Nephrol Dial Transplant (1992) 7 216–220

Nephrology
Dialysis
Transplantation

Original Article

Renal haemodynamics and organ damage in young hypertensive patients with different plasma renin activities after ACE inhibition

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Abstract. We describe our observations concerning differences in two groups of young hypertensive patients according to their renin activities after ACE inhibition. Seventeen of these patients (age 26±7 years), so far untreated, were investigated prospectively for hormone levels (renin, aldosterone, vasopressin), microalbuminuria, renal haemodynamics (inulin and PAH clearance) and signs of organ damage (echocardiography, fundoscopy). Secondary forms of hypertension were excluded by routine methods, including angiography. We differentiated two groups of young hypertensive patients. Group 1 ($n=9$) had a false positive captopril test with elevated renin activities after ACE inhibition with captopril (8.4±5 ng/ml per hour) compared to group 2 (renin activity: 2.2±1.3 ng/ml per hour) or an increase of >400% of renin activity after ACE inhibition. Baseline renin activities and sodium excretion did not differ between the groups. Group 1 also showed significantly greater GFR, FF, and microalbuminuria, as well as signs of organ damage, with left ventricular hypertrophy and hypertensive changes in fundoscopy. There were no differences between the groups concerning mean arterial blood pressure and duration of hypertension. In conclusion, we were able to demonstrate that patients with highly stimulated renin activities showed signs of visceral organ damage and renal hyperfiltration compared to the normal renin activity group after ACE inhibition. Investigations of the renin–angiotensin–aldosterone system with ACE inhibitors might constitute a helpful indicator of renal changes and organ damages in young hypertensive patients.

Key words: ACE inhibition; glomerular hyperfiltration; hypertension; left ventricular hypertrophy; microalbuminuria; renin

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Introduction

Recently we reported the failure of the captopril test to detect renal artery stenosis in young hypertensive patients [1]. Nearly 40% of our young hypertensive outpatients showed a marked increase of plasma renin activities after ACE inhibition without showing evidence of renal artery stenoses, as excluded by angiography. Baseline renin activities did not differ between the groups and pronounced responses to captopril stimulation could not be explained by different sodium excretion rates. This cohort of young hypertensive patients with a false positive captopril test showed microproteinuria significantly more often compared to a control group.

As it is of great potential importance to evaluate the association of renin concentrations, renal haemodynamics, microalbuminuria, and vascular damage in patients with essential hypertension we started a prospective study in young hypertensive patients. This article will report on our observations in 17 young hypertensive patients matched for blood pressure as well as age and separated according to their response to ACE inhibition.

Subjects and methods

From April 1990 to November 1990 we prospectively investigated 17 young outpatients with hypertension according to their response to ACE inhibition and to signs of organ damage including microalbuminuria. Twelve men and five women with essential arterial hypertension were selected for the study (mean age 27±6 years). They persistently had an outpatient systolic blood pressure greater than 160 mmHg and a diastolic blood pressure greater than 100 mmHg on an unrestricted diet and without drug therapy, as measured on three different days after 5 min in the supine position. Secondary forms of hypertension were excluded by physical examination and routine laboratory investigations. Examinations concerning renal haemodynamics and organ damage were done in a blind manner by independent physicians without knowing renin values. Left ventricular wall thickness was measured by echocardiography (two-dimensional echocardiography combined with M-mode). Hormone concentrations were determined at the end of the study period. In patients with high concentrations of renin activity a transarterial angiography was performed to exclude renal artery stenosis.

At the end of the investigation patients were assigned to two groups according to their renin concentrations after ACE inhibition. Group 1 was defined as having a false positive captopril test, according to the criteria of Muller *et al.* [2]. Most of these patients had elevated stimulated renin activities (>4 ng/ml per hour) or showed an increase >400% of renin activities after ACE inhibition.

Patient characteristics are described in Table 1. There was no difference concerning protein or sodium intake. All patients were allowed to stay on their normal diet.

Blood pressure and microalbuminuria were measured on at least three consecutive days. A so-called white coat hypertension was ruled out by 24 h blood-pressure measurements (Spacelabs 90202, Spacelabs Inc., Redmond Wash). Blood pressure values given in Table 1 were also obtained by these measurements and are given as mean values. This device uses a standard upper arm cuff which is inflated at regular preset intervals (every 20 min). Systolic, diastolic, and mean arterial blood pressures were calculated and interpreted by the help of an algorithm as the arterial pressure fluctuations are transmitted to the cuff and tubing system oscillometrically.

Concentrations of renin, aldosterone, and antidiuretic hormone were assessed. According to Muller *et al.* [2] blood for determining plasma renin activity was drawn only when a normal sodium excretion rate was guaranteed (urinary sodium was >80 mval l in all patients). For routine blood investigations and evaluation of hormone concentrations blood was obtained after lying supine for 30 min. Then 25 mg captopril were administered orally. Sixty minutes later venous blood samples were drawn for measurement of stimulated plasma renin activities. Arterial blood pressure was measured at the beginning and every 15 min.

Sodium, potassium, chloride, creatinine, urea nitrogen, and glucose concentrations in serum samples were measured with an automated system of chemical analysis (Hitachi, Boehringer). The peripheral venous haematocrit was determined by microhaematocrit technique. Urinary albumin was measured by enzyme-linked immunosorbent assay [3]. Urine samples were collected in 2-l casein-coated polyethylene containers. Plasma renin activity, vasopressin, and aldosterone values were determined with commercially available radioimmunoassays.

Glomerular filtration rate (GFR) and renal blood flow were assessed by means of a constant infusion technique of inulin (Inutest; Laevosan; 20 ml contains 5.0 g polyfructosan) and PAH (*p*-aminohippurate; Nephrotest; BAG; 10 ml contain 2.2 g sodium aminohippurate) after an initial loading dose starting at 8.30 a.m. (loading dose for inulin: 36 ml/m^2 body surface area; loading dose for PAH: 6 ml/m^2 body surface area) [4]. The C_{IN} and C_{PAH} were calculated as urine concentration divided by plasma concentration, multiplied by urine volume in millilitres per minute, and corrected for body surface area (1.73 m^2). Since there were no significant differences in urine flow rates or clearances from one collection period to another, all results were expressed as single mean values of the triplicate determinations for each patient. The filtration fraction was calculated as C_{IN}/C_{PAH} and was expressed as a percentage of C_{PAH}.

Student's *t*-test was used to determine statistical significance ($P<0.05$). Linear regressions and correlation coefficients were calculated to relate albuminuria and plasma renin activities after ACE inhibition.

Table 1. Patient characteristics

Characteristics	Group 1*	Group 2*
Age (years)	25.7±7.3	28±3.9
Body mass index (kg m^2)	22.6±1.9	26.2±4.8
Basal systolic BP (mmHg)	172±12	168±21
Basal diastolic BP (mmHg)	99±8	100±7
Mean arterial pressure (mmHg)	123±7	122±10
Basal pulse (beats min)	75±10	76±15
Duration of hypertension (months)	23±24	31±14
Creatinine (mg dl)	0.9±0.1	0.9±0.1
Sodium excretion (mval l)	114±16	96±19
Positive family history for hypertension (total numbers)	7	3
Subjects (*n*)	9	8

*Mean values±SD.
Group 1, patients with elevated plasma renin activity after ACE inhibition; see Table 2.
Group 2, patients with normal plasma renin activity after ACE inhibition, see Table 2.
BP, blood pressure.

Results

Both study groups were comparable with regard to age and arterial blood pressure measured by 24 h blood pressure measurement. There were no statistically significant differences regarding history of hypertension and body mass index, nor in serum concentrations of electrolytes, glucose, blood urea nitrogen, venous haematocrit, and creatinine. The difference in sodium excretion (114±16 mval l *versus* 96±19 mval l) was not statistically significant.

There were significant ($P<0.01$) differences in plasma renin activities after ACE inhibition (group 1, 8.4±5.3 ng ml per hour; group 2, 2.2±1.3 ng ml per hour; see also Table 2). Baseline plasma renin activities were slightly but not significantly increased in group 1 (group 1, 2.0±1.1; group 2, 1.5±0.3). The increase in renin activity after ACE inhibition

Table 2. Patient renin, aldosterone and vasopressin profile

Profile	Group 1	Group 2
Baseline renin activities (supine position) (ng/ml per hour)	2.0±1.1	1.5±0.3
Renin activities after oral administration of 25 mg captopril (ng/ml per hour)	8.4±5.3	2.2±1.3*
Increase of renin activities after ACE inhibition (%)	610±175	190±44**
Aldosterone (pg/ml)	116±37	116±41
Vasopressin (pg/ml)	6±4	3±2*

*Statistically significant.
**Mean values ±SD of the respective individual increase.

Table 4. Organ involvement and microalbuminuria

	Group 1	Group 2
Abnormal fundoscopy (*n*) hypertensive fundus	7	4
grade 1 (*n*) hypertensive fundus	5	4
grade 2 (*n*)	2	0
Diameter of end-diastolic septum (mm)	11.1±1.4	9.5±0.9*
Diameter of posterior wall, end-diastolic (mm)	11.7±1.3	9.4±0.7*
Microalbuminuria (mg/24 h)	102±57	17±7*

*Statistically significant.

expressed as mean values of the individual increase was more pronounced in group 1 (610±175%) than in group 2 (190±44%). Unlike plasma renin activity, there were essentially no notable differences in plasma aldosterone between the groups. Vasopressin concentrations were higher in group 1, with elevated renin activities after ACE inhibition. This difference was not statistically significant.

As regards renal function, the differences of inulin clearance (119±13 ml/min per 1.73 m^2 in group 1 versus 105±5 ml/min per 1.73 m^2 in group 2) and filtration fraction (28±3% in group 1 versus 22±3% in group 2) were significant. PAH clearance and effective renal plasma flow (ERPF) were slightly but not significantly elevated in group 2 (Table 3).

Investigations concerning organ involvement (Table 4) showed that in group 1 seven of nine patients showed hypertensive fundoscopic changes ($n=5$ for grade 1, $n=2$ for grade 2). In contrast, in group 2 only four of eight patients showed fundoscopic changes which were less severe than in group 1 (no grade 2). Echocardiographic diameters of the interventricular septum and posterior wall were elevated in group 1 and normal in group 2. Microalbuminuria was significantly higher in group 1 (102±57 mg/24 h versus 17±7 mg/24 h).

Patients with elevated plasma renin activities after ACE inhibition (group 1) had a positive correlation of albuminuria and stimulated plasma renin activities (Figure 1).

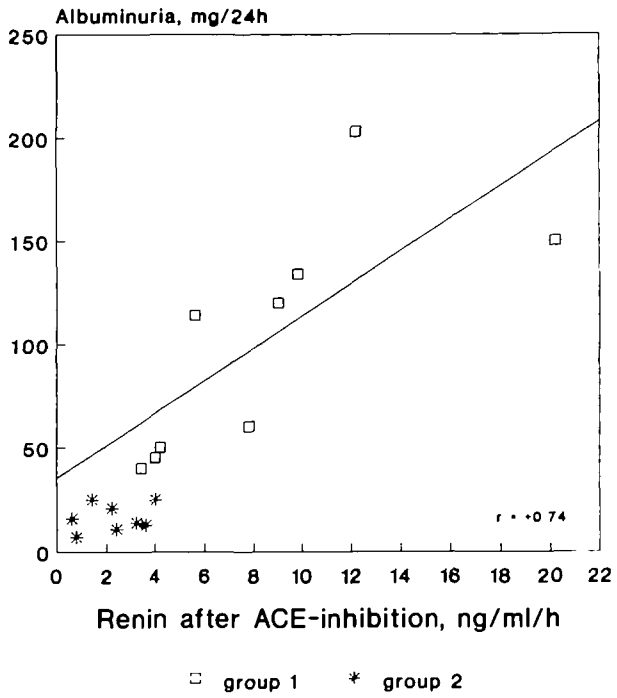

Fig. 1. Correlation of stimulated renin activities (renin after ACE inhibition) and microalbuminuria in young hypertensive patients. Group 1, patients with elevated plasma renin activity after ACE inhibition (25 mg captopril, see Table 2); Group 2, patients with normal plasma renin activity after ACE inhibition (25 mg captopril, see Table 2).
r = correlation coefficient.

Table 3. Renal function and haemodynamics

Parameters	Group 1	Group 2
Inulin clearance (C_{IN}) (ml/min per 1.73 m^2)	119±13	105±5*
p-aminohippurate clearance (C_{PAH}) (ml min per 1.73 m^2)	430±83	482±57
Filtration fraction (C_{IN} C_{PAH} × 100%)	28±3	22±3*

*Statistically significant.

Discussion

In a population of young hypertensive patients up to 40% showed an elevation of plasma renin activities after ACE inhibition [1]. We performed this prospective investigation in order to clarify whether there are differences between young hypertensive patients with elevated and normal renin activity responses after ACE inhibition. We chose 17 patients without previous medication, matched for blood pressure, duration of hypertension, and age, and divided them into two

groups according to their renin response to ACE inhibition.

In contrast to other investigations about differences in the renin system of hypertensives [5–9], baseline renin activities of our groups were nearly equal, with a slight but not significant advantage of group 2. The strong response to ACE inhibition in group 1 could not be explained by differences of sodium excretion, age, or aldosterone concentrations (Tables 1,2). Despite nearly identical baseline renin activities, the responses to ACE inhibition in group 1 are comparable to those in high-renin hypertensive patients described by previous investigators [6,10–13]. The slightly elevated aldosterone in group 1 seems to be related to the overall increased renin concentration. Vasopressin was higher in group 1 than in group 2 despite comparable blood pressures. The same observation was made in patients with high-renin hypertension and was thought to be related to hypovolaemia [14]. Due to normal baseline renin activities these patients could not be clearly classified as a group of high-renin hypertensives, although we cannot exclude that we may have studied patients in an early stage of this disease.

There have been several observations on the relation of renin concentrations, renal haemodynamics, microalbuminuria, organ damage, and risk of stroke and heart attack [7,11,13,14]. In this context our investigation concerning renal haemodynamics and organ damage in young patients is of interest.

The assessment of renal haemodynamics (Table 3) showed a slight but significantly higher inulin clearance in group 1. Renal blood flow was slightly diminished compared to group 2. Group 1 showed a significantly higher filtration fraction (Table 3). The observed renal haemodynamic changes in our patients could be interpreted as a more pronounced vasoconstriction of efferent arterioles in patients of group 1 (increased renin activities). Probably patients suffering from this form of hypertension will develop nephron damage at a later state of their disease. This might occur as sequel of the high glomerular pressure in the early state of the disease, according to observations in the rat model [15–17]. Our observations on renal haemodynamics are in accordance with those previously published for patients with microalbuminuria [18]. Other results concerning renal haemodynamic changes in patients with essential hypertension as to their renin status are conflicting [5,7,9,19]. Some investigators described a reduced glomerular filtration rate, others reported a normal or slightly elevated glomerular filtration rate. Most of these differences may be explained by heterogeneities of age, medication, and duration of hypertension. As our study groups were matched, we attach importance to the observations made, especially with reference to the differences in renal haemodynamics and renin activities in young hypertensive patients.

Microalbuminuria was evident in group 1 and there was a correlation between renin values after ACE inhibition and microalbuminuria, especially in patients with a markedly increased renin activity after ACE inhibition (Figure 1). We consider microalbuminuria to reflect the exposition of nephrons to renin and angiotensin II. A correlation between albuminuria and filtration fraction or glomerular filtration rate as reported by other investigators [18] could not be reproduced in our study.

In accordance with observations that microalbuminuria is related to other organ damage [20–22], we were able to demonstrate that group 1 patients more frequently showed signs of left ventricular hypertrophy and of vascular damage during fundoscopy. Although microalbuminuria seems to reflect the situation at the renal microvascular site only, our findings of a correlation between microalbuminuria and serum renin concentrations may be the link between microalbuminuria and overall vascular organ damage. This suggests a direct renin-dependent vascular damage of the whole vascular system. This would be supported by data that in larger populations patients with high-renin hypertension showed stroke and myocardial infarction more often [23].

In conclusion, patients with increased renin concentrations after ACE inhibition more frequently showed signs of organ damage and a more pronounced microalbuminuria. Renal haemodynamics of these patients showed increased glomerular filtration and filtration fraction. This could be interpreted as an adaptation of nephrons exposed to increased concentrations of renin and angiotensin II. Thus far it remains unclear whether increased concentrations of renin are the key to the disease or just a response to other damage. Further follow-up investigations about the vascular system, kidney morphology and clinical outcome of these patients may answer this question and will also indicate whether our patients belong to a special form of hypertension or represent an early state of so-called high-renin hypertension.

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Received for publication 10 4.91
Accepted in revised form 11 7.91