Renal Effects of Nifedipine and Captopril in Patients With Essential Hypertension and Reduced Renal Reserve

Carlo Buzio, Giuseppe Regolisti, Franco Perazzoli, Antonio Mutti, Enrico Bergamaschi, Alberico Borghetti

Abstract In this study we investigated the short-term effects of calcium channel blockers and angiotensin-converting enzyme inhibitors on renal hemodynamics and the urinary excretion of proteins with different relative mass in subjects with mild to moderate essential hypertension and apparently normal glomerular filtration rate but reduced renal functional reserve. Sixteen subjects underwent the following four treatments: (1) low-protein meal (0.2 g protein/kg body wt), (2) high-protein meal (1.3 g protein/kg body wt), (3) high-protein meal plus oral nifedipine (20 mg), and (4) high-protein meal plus oral captopril (50 mg). Two urine samples were obtained after meals. Blood samples were drawn at the midpoint of each 120-minute urine collection period. Urine and serum were tested for total protein, immunoglobulin G, albumin, α₂-microglobulin, retinol binding protein, and β₂-microglobulin. Glomerular filtration rate and renal plasma flow were assessed by iothalamate and p-aminomethylascorbaric clearance, respectively. Compared with the high-protein meal alone, nifedipine elicited a clear-cut increase in the urinary excretion of total protein (+60%, P<.01), immunoglobulin G (+58%, P<.01), albumin (+25%, P<.05), retinol binding protein (+47%, P<.05), and β₂-microglobulin (+52%, P<.05); captopril decreased the urinary excretion rate of immunoglobulin G (-26%, P<.05), albumin (-22%, P<.05), and β₂-microglobulin (-34%, P<.05). The ratio between the clearances of immunoglobulin G and albumin was higher after nifedipine (+21%, P<.01) and unchanged after captopril (-9%, P=NS) compared with the high-protein meal alone. Glomerular filtration rate and renal plasma flow were higher after nifedipine (+10%, P<.05 and +9%, P<.05, respectively) and lower after captopril (-2%, P<.05 and -9%, P=NS, respectively) than after the high-protein meal alone. Thus, single doses of nifedipine, preceding a protein load in the form of a meat meal, raise both glomerular filtration rate and renal plasma flow and increase urinary protein excretion rate. Changes in both glomerular selectivity and tubular reabsorption seem to account for increased proteinuria. (Hypertension. 1994;24:763-769.)

Key Words • angiotensin-converting enzyme inhibitors • calcium channel blockers • hypertension, essential • kidney • albumins • β₂-microglobulin • retinol-binding proteins

Calcium channel blockers (CaCBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been recommended as first-line drugs in antihypertensive therapy.1 CaCBs and ACEIs also reduce urinary protein excretion rate and slow the progression of renal failure in different glomerular diseases.2,3,6 Although CaCBs and ACEIs may have different effects on renal function depending on their predominant site of action on afferent and efferent glomerular arterioles, respectively, both drugs seem to ensure a similar degree of renal protection, at least in nephropathic patients.

Renal responses to vasoactive drugs depend on basal renal hemodynamics.7 Previous studies have shown that the renal functional reserve, as assessed by the increase in glomerular filtration rate (GFR) after a short-term oral protein load or an intravenous infusion of amino acids, may be either preserved or reduced in patients with essential hypertension and normal kidney function.8,9

Early in the course of essential hypertension, renal plasma flow (RPF) may be reduced, a normal GFR being maintained by efferent arteriolar constriction with increased filtration fraction (FF).2,10 Such a persistent derangement in renal hemodynamics may lead to reduced renal reserve and progressive glomerular damage.8,11,12 Pharmacological antihypertensive therapy should therefore be aimed at both controlling systemic hypertension and preventing or reversing the pathophysiological changes occurring in the kidney of hypertensive patients.

We designed this study in subjects with mild to moderate hypertension and apparently normal GFR but reduced renal functional reserve to evaluate the effects of a CaCB (nifedipine) or an ACEI (captopril) on renal hemodynamics and urinary excretion of proteins with different relative mass.

Methods

Experimental Protocol

Subjects

Sixteen consecutive subjects (9 men, 7 women) with mild to moderate essential hypertension and reduced renal reserve (less than 8% increase in GFR after a high-protein meal) were enrolled. All subjects were fully informed about the aims of this investigation and volunteered to participate in the study, which was authorized by the local Ethics Committee. Their mean age was 47 ± 5 years (range, 43 to 52). The known duration of
hypertension (time since first diagnosis) was 2.0 years on average (range, 0.5 to 3.0). Basal GFR ranged from 90 to 130 mL/min per 1.73 m². A family history of hypertension was documented in all cases. Secondary forms of hypertension were excluded by physical examination, routine blood tests, urinalysis, and isotope renography. Subjects with a history and/or clinical and/or laboratory findings of glomerulonephritis, systemic or metabolic diseases, congestive heart failure, prostatism, or bladder dysfunction were excluded. Antihypertensive drugs were withdrawn at least 2 weeks before the beginning of the study. Office diastolic blood pressure ranged from 95 to 105 mm Hg with subjects in the supine position on three consecutive occasions.

Study Design

At 1-week intervals, each subject underwent the following four treatments: (1) low-protein meal, (2) high-protein meal, (3) high-protein meal plus oral nifedipine, and (4) high-protein meal plus oral captopril. Only those subjects showing a blunted response to a meat meal underwent subsequent treatments with a balanced design (Latin squares). A "blunted response" was defined as an increase in GFR not exceeding the coefficient of variation of baseline values (8%). The low-protein meal consisted of Italian pasta (0.2 g protein/kg body wt). The high-protein meal provided 1.3 g protein/kg body wt in the form of cooked red meat. The sodium content of the meals was approximately 40 mEq. Captopril (50 mg, 0.6 to 0.8 mg/kg body wt) or nifedipine (20 mg, 0.2 to 0.3 mg/kg body wt) was administered 20 minutes before the meal. Owing to the existence of a circadian rhythm for most of the studied parameters, all experiments were carried out at the same time of day. Meals were given at noon and were eaten over a 20-minute period. To prevent interference caused by physical activity, subjects remained recumbent throughout the study period and were allowed to stand only to void.

During washout and study periods, all subjects followed a diet with known intakes of protein (1 g/kg body wt per day), calories (30 kcal/kg body wt per day), and salt (NaCl, 2 g/d). Urinary excretions of urea and sodium were measured on 24-hour urine samples collected during the last 3 consecutive days preceding the beginning of the study and on each posttest day during the study period to check diet compliance. Variations in urea and sodium excretions up to 10% and 20%, respectively, were regarded as acceptable throughout the study.

Sample Collection and Laboratory Procedures

On the experimental day, subjects were admitted to the hospital at 9 AM after an overnight fast. At 10 AM, an intravenous priming dose of 60% iothalamate meglumine (Bracco Chemical Industry) and p-aminohippuric acid (Monico Laboratories) was administered, followed by continuous infusion to achieve steady plasma levels. An intravenous heparin-filled needle was placed in the contralateral forearm for blood sampling. The subjects were then encouraged to drink water (3 mL/kg body wt per hour) to ensure adequate diuresis.

Two exactly timed urine collection periods of 120 minutes each were obtained after meals. Blood samples were drawn at the midpoint of each urine collection period. Urine was collected by spontaneous voiding. All samples were frozen and stored at −20°C until assay, and each subject's samples were processed within the same run.

Urine and serum samples were tested for iothalamate, p-aminohippuric acid (PAH), sodium, total protein, immunoglobulin G (IgG), albumin, α₂-microglobulin (A₂-M), retinol binding protein (RBP), and β₂-microglobulin (B₂-M). Sodium was measured in serum and urine by flame photometry. Urinary and serum concentrations of iothalamate and PAH were determined by a high-performance liquid chromatographic micromethod. Urinary total protein and albumin were assessed by the Heremans colorimetric and the Laurell electroimmunodiffusion methods, respectively, as previously described. Serum total protein and albumin were measured with an autoanalyzer (Scalvo) by colorimetric methods based on the biuret EDTA and bromcresol green reactions, respectively. Measurements of IgG and A₁-M were performed in serum and concentrated urine by single radial immunodiffusion (Nor- and LC-Partigen, Behringwerke AG). Urine samples were concentrated in a speed-vacuum concentrator (S̄Sı Speedvac System, Savant). Protein recovery by this concentration method was more than 99%. Enzyme-linked immunosorbent assay was used to measure urinary and serum RBP and B₂-M.

Pulse rate was taken and blood pressure recorded by the same observer at 1-hour intervals throughout the entire study period. A standard mercury sphygmomanometer was used to record systolic (first phase) and diastolic (fifth phase) blood pressures.

Calculations

GFR and RPF were assessed by iothalamate and PAH clearances, respectively. Clearance values were adjusted for a body surface area of 1.73 m². RPF was estimated as PAH clearance/extraction ratio of hippuran (assumed as 0.85). The FF was given as the ratio of GFR to RPF. Renal blood flow (RRF) was calculated as RPF/(1–hematocrit). Renal vascular resistance (RVR) was calculated as the ratio of mean arterial pressure to RBF.

Urinary excretion rates and fractional clearances of endogenous proteins with a wide range of molecular weights and sizes (B₂-M: 11.8 kD; RBP: 21.4 kD; A₂-M: 31 kD; albumin: 66.3 kD; IgG: 150 kD) were assessed. Fractional clearance was calculated as the ratio of the urinary clearance of a protein to GFR. The renal handling of three smaller proteins, B₂-M, RBP, and A₁-M, was determined to quantify protein reabsorption rates. Reabsorption rate was calculated by subtracting the amount of the protein excreted from the amount filtered, assuming no restriction to filtration. Fractional excretion of sodium (FESNa) was determined as sodium clearance/GFR and was expressed as a percent of GFR.

A single mean value was obtained in each subject from two determinations for all measurements. Mean arterial pressure was calculated as diastolic pressure plus one third pulse pressure.

Statistics

Statistical analysis was primarily based on repeated measures ANOVA. The ANOVA model was adapted to a Latin square randomized blocks design with repeated measurements between conditions. If ANOVA showed significant effects of treatments, additional ANOVAs were carried out to test differences between conditions. A probability value less than .05 was considered to be statistically significant. Data are presented as mean±SEM.

Results

Protein Excretion

Table 1 shows mean values of serum concentrations and urinary excretion rates of all the investigated proteins after a low-protein meal and after an oral protein load given alone or together with either the CaCB or ACEI. Compared with the low-protein meal, the high-protein meal alone had negligible effects on protein levels in both serum and urine. Serum concentrations of total protein and IgG displayed slight but significant rises after the high-protein meal plus nifedipine compared with the high-protein meal alone (+5%, P=.0078 and +7%, P=.027, respectively), whereas serum concentrations of albumin, A₁-M, RBP, and B₂-M did not change. Urinary protein excretion rates observed after the high-protein meal plus nifedipine were significantly described.
TABLE 1. Serum Concentrations and Urinary Excretion Rates of Total Protein, Immunoglobulin G, Albumin, α1-Microglobulin, Retinol Binding Protein, and β2-Microglobulin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-Protein Meal</th>
<th>High-Protein Meal</th>
<th>High-Protein Meal Plus Nifedipine</th>
<th>High-Protein Meal Plus Captopril</th>
<th>ANOVA (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentration</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP, g/dL</td>
<td>6.4±0.1</td>
<td>6.5±0.1</td>
<td>6.8±0.1†</td>
<td>6.7±0.1</td>
<td>&lt;.009</td>
</tr>
<tr>
<td>IgG, g/L</td>
<td>12.2±0.5</td>
<td>12.2±0.4</td>
<td>13.0±0.4*</td>
<td>12.6±0.5§</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>A, g/dL</td>
<td>4.0±0.1</td>
<td>4.1±0.1</td>
<td>4.2±0.1</td>
<td>4.0±0.1§</td>
<td>&lt;.015</td>
</tr>
<tr>
<td>A1-M, mg/dL</td>
<td>2.6±0.1</td>
<td>2.6±0.1</td>
<td>2.6±0.1</td>
<td>2.6±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>RBP, mg/L</td>
<td>44.2±5.5</td>
<td>48±2.1</td>
<td>47±1.8</td>
<td>46±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>B2-M, mg/L</td>
<td>2.0±0.2</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
<td>2.1±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary excretion rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP, µg/min</td>
<td>44±5.5</td>
<td>40±4.5</td>
<td>64±8.6†</td>
<td>39±3.9§</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>IgG, µg/min</td>
<td>2.8±0.3</td>
<td>3.1±0.4</td>
<td>4.9±0.3†</td>
<td>2.3±0.2§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>A, µg/min</td>
<td>9.4±1.3</td>
<td>9.2±1.5</td>
<td>11.5±1.6*</td>
<td>7.2±0.9§</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>A1-M, µg/min</td>
<td>3.2±0.5</td>
<td>3.4±0.4</td>
<td>6.0±0.6‡</td>
<td>3.1±0.4§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>RBP, ng/min</td>
<td>67±13</td>
<td>53±8.8</td>
<td>78±13*</td>
<td>48±7.7</td>
<td></td>
</tr>
<tr>
<td>B2-M, ng/min</td>
<td>187±35</td>
<td>232±52</td>
<td>352±58*</td>
<td>153±21*</td>
<td>&lt;.0002</td>
</tr>
</tbody>
</table>

TP indicates total protein; IgG, Immunoglobulin G; A, albumin; A1-M, α1-microglobulin; RBP, retinol binding protein; and B2-M, β2-microglobulin. Values are mean±SEM.

*P<.05, †P<.01 vs high-protein meal alone.
‡P<.01, §§P<.001 vs high-protein meal plus nifedipine.

Increased compared with the high-protein meal alone (total protein: +60%, P=.0075; IgG: +58%, P=.0019; albumin: +25%, P=.046; A1-M: +76%, P=.0002; RBP: +47%, P=.023; B2-M: +52%, P=.021). After the high-protein meal plus captopril, urinary excretion rates of IgG, albumin, and B2-M were decreased compared with the high-protein meal alone (−26%, P=.022; −22%, P=.028; and −34%, P=.029, respectively); no significant differences were observed in excretion rates of total protein, RBP, and A1-M.

Table 2 shows mean values of protein fractional clearances as well as absolute reabsorption rates of low molecular weight proteins. Compared with the low-protein meal, the fractional clearances and calculated reabsorption rates of all proteins were not significantly affected by the high-protein meal alone. Fractional clearances of IgG, A1-M, and B2-M were higher after the high-protein meal plus nifedipine than after the high-protein meal alone (IgG: +30%, P=.043; A1-M: +58%, P=.0011; B2-M: +39%, P=.039), whereas fractional clearances of RBP and albumin were unaffected. No significant differences were found between the protein fractional clearances after the high-protein meal plus captopril and those after the high-protein meal alone.

TABLE 2. Fractional Clearances of Immunoglobulin G, Albumin, α1-Microglobulin, Retinol Binding Protein, and β2-Microglobulin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-Protein Meal</th>
<th>High-Protein Meal</th>
<th>High-Protein Meal Plus Nifedipine</th>
<th>High-Protein Meal Plus Captopril</th>
<th>ANOVA (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional clearance</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IgG/lot, ×10⁻⁶</td>
<td>1.99±0.25</td>
<td>2.18±0.31</td>
<td>2.84±0.20*</td>
<td>1.79±0.19§</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>A/lot, ×10⁻⁶</td>
<td>2.00±0.29</td>
<td>1.90±0.37</td>
<td>2.05±0.07</td>
<td>1.69±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>A1-M/lot, ×10⁻⁴</td>
<td>1.05±0.13</td>
<td>1.06±0.11</td>
<td>1.68±0.13†</td>
<td>1.09±0.11§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>RBP/lot, ×10⁻⁶</td>
<td>1.31±0.25</td>
<td>0.93±0.16</td>
<td>1.25±0.21</td>
<td>10.5±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>B2-M/lot, ×10⁻³</td>
<td>0.95±0.20</td>
<td>1.09±0.23</td>
<td>1.52±0.30*</td>
<td>0.89±0.16‡</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Reabsorption rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1-M, mg/min</td>
<td>2.84±0.14</td>
<td>3.00±0.13</td>
<td>3.28±0.11*</td>
<td>2.62±0.12§</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td>RBP, mg/min</td>
<td>4.83±0.36</td>
<td>5.40±0.34</td>
<td>5.96±0.31*</td>
<td>4.62±0.21‡</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>B2-M, mg/min</td>
<td>0.22±0.02</td>
<td>0.21±0.02</td>
<td>0.25±0.03†</td>
<td>0.21±0.03‡</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

Definitions are as in Table 1; and lot, iohthalamate. Values are mean±SEM. Reabsorption rates assume sieving coefficient as 1.

*P<.05; †P<.01 vs high-protein meal alone.
‡P<.01, §§P<.001 vs high-protein meal plus nifedipine.
Nifedipine administration was associated with a significant increase in the absolute reabsorption rates of A1-M (+9%, P=.042), RBP (+10%, P=.026), and B2-M (+20%, P=.01) compared with the high-protein meal alone. The reabsorption rates of A1-M and RBP were lower after the high-protein meal plus captopril than the high-protein meal alone (-13%, P=.0051 and -14%, P=.03, respectively), whereas the reabsorption rate of B2-M was not statistically different.

Direct comparison between nifedipine and captopril magnified their different effects, causing a significant deviation from control values (Tables 1 and 2).

Systemic and Renal Hemodynamics

Table 3 shows mean values of mean arterial pressure, pulse rate, GFR, RPF, FF, RBF, and RVR. Systemic and renal hemodynamics observed after the low-protein meal were unaffected after the high-protein meal alone. Both antihypertensive drugs induced significant decreases in the absolute reabsorption rates of A1-M and RBP, whereas the levels attained after nifedipine administration were lower than those after captopril (P=.014). An increase in GFR, RPF, and RBF was apparent after the high-protein meal plus nifedipine compared with the high-protein meal alone (+10%, P=.045; +9%, P=.022; +10%, P=.019, respectively). GFR decreased (-21%, P=.024) after the high-protein meal plus captopril compared with the high-protein meal alone. FF remained unchanged under the four experimental conditions. Compared with the high-protein meal alone, RVR fell (-22%, P=.0001) after the high-protein meal plus nifedipine, whereas it was unchanged after the high-protein meal plus captopril.

When a direct comparison was made between the two investigated drugs, almost all parameters showed significant differences.

Water and Sodium Excretions

As shown in Table 4, no significant differences were observed in urine flow rate, urinary sodium excretion rate, and FE\textsubscript{Na} between the low- or high-protein meal alone and the high-protein meal plus captopril. After nifedipine administration, clear-cut increases in the values of the above parameters were seen compared with the high-protein meal alone (urine flow: +68%, P=.0051; sodium excretion: +119%, P=.0001; FE\textsubscript{Na}: +84%, P=.0002).

Discussion

Five percent to 15% of patients with essential hypertension seem to develop clinical proteinuria and a significant reduction in renal function.\textsuperscript{19-21} This relatively low prevalence of renal involvement in the face of a frequent development of cardiovascular disease in essential hypertension\textsuperscript{22} is consistent with the efficiency of adaptive mechanisms protecting the glomerulus against the detrimental effects of capillary hypertension.\textsuperscript{23} Although CaCBs and ACEIs have different effects on renal hemodynamics,\textsuperscript{24,25} the same degree of renal protection is attributed to both drug type.\textsuperscript{4,6} In this short-term study, we have shown that, compared with a high-protein meal alone, nifedipine but not captopril decreased RVR and increased both GFR and RBF. Glomerular hyperfiltration would therefore result from short-term nifedipine administration. On the other hand, the reported protective effect of CaCBs may depend on factors other than CaCBs administration.

Table 4. Urine Flow and Urinary and Fractional Excretion of Sodium

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-Protein Meal</th>
<th>High-Protein Meal</th>
<th>High-Protein Meal Plus Nifedipine</th>
<th>High-Protein Meal Plus Captopril</th>
<th>ANOVA (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U\textsubscript{v}, mL/min</td>
<td>2.6±0.2</td>
<td>2.2±0.2</td>
<td>3.7±0.4*</td>
<td>2.3±0.2§</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>U\textsubscript{Na}, mmol/min</td>
<td>136±12</td>
<td>157±14</td>
<td>329±26§</td>
<td>159±9.3§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FE\textsubscript{Na}, %</td>
<td>0.82±0.1</td>
<td>0.93±0.1</td>
<td>1.71±0.1</td>
<td>1.01±0.1</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

U\textsubscript{v}, urine flow; U\textsubscript{Na}, urinary excretion of sodium; and FE\textsubscript{Na}, fractional excretion of sodium. Values are mean±SEM.

\(*P<.01; \#P<.001; \$P<.0001\) vs high-protein meal alone.

\(\textsuperscript{§}P<.001\) vs high-protein meal plus nifedipine.
than glomerular hemodynamics, such as prevention of calcium salt deposition, inhibition of platelet aggregation, and/or reduced metabolic activity.

In essential hypertensive patients, the renal functional reserve (ie, the increase in GFR under a short-term protein load) seems to be variable, conceivably because of individual differences in renal hemodynamics. No obvious explanation is available for the reasons why some hypertensive individuals exhibit a reduced renal reserve. Although in our subjects the known onset of hypertension dated from 0.5 to 3 years, we cannot exclude the possibility that the actual duration of hypertension may have been longer, and therefore anatomic as well as functional alterations of renal vasculature might have occurred. Since renal responses to vasodilator stimuli depend on basal renal hemodynamics,7 in our experiments nifedipine and captopril were administered together with an oral protein load to compensate for possible confounding differences in individual renal functional reserve.

Microalbuminuria is frequently observed in essential hypertension in the absence of overt clinical nephropathy,28 and various studies have shown a significant correlation between albumin excretion rate and blood pressure levels, suggesting that microalbuminuria might be a consequence of hypertension.29,30 A reduced renal functional reserve in hypertensive patients showing microalbuminuria has also been suggested.8 Although no evidence has been produced that microalbuminuria may predict the development of overt renal damage in essential hypertension, an increased mesangial protein load caused by hyperfiltration may turn out to be detrimental to glomerular function in the long term.

In our subjects with essential hypertension and normal renal function, albumin and IgG excretion rates rose during nifedipine but not during captopril. Since changes in the filtered load of a given macromolecule lead to proportional changes in the excretion rate of that macromolecule if tubular transport is not affected, a comparison between absolute urinary excretion rates (Table 1) and fractional clearances (Table 2) of studied proteins may highlight the relative role of changes in GFR and tubular handling associated with each treatment. The increase in IgG fractional clearance after nifedipine suggests that variations in glomerular selectivity and/or tubular reabsorption occur in addition to changes in filtered load; however, an increase in the ratio between fractional clearances of IgG and albumin after nifedipine compared with the other experimental conditions (Figure) may reflect a reduced glomerular selectivity toward the relative mass of macromolecules. However, we cannot exclude the possibility that the immunochemical methods used to quantify IgG may actually measure protein fragments in the low molecular weight range. Should this be the case, the ratio of IgG to albumin fractional clearance would be affected not only by filtered load but also by tubular reabsorption. Compared with the protein meal alone, captopril decreased albumin and IgG excretion rates without changing the fractional clearances of the same proteins. These results suggest that the effect of captopril on proteinuria may be related to a parallel decrease in GFR, resulting in a reduced glomerular filtered protein load. In addition, this drug did not seem to affect glomerular selectivity toward the mass of the investigated macromolecules, as shown by the unchanged ratio of IgG to albumin clearance (Figure).

In contrast with the results reported in hypertensive nephropathic patients showing that both ACEIs and CaCBs significantly reduce urinary protein excretion,2,3,4 our data suggest that in hypertensive individuals with normal renal function, a single dose of either nifedipine or captopril differently affects the renal handling of proteins. Such findings are in agreement with previous studies showing that the urinary excretion rate of albumin is unchanged or increased by dihydropyridine CaCBs and decreased by ACEI treatment prolonged for 4 or more weeks in essential hypertensive patients without primary renal disease.31,34 In addition, preliminary results of a prospective study ongoing in our laboratory indicate that the excretion rates of proteins of different relative mass are indeed higher even after 1 month of treatment with nifedipine compared with baseline values (unpublished observations). On the other hand, Erlsey et al35 have recently shown a reduction of albumin excretion in patients with mild to moderate essential hypertension and normal renal function after 12 weeks of treatment with different antihypertensive drugs, including felodipine.

When nifedipine was administered, we observed a profound fall in both systemic mean arterial pressure and RVR; since both GFR and RPF rose in parallel, no changes were elicited in FF. Although the absence of changes in FF hinders any speculation concerning intra-glomerular pressure, it could be argued that a putative increase of hydraulic pressure within the glomerular capillaries, enhancing mostly the convective flux of high molecular weight proteins,36 may have counterbalanced the expected reduction in the traffic of macromolecules across the glomerular capillary barrier that is associated with a rise in plasma flow.37 However, CaCBs may affect the protein filtration process without changes in FF, ie, increasing the total surface area available for glomerular filtration through direct effects on mesangial cells and/or enhancing the urinary excretion of high molecular weight proteins evoking large nonselective pores by elevated glomerular capillary pressure as reported by Yoshioka et al38 in experimental models.
we observed in the urinary excretion of the proteins after captopril does not appear to be necessarily linked to its antihypertensive activity, because nifedipine increased the excretion rate of the same proteins despite a more pronounced antihypertensive effect. On the other hand, captopril decreased both GFR and RPF without changing FF. Our results therefore suggest two possible mechanisms to explain the beneficial effects of captopril on proteinuria despite unchanged FF: ACEIs may reduce proteinuria by decreasing the glomerular filtered load of proteins, by preserving the selectivity of the glomerular basement membrane, or both.

Although ACE inhibition is usually associated with a clear-cut increase in RPF, we did not observe such a renal vasodilation after the high-protein meal plus captopril. An interaction between the effects of the high-protein meal and the ACEI on renal hemodynamics may have occurred, thus preventing a captopril-induced increase in renal perfusion. Although no significant changes in either GFR or RPF were elicited in our subjects by a protein meal alone, the study design did not allow the assessment of meal-by-treatment interactions.

On the other hand, it has been shown that captopril has no effects on the increase in RPF following a meat meal in conscious dogs, and Slomowitz et al. interestingly reported that pretreatment with captopril did not affect the increase in both RPF and GFR brought about by amino acid infusion in healthy humans. Other researchers have reported thatenalapril blunted the increase in creatinine clearance following a meat meal in humans and attenuated glycine-induced renal hyperemia and hyperfiltration in rats.

Captopril was administered 20 minutes before the meal; the drug is rapidly absorbed and begins to exert its pharmacological effects within 15 minutes of ingestion. Maximal blood levels of captopril do not occur until approximately 1 hour after administration, and bioavailability might be reduced by food; hence, it is probably fair to state that the effective dose of captopril was lower compared with that of nifedipine. Thus, we can speculate that our results with captopril would have been more evident if the renal vascular effects of the two antihypertensive drugs had been exactly synchronized.

The tubular reabsorption of low molecular weight proteins is thought to occur by a high-capacity, low-affinity transport system. Therefore, over a wide range of filtered loads, percent tubular uptake of low molecular weight proteins are nearly constant, and increases in filtered loads lead to proportional increases in urinary excretion rates. Since in the present study nifedipine increased the absolute reabsorption rates less than the fractional clearances of low molecular weight proteins (Table 2), one could argue that dihydropyridine CaCBs may impair tubular reabsorption to some extent. Three hypotheses might explain such an abnormal glomerulotubular balance of low molecular weight proteins following nifedipine administration: (1) direct interference on the transport system of the proximal tubule; CaCBs also affect tubular reabsorption of uric acid, sodium, phosphate, calcium, and magnesium; (2) a drag solvent effect caused by the high urine flow rate, which has been observed after calcium channel blockade in the present and previous studies; and (3) competition between low and high molecular weight proteins for tubular uptake. In our subjects, captopril administration decreased both fractional clearances and absolute reabsorption rates of low molecular weight proteins. This finding supports the hypothesis that the effects of ACEIs on renal protein handling are linked to changes in glomerular filtered load rather than in tubular function.

Although the behavior of the absolute reabsorption rates of A1-M and RBP is similar to that of B2-M, the values of A1-M and RBP tubular uptakes were abnormally higher (13- and 23-fold on average, respectively) than that of B2-M in all four experimental conditions. This could be due to the fact that the glomerular sieving coefficients of A1-M and RBP obtained in experimental studies are lower than that of B2-M; thus, calculation of filtered loads of A1-M and RBP, assuming their glomerular sieving coefficients as approximating 1, leads to an overestimation of the absolute tubular reabsorptions of the two proteins.

It must be pointed out that, because the subjects enrolled in this study displayed basal hyperfiltration (i.e., reduced renal reserve), they are not representative of the entire hypertensive population. Moreover, drugs were acutely administered together with an oral protein load to abolish confounding effects of variable renal reserve in different subjects. Thus, the design of the present study does not allow either generalization of our results to all hypertensive patients or the extrapolation from short- to long-term effects of the antihypertensive treatment.

In summary, this study performed in essential hypertensive subjects with normal GFR but reduced renal reserve shows that the short-term administration of nifedipine but not captopril raised both GFR and RPF by lowering RVR and, as a trade-off, increased the urinary protein excretion rate by acting on both glomerular selectivity and tubular reabsorption.

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