduction initiates the antiproteinuric effect of ACE inhibition

MARC H. HEMMELDER, DICK DE ZEEUW, RON T. GANSEVOORT, and PAUL E. DE JONG

Groningen Institute for Drug Studies (GIDS),[1] Department of Medicine, Division of Nephrology, University Hospital, Groningen, the Netherlands

Blood pressure reduction initiates the antiproteinuric effect of ACE inhibition. Several observations question the role of blood pressure and renal hemodynamic changes in the long-term antiproteinuric effect of ACE inhibition. To differentiate blood pressure and renal effects in the initial antiproteinuric response, the placebo-controlled acute effects of the ACE inhibitor enalaprilat (10 mg i.v.) on blood pressure, renal hemodynamics, and proteinuria were compared with those of nitroprusside in nine patients with non-diabetic proteinuria. In addition, we studied whether an exogenous angiotensin II infusion reverse the initial enalaprilat-induced antiproteinuric response. Enalaprilat and nitroprusside reduced MAP by $-11.3 \pm 2.4\%$ and $-14.1 \pm 2.3\%$, respectively, whereas only enalaprilat showed renal hemodynamic effects, reflected by an increase in ERPF of $18.4 \pm 5.4\%$ and a decrease in FF of $-17.1 \pm 2.6\%$. Despite the contrasting renal hemodynamic profiles, enalaprilat ($-10.6 \pm 4.8\%$) and nitroprusside ($-12.8 \pm 5.1\%$) equally decreased proteinuria. Exogenous infusion of angiotensin II completely reversed the blood pressure reduction and renal efferent vasodilatation induced by enalaprilat. Proteinuria also increased by $13.1 \pm 7.8\%$ to placebo level, albeit statistically non-significant. We conclude that the initial antiproteinuric effect of ACE inhibition appears to be mediated by blood pressure reduction and does not require its specific renal hemodynamic effect. Further studies should clarify whether the renal efferent vasodilatation during ACE inhibition is required to gradually induce renal structural changes that prevent the abundant passage of proteins.

Although the capacity of ACE inhibitors to lower blood pressure is comparable to that of other antihypertensives, long-term treatment with ACE inhibition results in a 40 to 50% lowering of proteinuria, whereas other antihypertensive agents have a slight or no effect on proteinuria [1–4]. Many studies have tried to clarify the mechanism involved in this additional reduction of proteinuria by ACE inhibitors. At first, the renal efferent vasodilatation characteristic of ACE inhibition was held responsible [5–9]. Several of the following observations question the role of renal hemodynamic changes in the long-term antiproteinuric effect of ACE inhibition. First, the antiproteinuric effect has a slow onset reaching a maximum approximately four weeks after start of treatment, whereas the blood pressure and renal hemodynamic effect appear maximal already after several hours of ACE-inhibition [10]. Second, the blood pressure and renal hemo-

dynamic changes after three months of ACE inhibition can be completely reversed by acute exogenous angiotensin II, whereas the antiproteinuric response is unaffected [11]. These data suggest that both blood pressure and renal hemodynamic factors play a minor role in the antiproteinuric effect at least during long-term ACE inhibition.

The acute lowering of proteinuria by ACE inhibitors, however, may well be explained by their concomitant blood pressure or renal hemodynamic changes. Several reports in non-diabetic [10, 12] and diabetic renal disease [13, 14] showed the 15 to 20% reduction of proteinuria after a single dose of an ACE inhibitor to be related to changes in blood pressure and/or renal hemodynamics. The magnitude of the acute antiproteinuric response to ACE inhibition is well comparable to that of the long-term reduction of proteinuria by other antihypertensives. It may therefore be hypothesized that blood pressure reduction, rather than renal hemodynamic changes, mediates the acute small reduction of proteinuria by ACE inhibitors, whereas the long-term more marked reduction is governed by non-hemodynamic factors. To date, no study has been performed evaluating the causal role of blood pressure reduction and/or that of renal hemodynamic effects in the acute antiproteinuric response of ACE inhibition. Since it has been demonstrated in rat models that exogenous angiotensin II infusion or increased levels of endogenous angiotensin II are able to increase urinary protein loss in parallel with increases in blood pressure and renal efferent vasoconstriction [15–19], it may be hypothesized that the acute, hemodynamically mediated antiproteinuric response of ACE inhibition can well be reversed by angiotensin II.

In the present study, we therefore compared the acute effects of the ACE inhibitor enalapril on proteinuria, blood pressure, and renal hemodynamics to those of nitroprusside. To study the importance of the renin-angiotensin system (RAS) in the acute response to ACE inhibition, we furthermore tested whether the acute antiproteinuric effect of enalapril could be reversed by an infusion of exogenous angiotensin II.

Methods

Patients and protocol

Nine non-diabetic patients with chronic renal disease were enrolled in this study. Entry criteria were stable proteinuria exceeding 3.0 g/day, a stable creatinine clearance of $50 \ ml \cdot min^{-1}$ or more, and a diastolic blood pressure of less than 110 mm Hg. Patients with diabetes mellitus, edema, or renovascular hypertension were excluded. Before entry all antihypertensive drugs were
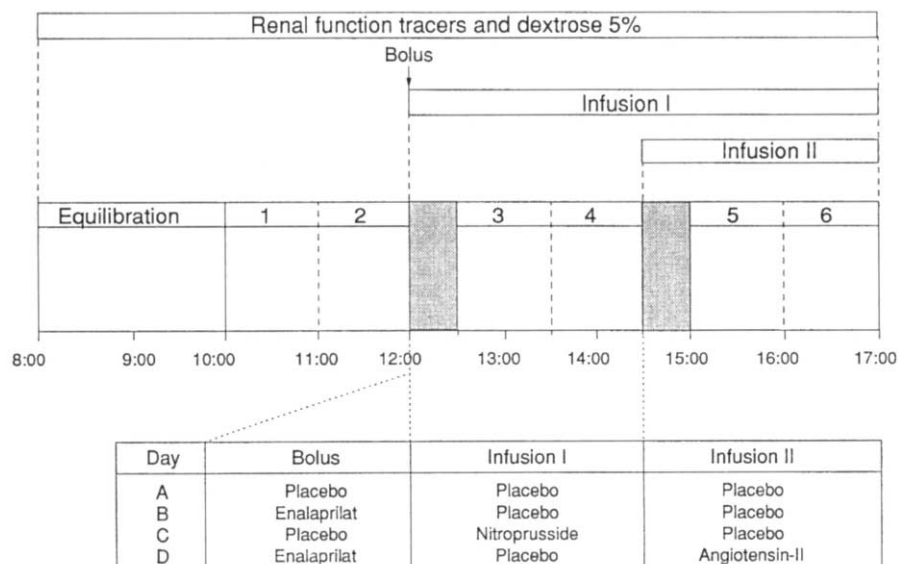

Fig. 1. *Study protocol.*

withdrawn for at least four weeks, except for one patient who needed diuretic treatment to avoid edema. The responses in this patient were not different from the other patients. All patients adhered to a 100 mmol sodium restricted diet. The study was approved by the local Medical Ethical Committee and all subjects gave their informed consent to participate in this study.

Patients underwent four in-hospital renal function assessments once weekly during four weeks. One 24-hour urine collection was performed the day before each visit. During the study day patients remained in supine position, except when voiding. A bolus injection of renal function tracers was administered at 8:00 hours followed by a constant infusion of these tracers in the right antecubital vein. At 8:30 hours the patients received their regular breakfast, whereafter 150 ml/hr of beverages were permitted, except for coffee. After a two-hour equilibration period to 10:00 hours, in which a constant plasma level of renal function tracers was obtained, two one-hour baseline clearance measurements were performed from 10:00 to 12:00 hours. At day A patients received an intravenous bolus of placebo (dextrose 5%) at 12:00 hours, followed by a continuous placebo infusion from 12:00 to 17:00 hours. At day B enalaprilat (10 mg i.v.) was given at 12:00 hours, followed by a continuous placebo infusion from 12:00 to 17:00 hours. At day C a continuous intravenous infusion of nitroprusside was administered from 12:00 to 17:00 hours, titrated between 12:00 and 12:30 hours to obtain a hypotensive effect comparable to that of enalaprilat in each patient. At day D patients again received enalaprilat (10 mg i.v.) at 12:00 hours, followed by a continuous placebo infusion from 12:00 to 17:00 hours, and a concomitant continuous exogenous angiotensin II infusion from 14:30 to 17:00 hours. The dose of exogenous angiotensin II was titrated between 14:30 and 15:00 hours to increase blood pressure to placebo level in each patient. Study days A and B as well as C and D were performed in a random cross-over and single-blinded order. A 30-minute placebo titration was performed when appropriate between 12:00 and 12:30, as well as between 14:30 and 15:00 hours, to assure a uniform study day design (Fig. 1). The total amount of infused fluids was 150 ml/hr. Blood pressure was measured every five minutes during the

clearance periods and every two minutes during the two 30 minutes titration intervals. Blood and urine samples were obtained for determination of renal hemodynamic parameters and proteinuria during each clearance period. At 12:00, 14:30, and 17:00 hours blood was drawn for determination of plasma renin activity (PRA), ACE, and angiotensin II.

After completion of the study protocol, all but one patient were admitted to prolonged treatment with the ACE inhibitor enalapril 10 mg o.i.d. Blood pressure, creatinine clearance and proteinuria were measured after 1, 7 and 28 days of treatment.

Clinical and laboratory procedures

Serum and urine electrolytes, urea and creatinine were determined with an automated multi-analyzer (SMA-C, Technicon®), while urinary protein concentration was determined with the pyrogallol red-molybdate method [20]. The intra-assay coefficient of variation of this method is less than 3.3%, while the inter-assay coefficient of variation is less than 3.0%. Blood pressure was recorded with an automated device (Dinamap®). Mean arterial pressure was calculated as the sum of one-third of the systolic and two-thirds of the diastolic blood pressure. The mean blood pressure during each one-hour clearance period was used for data analysis. GFR and ERPF were measured by a constant infusion of ^{125}I-iothalamate and ^{131}I-hippuran, respectively [21]. The intra-patient day-to-day coefficient of variation of this method is 2.2% for GFR and 5.0% for ERPF. Filtration fraction was calculated as the ratio of GFR and ERPF. Renal vascular resistance (RVR) was defined as MAP divided by ERPF. Serum ACE was measured using an HPLC-assisted assay [22]. PRA was assessed by the quantification of generated angiotensin I as measured by radio-immunoassay (Rianen® angiotensin I RIA kit). Blood for the determination of angiotensin II was collected in prechilled glass tubes containing 1,10-phenanthroline, EDTA, enalaprilat and neo-mycin to prevent *in vitro* generation of angiotensin II. Blood was immediately centrifuged at 4°C and plasma samples were stored at −20°C until analysis. Angiotensin II was determined using the Nichols Institute Diagnostics Angiotensin II radioimmunoassay

Table 1. Patient characteristics at entry

Patient	Gender	Age *years*	Renal diagnosis	Blood pressure *mm Hg*	Creatinine clearance *ml · min^{-1}*	Proteinuria *g/day*
1	M	30	FSGS	143/96	108	18.6
2	M	43	IgA	160/95	80	3.0
3	F	40	FSGS	116/74	71	5.6
4	M	62	FSGS	118/78	110	7.0
5	M	32	FSGS	145/91	47	5.5
6	M	32	IgA	122/77	93	4.0
7	M	44	MGP	132/81	165	12.1
8	M	59	MGP	139/87	104	7.8
9	M	39	MGP	119/70	82	3.4
Mean		42		133/83	96	7.4
SE		4		5/3	11	1.7

Abbreviations are: F, female; M, male; FSGS, focal segmental glomerulosclerosis; IgA, IgA nephropathy; MGP, membranous glomerulopathy.

with an inter-assay variation of 5.1% and an intra-assay variation of 4%. The lower detection range is 3.6 pg · ml^{-1}.

Data analysis

Data are expressed as mean ± standard error (SE), unless otherwise indicated. The effects of placebo, enalaprilat, nitroprusside, and angiotensin II during enalaprilat were tested as the percentage change from the mean of the two one-hour baseline values. To exclude the influence of circadian variation of the various parameters, the response to enalaprilat, nitroprusside, and angiotensin II during enalaprilat were also tested against the time corresponding placebo response. Statistical analysis was performed using a paired, non-parametric ANOVA (Friedmann) for repeated measurements or a paired Wilxocon's signed rank test. Correlations were calculated by Spearman's linear regression analysis. Statistical significance was assumed at a 5% level.

Results

Patient characteristics at entry are given in Table 1. None of the patients had signs of peripheral edema. None of the study parameters showed significant differences during the baseline clearance periods on each of the study days as shown in Table 2. Proteinuria, daily urinary excretion of sodium and urea, and body weight remained stable during the entire study period. Figure 2 shows the percentage change from baseline for each of the study parameters after infusion of placebo, enalaprilat, nitroprusside as well as angiotensin II during enalaprilat. The influence of the interventions on parameters of the renin-angiotensin system are given in Table 3.

Placebo

During placebo infusion no significant changes in ACE, PRA, and angiotensin II were observed. MAP increased from 103 ± 2 to 109 ± 4 mm Hg ($P < 0.01$). Although GFR and ERPF did not change, filtration fraction increased from 20.7 ± 1.2% to 21.9 ± 1.8% ($P < 0.01$), and RVR increased from 27.3 ± 3.7 to 30.2 ± 5.5 10^{-2} mm Hg · ml · min^{-1} ($P < 0.01$). Urinary protein excretion fell from 0.25 ± 0.03 to 0.23 ± 0.05 g · hr^{-1} ($P < 0.05$). Fractional sodium excretion did not change significantly.

Table 2. Baseline characteristics at each of the study days

	Baseline PLA	Baseline ENA	Baseline NIP	Baseline ENA + Ang II
Urinary sodium excretion *mmol/day*	103 ± 15	104 ± 16	106 ± 18	112 ± 20
Urinary urea excretion *mmol/day*	301 ± 36	303 ± 58	322 ± 33	325 ± 46
Proteinuria *g/day*	7.8 ± 1.4	7.0 ± 1.2	7.6 ± 1.1	7.2 ± 1.6
Body weight *kg*	79.6 ± 3.3	79.3 ± 3.1	79.4 ± 3.3	79.4 ± 3.3
MAP *mm Hg*	103 ± 2	103 ± 3	102 ± 2	102 ± 3
GFR *ml · min^{-1}*	91.9 ± 7.0	92.3 ± 6.5	91.9 ± 7.3	95.8 ± 7.9
ERPF *ml · min^{-1}*	477 ± 50	477 ± 45	490 ± 51	486 ± 47
FF %	20.7 ± 1.2	20.5 ± 1.1	20.1 ± 1.1	20.8 ± 1.2
RVR *10^{-2} mm Hg · min · ml^{-1}*	27.3 ± 3.7	26.7 ± 3.8	26.7 ± 3.9	26.2 ± 3.6
Proteinuria *g · hr^{-1}*	0.25 ± 0.03	0.30 ± 0.04	0.26 ± 0.03	0.28 ± 0.04

The upper part contains parameters measured in the 24-hour urine collection. The bottom part contains parameters of the study day. Abbreviations are: PLA, placebo; ENA, enalaprilat; NIP, nitroprusside; Ang II, angiotensin II; MAP, mean arterial pressure; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fracton; RVR, renal vascular resistance.

Enalaprilat

Infusion of 10 mg enalaprilat induced a complete inhibition of ACE ($P < 0.05$), an increase in PRA ($P < 0.05$), and a decrease in angiotensin II ($P < 0.05$). MAP lowered from 103 ± 3 to 95 ± 3 mm Hg ($P < 0.01$). ERPF increased from 477 ± 45 to 532 ± 73 ml · min^{-1} ($P < 0.05$). Since GFR non-significantly fell from 92.3 ± 6.5 ml · min^{-1} to 89.9 ± 9.7 ml · min^{-1}, FF decreased from 20.5 ± 1.1% to 18.2 ± 1.7% ($P < 0.05$). RVR decreased from 26.7 ± 3.8 to 21.7 ± 4.4 10^{-2} mm Hg · ml · min^{-1} ($P < 0.01$). Proteinuria fell from 0.30 ± 0.04 to 0.24 ± 0.05 g · hr^{-1} ($P < 0.01$). Fractional sodium excretion did not change significantly from baseline. When compared to placebo, enalaprilat induced a decrease in MAP ($P = 0.004$), FF ($P = 0.004$), RVR ($P = 0.004$), proteinuria ($P = 0.05$), and an increase in ERPF ($P = 0.004$), and fractional sodium excretion ($P = 0.01$). In patients number 4 and 6 enalaprilat did not decrease proteinuria compared to placebo.

Nitroprusside

Infusion of nitroprusside (0.46 ± 0.14 μg · kg^{-1} · min^{-1}) had no effect on ACE, PRA, or angiotensin II levels. It resulted in a lowering of MAP from 102 ± 2 to 91 ± 2 mm Hg ($P < 0.001$). Although GFR and ERPF did not significantly change, filtration fraction increased from 20.1 ± 1.1% to 21.2 ± 1.6% ($P < 0.05$). RVR decreased from 26.7 ± 5.8 to 24.2 ± 4.5 10^{-2} mm Hg · ml · min^{-1} ($P < 0.05$). Proteinuria also decreased during nitroprusside from 0.26 ± 0.03 to 0.20 ± 0.04 g · hr^{-1} ($P < 0.05$). In comparison to placebo, nitroprusside induced a decrease in MAP ($P = 0.004$), RVR ($P = 0.004$), proteinuria ($P = 0.02$), and fractional sodium excretion ($P = 0.03$). In comparison to enalaprilat, nitroprusside induced a slightly greater decrease in MAP ($P < 0.05$), and a smaller decrease in RVR ($P < 0.05$). Those two patients who showed no antiproteinuric response to acute ACE inhibition also had the lowest antiproteinuric response to nitroprusside.
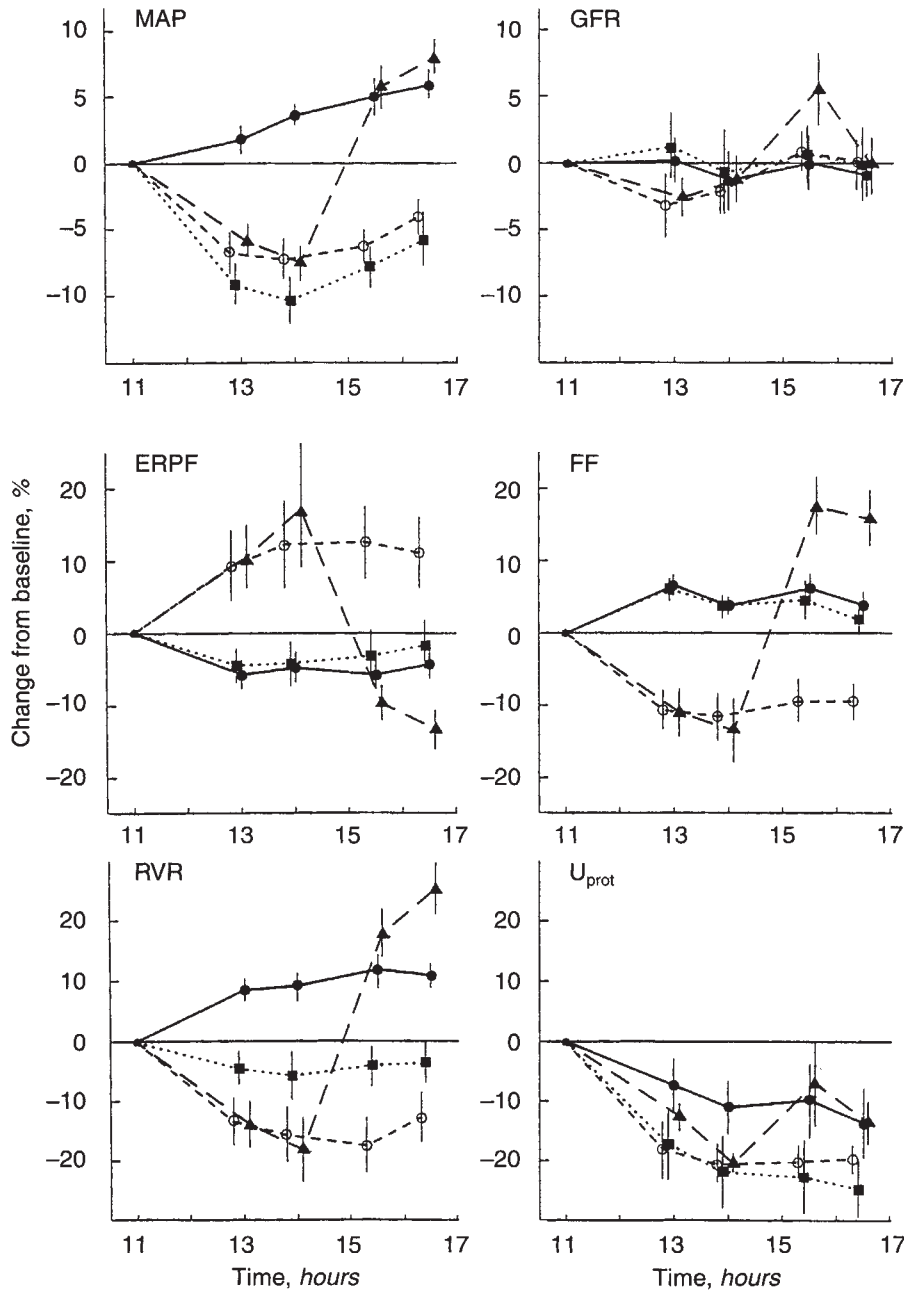
Fig. 2. *The acute effects of placebo (●——●), enalaprilat (○——○), nitroprusside (■——■), and angiotensin II during enalaprilat (▲——▲) on mean arterial pressure (MAP), glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF), renal vascular resistance (RVR), and proteinuria (U$_{prot}$).* Parameters are expressed as percentage change from the mean of two one-hour baseline values. Data are given as mean ± SE.

Angiotensin II during enalaprilat

The repeated enalaprilat infusion induced similar responses of all parameters as the previous enalaprilat infusion (Fig. 2). The two patients who had no antiproteinuric response to the first enalaprilat infusion did again fail to respond during the second. Concomitant infusion of angiotensin II (2.4 ± 1.0 ng · kg^{-1} · min^{-1}) during the last two clearance periods completely abolished the enalaprilat-induced increase in PRA and decrease in angiotensin II ($P < 0.05$). MAP increased from 94 ± 3 mm Hg during enalaprilat to 110 ± 4 mm Hg during the concomitant angiotensin II infusion ($P < 0.01$). GFR increased from 93.0 ± 10.7 to 100.5 ± 11.9 ml · min^{-1} ($P < 0.05$), ERPF decreased from 559 ± 78 to 412 ± 55 ml · min^{-1} ($P < 0.01$), and as a consequence FF increased from 18.1 ± 1.8% to 24.4 ± 2.3% ($P < 0.01$). RVR increased from 20.9 ± 4.1 to 31.5 ± 5.1 10^{-2} mm Hg · ml · min^{-1} ($P < 0.01$) and fractional sodium excretion fell from 6.66 ± 0.99 to 3.44 ± 0.88 mmol · hr^{-1} ($P < 0.01$). Angiotensin II increased proteinuria from 0.23 ± 0.05 to 0.26 ± 0.05 g · hr^{-1}. In comparison to placebo, angiotensin II decreased ERPF ($P = 0.008$) and fractional sodium clearance ($P = 0.008$), and increased FF ($P = 0.02$) and RVR ($P = 0.008$). In comparison to enalaprilat without a concomitant angiotensin II infusion, angiotensin II increased MAP ($P = 0.004$), FF ($P = 0.004$) and RVR ($P = 0.004$), and decreased ERPF ($P = 0.004$) and

Table 3. Parameters of the renin-angiotensin system at each of the study days

	Time hr	PLA	ENA	NIP	ENA + Ang II
ACE	12:00	24.2 ± 4.0	24.3 ± 3.0	27.0 ± 3.3	22.0 ± 3.2
$U \cdot liter^{-1}$	14:30	20.1 ± 3.0	1.7 ± 0.2[a]	25.0 ± 2.8	1.7 ± 0.2[a]
	17:00	21.3 ± 2.9	2.4 ± 0.2[a]	25.9 ± 3.4	3.1 ± 0.6[a]
PRA *Ang*	12:00	1.6 ± 0.2	1.9 ± 0.3	1.9 ± 0.5	1.9 ± 0.4
$I \cdot liter^{-1} \cdot$	14:30	1.6 ± 0.4	7.9 ± 5.9[a]	2.4 ± 0.4	6.7 ± 4.6[a]
hr^{-1}	17:00	1.5 ± 0.4	5.8 ± 3.9[a]	2.1 ± 0.3	1.7 ± 0.4[b]
Ang II	12:00	19 ± 3	20 ± 2	21 ± 3	19 ± 4
$pg \cdot ml^{-1}$	14:30	17 ± 5	9 ± 2	22 ± 4	11 ± 3
	17:00	22 ± 4	10 ± 2[a]	23 ± 6	33 ± 9[b]

Abbreviations are: PLA, placebo; ENA, enalaprilat; NIP, nitroprusside; Ang II, angiotensin II; ACE, ACE activity; PRA, plasma renin activity.
[a] $P < 0.05$ compared to time corresponding PLA
[b] $P < 0.05$ compared to time corresponding ENA

fractional sodium excretion ($P = 0.004$). Proteinuria during angiotensin II was not significantly different from the corresponding placebo periods, suggesting a complete reversal of the acute antiproteinuric response of ACE inhibition. However, the increase in proteinuria during angiotensin II compared to the preceding enalaprilat periods did not prove to be significantly different due to a great variability in the angiotensin II response. This analysis on the proteinuria response to angiotensin II may be confounded by the fact that two patients repeatedly showed no antiproteinuric response to enalaprilat. Repeated analysis excluding these two non-responders, however, still showed similar results. The two non-responders showed similar blood pressure and renal hemodynamic responses compared to the other patients during concomitant angiotensin II infusion, whereas proteinuria remained unchanged.

Correlations

The change in proteinuria during ACE inhibition and nitroprusside was related with the accompanying change in MAP in the last clearance period ($N = 18$, $r = 0.54$, $P < 0.05$). No relation could be observed with the changes in renal hemodynamics. The change in proteinuria during angiotensin II infusion was not related to changes in blood pressure or renal hemodynamics.

Prolonged ACE inhibition

During prolonged treatment with 10 mg enalapril o.i.d. in eight patients, proteinuria fell gradually by $-18.9 \pm 8.7\%$ after one day of treatment, $-32.2 \pm 8.2\%$ after seven days treatment, and $-43.3 \pm 9.1\%$ after 28 days treatment. The decrease in MAP was $-6.7 \pm 3.3\%$ after one day and $-10.4 \pm 1.9\%$ after seven days, and remained stable by $-10.8 \pm 2.4\%$ after 28 days of treatment. Creatinine clearance did not change during continued ACE inhibition.

Discussion

In the present study enalaprilat as well as nitroprusside acutely reduced blood pressure and proteinuria to a similar extent, whereas only enalaprilat induced a renal efferent vasodilatation. These data suggest that the acute lowering of proteinuria during single dose ACE inhibition is mediated by reduction in blood pressure, rather then by its specific renal hemodynamic effects. Exogenous angiotensin II infusion completely reversed the blood pressure and renal hemodynamic effect of acute ACE inhibition, whereas the acute antiproteinuric response of ACE inhibition was non-significantly reversed.

The acute effects of ACE inhibition compare well to those of previous reports in non-diabetic and diabetic patients with proteinuria. A recent study from our department showed that infusion of 10 mg enalaprilic acid induced a placebo-corrected decrease in blood pressure of 11%, an increase in ERPF of 30%, a decrease in FF of 30%, and a fall in proteinuria of 15% in non-diabetic patients with proteinuria [10]. Other studies show a reduction of proteinuria of approximately 20 to 25% during single dose ACE inhibition [12–14]. These studies were not placebo-controlled, but the numbers are in accordance with our non-placebo corrected data. The observed changes in MAP, FF, and proteinuria during placebo infusion, which may be explained by the sustained supine position or diurnal rhythm [23], emphasizes the importance of a placebo-controlled study design. To date no reports on the effects of nitroprusside in nephrotic patients have been presented. The potent and generalized vasodilatation of nitroprusside resulted in a lowering of blood pressure without specific renal hemodynamic effects. By comparing the effects of the two antihypertensives, one with and one without renal hemodynamic effects, we are the first to differentiate whether systemic or renal hemodynamics mediate the acute lowering of proteinuria by ACE inhibitors. The combined nitroprusside and ACE inhibition data clearly show that the acute fall in proteinuria is associated with a fall in blood pressure, and not with changes in renal hemodynamics. This acute lowering of proteinuria may thus be explained by the transmission of a lower systemic blood pressure into the glomerulus. In that case, however, one might also expect noticable changes in GFR. Since we could only demonstrate slight and non-significant changes in GFR during infusion of enalaprilat and nitroprusside, the techniques used to measure renal hemodynamics in humans may not be sensitive enough to detect subtle GFR changes. The mechanism of the acute fall in proteinuria thus remains as yet unexplained apart from the fact that it is associated with a fall in blood pressure.

The renal and systemic responses to exogenous angiotension II in the present study are opposite to the effects of acute ACE inhibition and as such in accordance with those found in several animal [15–19] and human studies [11, 24, 25]. Reversing the blood pressure lowering effect of ACE inhibition through angiotensin II should have induced a return of proteinuria to pretreatment values. Although this did indeed happen in some patients, the acute antiproteinuric response to ACE inhibition could not be statistically significantly reversed by angiotensin II. It may well be that systemic delivery of angiotensin II to the kidney, besides renal efferent vasoconstriction, also constricts the preglomerular vessel considerably, thus preventing the rise in blood pressure to fully affect the intraglomerular pressure [26]. Both Heeg et al [11] and Loon et al [25] found a reduced GFR together with an increased FF during angiotensin II infusion, reflecting renal afferent and efferent vasoconstriction. In contrast, we found an increase in GFR and FF during angiotensin II infusion, reflecting predominantly renal efferent vasoconstriction. This may explain why the acute antiproteinuric response of ACE inhibition was influenced by angiotensin II in some of our patients. In retrospect, exogenous infusion of angiotensin II may not have been the ideal tool to test the blood pressure dependence of the acute antiproteinuric effect, since it may also have induced renal hemodynamic changes

different from those of intrarenal angiotensin II perturbations [27].

The prevailing hypothesis to explain the antiproteinuric effect of chronic ACE inhibition suggests a relation between reduction in proteinuria and the ACE inhibition induced changes in renal hemodynamics [9]. The predominantly postglomerular vasodilatation by ACE inhibitors which results in a decrease of intraglomerular pressure has been suggested to be responsible for lowering of proteinuria [5, 6]. We conclude that in humans the short-term antiproteinuric effect of ACE inhibition appears to be mediated by blood pressure reduction and does not require the specific renal hemodynamic effects of ACE inhibition. This acute reduction of proteinuria is relatively small (20%), whereas a gradual increase of the antiproteinuric response to approximately 50% occurs during prolonged ACE inhibition in our patients. As was demonstrated previously, this gradual increase is not associated with any further change in blood pressure or renal hemodynamics [10]. Together with the results of the angiotensin II infusion during long-term ACE inhibition [11], this leads us to hypothesize that the long-term effects are mediated by tissue angiotensin II or by slowly appearing structural effects on the glomerular filtration barrier. This is supported by several studies which show that long-term ACE inhibition has beneficial effects on glomerular permselectivity [28–32]. Although the specific renal hemodynamic changes of ACE inhibition initially play no role in the antiproteinuric response, it may well be that they are still important because such hemodynamic changes may form the basis and may gradually induce the structural changes of the glomerular filtration barrier. This may also explain why other antihypertensives without a specific renal hemodynamic profile like ACE inhibitors do not lower proteinuria beyond their initial small effect. Indeed, several studies suggest a relation between renal hemodynamic conditions and structural alterations. It has been shown that angiotensin II induced intrarenal vasoconstriction is associated with early growth response genes [33] and increased hyperproliferative responses to mechanical strain [34]. Further studies should clarify whether the antiproteinuric mechanism of ACE inhibition requires a renal hemodynamically mediated phase that gradually induces renal structural changes that prevent the abundant passage of proteins.

Acknowledgments

Reprint requests to Dick de Zeeuw, M.D., Ph.D., Department of Medicine, Division of Nephrology, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.

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