Is Microalbuminuria a Marker of Early Intrarenal Vascular Dysfunction in Essential Hypertension?

Albert Mimran, Jean Ribstein, Guilhem DuCaillar

Abstract  The relation between basal intrarenal hemodynamics and the renal response to acute inhibition of angiotensin-converting enzyme by captopril and albuminuria was assessed in 106 lean patients with essential hypertension. It was observed that the microalbuminuric group (24.5% of the total population) was characterized by a higher systemic arterial pressure, a lower level of high-density lipoprotein cholesterol, and similar mean values of age, duration of hypertension, glomerular filtration rate, renal plasma flow, filtration fraction, and plasma renin activity when compared with normoalbuminuric subjects. In response to captopril, a significant renal vasodilatation without a change in glomerular filtration rate or a fall in filtration fraction was observed in normoalbuminuric patients only. In contrast, the renal vasodilator response was abolished in microalbuminuric subjects, together with blunting of the rise in plasma renin activity associated with captopril. This occurred despite similar indexes of activity of the endogenous renin-angiotensin system. It is suggested that microalbuminuria may be a marker of early functional or fixed intrarenal vascular dysfunction in never-treated lean patients with essential hypertension. (Hypertension. 1994;23[part 2]:1018-1021.)

Methods

Patients

One hundred six lean patients (34 women and 72 men) with mild to moderate essential hypertension and a body mass index lower than 26 kg/m² in women and 27 kg/m² in men. All subjects had never received antihypertensive medication before participating in the studies. Women on oral contraceptives as well as patients with albustix-positive proteinuria were excluded. Informed consent was obtained from all subjects before beginning the studies.

Protocol

Studies were performed between 8 AM and 1 PM. After an overnight fast, patients came to the ward with two consecutive 24-hour urine collections for the determination of levels of creatinine, electrolytes, uric acid, and urinary albumin excretion (UAE). Throughout the study, with the subject in the supine position, arterial pressure and heart rate were monitored every 3 minutes with a Dynamap 845 XT (Critikon). After a 30-minute period of rest, blood was collected for the determination of levels of creatinine, electrolytes, uric acid, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Glomerular filtration rate (GFR) and effective renal plasma flow (RPF) were estimated by the constant infusion technique, using ⁵¹Cr-diethylenetriaminepentaacetic acid and ¹³¹I-sodium ortho-iodohippurate, respectively, in subjects maintained on water diuresis. After an equilibrium period of 90 minutes, three 20- to 30-minute control clearances were obtained (urine collected by spontaneous voiding). A 50-mg dose of captopril was then given orally, and the urine collected within 30 to 45 minutes was discarded. Thereafter, two 20- to 30-minute clearance determinations were obtained. After completion of renal function studies, left ventricular mass was estimated by two-dimensional echocardiography.

Analytical Methods

Clearances obtained during the precaptopril and postcaptopril periods were averaged and proportioned to 1.73 m² of body surface area, and renal resistance was calculated as the ratio of mean arterial pressure to renal blood flow (RPF/1-hematocrit). Plasma renin activity, plasma aldosterone concentration, and urinary albumin were estimated by radioimmunoassay techniques.

Statistical Analysis

Data are presented as mean and SEM unless stated. Statistical analysis was carried out using paired or unpaired t tests.
Demographic, Clinical, Renal, and Hormonal Characteristics of Patients With or Without Microalbuminuria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Microalbuminuria Absent (MA−)</th>
<th>Microalbuminuria Present (MA+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>80</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41±1</td>
<td>43±2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio (women/men)</td>
<td>27/53</td>
<td>7/19</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.4±0.3</td>
<td>24.1±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>157±1</td>
<td>163±3</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>97±1</td>
<td>101±2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>117±1</td>
<td>121±2</td>
<td>.05</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.05±0.02</td>
<td>1.02±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>4.7±0.1</td>
<td>4.9±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>216±4</td>
<td>225±9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>56±2</td>
<td>47±3</td>
<td>.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>104±6</td>
<td>129±14</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>112±4</td>
<td>115±8</td>
<td>NS</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m²</td>
<td>103±2</td>
<td>108±4</td>
<td>NS</td>
</tr>
<tr>
<td>Effective renal plasma flow, mL/min per 1.73 m²</td>
<td>446±9</td>
<td>471±18</td>
<td>NS</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>23.5±0.4</td>
<td>23.3±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>153±7</td>
<td>155±15</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary urea, mmol/24 h</td>
<td>364±15</td>
<td>434±29</td>
<td>.05</td>
</tr>
<tr>
<td>Urinary albumin excretion, µg/min</td>
<td>7±1</td>
<td>37±5</td>
<td>.001</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL per hour</td>
<td>1.53±0.14</td>
<td>1.34±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>14.0±0.7</td>
<td>15.2±1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. HDL indicates high-density lipoprotein.

**Results**

**Characteristics of the Entire Population**

In this group of never-treated patients with mild to moderate hypertension of rather short duration, albuminuria ranged between 0.4 and 106 µg/min; 26 of 106 patients (24.5% of the population) had microalbuminuria defined as UAE higher than 14 µg/min. This cutoff value was chosen after measurement of UAE in 59 lean normal subjects (aged 14 to 60 years) in whom a median UAE value of 4 µg/min (5±3 µg/min, mean±SD) was obtained.

The logarithm of UAE was positively correlated with systolic and mean arterial pressure ($r$ values of .32 and .25, respectively, $P<.01$) and urinary urea excretion ($r=.28$, $P<.006$). No correlation between UAE and baseline parameters of renal function or left ventricular mass index was observed. Interestingly, a negative correlation with HDL cholesterol level was found ($r=-.34$, $P<.0007$).

**Characteristics of Microalbuminuric and Normoalbuminuric Patients**

**Baseline**

The two groups were similar in age, body mass index, sex repartition, and estimated duration of hypertension (26±4 and 25±5 months for MA− and MA+, respectively). The prevalence of a smoking history was higher in the MA+ (42%) than in the MA− (29%) group; however, it did not reach statistical significance ($P<.10$). As summarized in the Table, higher mean values of systolic and mean arterial pressure as well as urinary excretion of urea (an index of protein intake) were found in the MA+ group. No difference in renal function and hemodynamics as well as hormonal parameters (plasma renin activity and plasma aldosterone concentration) between the two groups was observed. HDL cholesterol but not total serum cholesterol was lower in the MA+ group.

**Renal Response to Acute Administration of Captopril**

As shown in the Figure, the two groups were similar with respect to the response to captopril of mean arterial pressure (−6.3±3% and −5.8±1% in MA− and MA+, respectively) and plasma aldosterone concentration (−24±3% and −25±4% in MA− and MA+, respectively). In contrast, the renal vasodilator response to captopril was significantly blunted in MA+ patients (2.9±2.1% versus 11.3±1.5%, $P<.005$ for RPF), whereas GFR was unaltered in both groups. Calculated filtration fraction was unchanged in MA+ patients (2.2±1.2%) and decreased by 5.4±1% in the MA− group ($P<.05$). Moreover, the increase in plasma renin activity associated with captopril was blunted ($P<.005$ in the MA+ group) (33±13%) when compared with the normoalbuminuric group (100±19%).
The mechanism of microalbuminuria in essential hypertension is poorly understood. For the first time, an attempt was made to assess the relation between intrarenal hemodynamics and UAE. RPF and GFR were similar in microalbuminuric and normoalbuminuric groups, and filtration fraction was not altered. If the presence of an elevated GFR and filtration fraction truly indicates the existence of an increase in intraglomerular pressure, by analogy to animal models of renal injury, several questions arise. The inability of captopril to dilate the renal vasculature was observed despite the existence of a similar degree of endogenous activity of the renin-angiotensin system, as suggested by identical baseline plasma renin activity as well as a similar fall in mean arterial pressure and decline in plasma aldosterone concentration in response to captopril. This indicates that the renal vasculature of microalbuminuric patients may have lost responsiveness to endogenous angiotensin II, in contrast to systemic resistance vessels and adrenals. Interestingly, the rise in plasma renin activity in response to chronic elevation in protein intake, thus suggesting that microalbuminuria may represent an early sign of renal inability to adapt to chronic changes in protein intake.

The finding of an abolished vasodilator response to acute inhibition of angiotensin-converting enzyme in microalbuminuric patients, in contrast to normoalbuminuric patients and normal subjects (A.M., unpublished observation), raises several questions. The inability of captopril to dilate the renal vasculature was observed despite the existence of a similar degree of endogenous activity of the renin-angiotensin system, as suggested by identical baseline plasma renin activity as well as a similar fall in mean arterial pressure and decline in plasma aldosterone concentration in response to captopril. This indicates that the renal vasculature of microalbuminuric patients may have lost responsiveness to endogenous angiotensin II, in contrast to systemic resistance vessels and adrenals. Interestingly, the rise in plasma renin activity in response to chronic elevation in protein intake, thus suggesting that microalbuminuria may represent an early sign of renal inability to adapt to chronic changes in protein intake.
angiotensin-converting enzyme inhibition, or a defect in
the production of an endothelium-derived relaxing fac-
tor indispensable to the vasodilator effect of kinins
remains hypothetical. It was demonstrated in isolated
vessels and cultured human and bovine endothelial
cells that the effect of various types of angiotensin-
converting enzyme inhibitors may be mediated through
an increased production of endothelium-derived relax-
ing factors. The present observation may thus suggest
that microalbuminuria could be a marker of intrarenal
endothelial dysfunction. It would be of interest to
compare the renal effect of angiotensin-converting en-
zyme inhibitors and calcium antagonists, since these
agents are known to exert their vasodilator action
through non-endothelium-dependent mechanisms in
hypertensive patients with or without microalbumi-
uria. In patients with mild hypertension, Hollenberg et
al observed that the renal vasculature was exquisitely
sensitive to the intrarenal infusion of the endothelium-
dependent dilator acetylcholine; in contrast, the
response to acetylcholine was abolished in subjects with
severe hypertension and advanced nephrosclerosis.
However, the study was conducted in a small number of
patients, and no mention of albuminuria was available.

In recent years, microalbuminuria was proposed as a
marker of cardiovascular risk in nondiabetic and diabe-
etic patients. In the diabetic population, the HDL
cholesterol level was lower in microalbuminuric than
normoalbuminuric patients. In patients with treated
essential hypertension, it was reported that proteinuria
at entry was higher in those patients who developed
cardiovascular complications within a 10-year follow-up
period. Our observation that HDL cholesterol was
lower in microalbuminuric subjects suggests that mi-
croalbuminuria may be an early marker of renal vascu-
lar dysfunction as well as cardiovascular risk. Long-term
follow-up of renal function in our population may be of
great interest with regard to an eventual development of
renal impairment despite effective antihypertensive ther-
apy, whether associated or not with a reduction in
albuminuria.

References
1. Mogensen CE. Microalbuminuria as a predictor of clinical diabetic
2. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of
cardiovascular mortality in insulin-dependent diabetes mellitus. Br
3. Jensen T, Knudsen J, Feldt-Rasmussen B, Deckert T. Features of
endothelial dysfunction in early diabetic nephropathy. Lancet.
4. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as pre-
530-533.
5. Ribstein J, DuCailar G, Minram A. Renal consequences of over-
3:535.
6. Minram A, Deschodi G. The role of the renin-angiotensin system
in the hormonal and renal response to tilt in normal man. Renal
Physiol Biochem. 1983;6:36-42.
7. Du Cailar G, Ribstein J, Daures JP, Minram A. Sodium and left
ventricular mass in never-treated hypertensive and normotensive
microalbuminuria in a large population of patients with mild to
Palombo C, Ghione S. Microalbuminuria and casual and ambu-
labory blood pressure monitoring in normotenives and in patients
with borderline and mild essential hypertension. Am J Hypertens.
10. Cerasola G, Cottone S, D'Ignoto G, Grasso L, Mangano MT,
Carapelle E, Nardi E, Andronico G, Fulantelli MA, Marcellino T,
Seddio G. Micro-albuminuria as a predictor of cardiovascular
11. Brenner BM. Nephron adaptation to renal injury or ablation. Am J
pressure: less of one, more of the other? Am J Hypertens. 1988;1:
335-347.
13. Mathiesen ER, Hommel E, Giese J, Parving HH. Efficacy of
captopril in postponing nephrophy in normotensive insulin-
dependent diabetic patients with microalbuminuria. Br Med J.
1991;303:81-86.
stabilizing effect of angiotensin-converting enzyme inhibition on
plasma creatinine and on proteinuria in normotensive type II
15. Losito A, Fortunati F, Zampi I, Del Favero A. Impaired renal
functional reserve and albuminuria in essential hypertension. Br
16. Ritz E, Fliser D, Siebels M. Pathophysiology of antihypertensive
renal damage. Am J Hypertens. 1993;6:241s-244s.
17. Momboul JV, Nephatali M, Vanhoupte PM. Effect of the con-
verting enzyme inhibitor cilazaprilat on endothelium-dependent
18. Wiemer G, Scholkens BA, Becker RHA, Busse R. Ramiprilat
enhances endothelial autacoid formation by inhibiting breakdown
of endothelium-derived bradykinin. Hypertension. 1991;128:
558-563.
of TA 3090, a novel analog of diltiazem: interaction with endothe-
lum-dependent relaxation in canine femoral and coronary arteries.
20. Hollenberg NK, Adams DF, Solomon H, Chenitz WR, Burger BM,
Abrams Hl, Merrill JP. Renal vascular tone in essential and
21. Samuelsson G, Wilhelmsen L, Einfeldt D, Pennert K, Wedel H,
Wikstrand J, Berglund G. Predictors of cardiovascular morbidity
in treated hypertension: results from the primary preventive trial in
Is microalbuminuria a marker of early intrarenal vascular dysfunction in essential hypertension?
A Mimran, J Ribstein and G DuCailar

_Hypertension_. 1994;23:1018-1021
doi: 10.1161/01.HYP.23.6.1018

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/23/6_Pt_2/1018