Direct Comparison of the Effects of Valsartan and Amlodipine on Renal Hemodynamics in Human Essential Hypertension

Christian Delles, Arnfried U. Klingbeil, Markus P. Schneider, Renate Handrock, Gottfried Weidinger and Roland E. Schmieder

**Background:** To elucidate the renoprotective mechanism of AT₁-receptor blockers, we compared the effects of the AT₁-receptor blocker valsartan with those of the calcium channel blocker amlodipine on renal hemodynamics and microcirculation.

**Methods:** A total of 58 patients (50.2 ± 9.0 years) with mild to moderate essential hypertension were included in a randomized, double-blind study to receive either valsartan (80 to 160 mg) or amlodipine (5 to 10 mg). Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured before and after 8 weeks of treatment. Glomerular hydrostatic pressure (P Glo ) and resistances of the afferent (R A ) and efferent (R E ) arterioles were calculated according to the Gomez formulas.

**Results:** Blood pressure control was similar in both groups. RPF did not change with either treatment. In contrast, GFR increased with amlodipine (+8 ± 14 mL/min; P < .01) but was preserved with valsartan. Amlodipine caused a more marked increase in the R E /R A ratio than valsartan (+0.26 ± 0.26 v +0.13 ± 0.24, P < .05), which was paralleled by an increase in P Glo in patients treated with amlodipine (+1.9 ± 4.3 mm Hg; P < .05) but not in those treated with valsartan.

**Conclusions:** At similar blood pressure control, valsartan maintained GFR and P Glo , whereas amlodipine led to glomerular hyperfiltration and an increase in P Glo . The results might explain the favorable renal outcome with AT₁-receptor blocker therapy. Am J Hypertens 2003;16:1030–1035 © 2003 American Journal of Hypertension, Ltd.

**Key Words:** Angiotensin II receptor blocker, calcium channel blocker, renal hemodynamics, humans.

Delayed the progression of renal disease is an important goal in the treatment of arterial hypertension. Clinical trials have demonstrated disparate effects of various antihypertensive agents on renal outcome. Recently, angiotensin AT₁-receptor blockers (ARB) have been found renoprotective in patients with overt and incipient diabetic nephropathy. In terms of progression of renal disease and reduction of albuminuria, superiority of ARB over dihydropyridine calcium channel blockers has been demonstrated in hypertensive patients with type 2 diabetes.

Several investigators have examined the effects of ARB and calcium channel blockers on renal hemodynamics. In general, dihydropyridine calcium channel blockers dilate the afferent glomerular arteriole, whereas effects on the efferent arteriole appear to be substance-specific. An increase in filtration fraction by the calcium channel blocker amlodipine is a consistent finding in most studies but not in all. ARB predominantly dilate the efferent but also the afferent glomerular arteriole. In contrast to amlodipine, ARB have been found to decrease filtration fraction in humans in most studies; however, no change was observed in other studies. These observations emphasize the need to compare directly the effects of an ARB and a calcium channel blocker on renal hemodynamics in humans.

**Materials and Methods**

**Study Population**

Patients between 35 and 65 years of age were eligible for the study if they had mild to moderate essential hypertension (diastolic blood pressure ≥95 mm Hg but <115 mm Hg, obtained with a standard sphygomanometer after 5
min of rest). Patients meeting these criteria underwent a thorough examination including medical history assessment, physical examination, 12-lead electrocardiography, routine laboratory examination, and 24-h urine sampling. Exclusion criteria were the presence of any form of secondary hypertension; any irreversible end-organ damage due to arterial hypertension; any significant disease other than mild essential hypertension; cigarette smoking within 1 year before the study; hypercholesterolemia (LDL cholesterol >160 mg/dL); serum creatinine >150% of the upper normal value; and a dip stick test (Albstix; Bayer, Leverkusen, Germany) positive for albumin. Sodium intake was assessed from urinary sodium excretion (24-h urine collection). A total of 58 subjects finally were included in the study after giving written informed consent. Baseline characteristics of the participants are shown in Table 1.

### Study Design

The study protocol was approved by the Clinical Investigation Ethics Committee of the University of Erlangen-Nürnberg. After entry into the study, previous antihypertensive therapy was discontinued in the participants for 4 weeks. After 2 weeks of washout all participants received placebo once daily for 2 weeks. An initial hemodynamic examination was performed after the placebo run-in phase (as discussed later here). Participants were then assigned to either treatment with valsartan 80 mg once per day or amlodipine 5 mg once per day. Assignment to active treatment was randomized and double-blind. After 4 weeks of treatment, blood pressure (BP) was measured, and the dose of active treatment was doubled (160 mg valsartan once per day and 10 mg amlodipine once per day, respectively) if diastolic BP was still > 90 mm Hg. Based on this criterion, the amlodipine dose was increased in 19 patients and the valsartan dose increased in 16 patients. After another 4 weeks of treatment (ie, 8 weeks of total double-blind treatment), a second hemodynamic examination was performed. Participants were asked to take the study medication at a fixed time in the morning. All analyses of the effect of treatment on hemodynamic parameters were made in comparison to the placebo phase.

### Determination of Renal Hemodynamics

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were determined by constant input clearance technique with para-aminohippurate (Nephrotest; Merck, Sharp & Dohme, Hertfordshire, UK) and inulin (Inutest; Fresenius, Linz, Austria), respectively, as suggested by Cole et al\(^\text{15}\) and as previously described in detail.\(^\text{16}\) In brief, after administration of a loading dose, a steady state between infusion and renal excretion of the tracer substances was reached after 120 min. Blood samples for the determination of para-aminohippurate and inulin to assess baseline RPF and GFR were drawn at this time and before infusions were started. All participants drank 10 mL/kg of mineral water during the clearance studies. Blood pressure was measured with an oscillometric device (Dinamap 1846 SX; Criticon, Norderstedt, Germany) in parallel with blood sampling. Clearance studies were performed 24 h after the last intake of study medication in the morning (8 AM to 12 AM).

Blood samples were centrifuged immediately at 4°C and were stored at −21°C until measurement. Measurement of para-aminohippurate and inulin was performed after completion of the study with the investigators still unaware of active treatment (valsartan or amlodipine) in individual study participants. Details concerning the measurement of inulin and para-aminohippurate have been published previously.\(^\text{16}\) Each blood sample was measured in duplicate with a coefficient of variation of <5%.

Filtration fraction was calculated by dividing GFR by RPF. Glomerular hydrostatic pressure (\(P_{\text{Glo}}\)) and resistances of the afferent (\(R_A\)) and efferent glomerular artery (\(R_E\)) were determined according to the model established by Gomez,\(^\text{17}\) which has been recently discussed in detail by Guidi et al.\(^\text{18}\)

### Statistical Analysis

All statistical analysis was carried out using SPSS software (release 10.0; SPSS Inc., Chicago, IL). Paired and unpaired Student \(t\) tests were used for comparisons within and between the treatment regimens, respectively. Analysis of variance was used to examine the contribution of factors other than treatment allocation on changes in renal hemodynamics. Before such tests were performed, significant deviations from normal distribution were excluded by the Kolmogorov-Smirnov test. Where indicated, Pear-

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**Table 1.** Baseline characteristics of the study cohort

<table>
<thead>
<tr>
<th></th>
<th>Valsartan ((n = 29))</th>
<th>Amlodipine ((n = 29))</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>51.0 ± 8.4</td>
<td>49.4 ± 9.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.5 ± 13.9</td>
<td>83.7 ± 15.5</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ± 0.09</td>
<td>1.73 ± 0.10</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>28.0 ± 4.4</td>
<td>27.8 ± 4.0</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.95 ± 0.20</td>
<td>1.98 ± 0.22</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165 ± 14</td>
<td>160 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>102 ± 8</td>
<td>105 ± 9</td>
</tr>
<tr>
<td>Serum creatinine concentration (mg/dL)</td>
<td>0.91 ± 0.19</td>
<td>0.93 ± 0.14</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>177 ± 40</td>
<td>176 ± 58</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between the two treatment groups.
son’s correlation coefficients were calculated. A two-tailed P value < .05 was considered to be significant. All values are expressed as mean ± SD.

Results

Data on the effect of treatment on systemic and renal hemodynamic parameters are given in Table 2. Valsartan and amlodipine reduced BP by 12 ± 15/7 ± 8 mm Hg and 17 ± 11/10 ± 7 mm Hg, respectively, with no significant difference between the two treatment regimens. Also, the antihypertensive effects of valsartan and amlodipine were not correlated to urinary sodium excretion as a measure of sodium intake (reduction in systolic BP: r = −0.11, P = NS, and r = 0.19, P = NS, respectively; reduction in diastolic BP: r = −0.07, P = NS, and r = 0.12, P = NS, respectively).

The RPF was maintained with both valsartan and amlodipine treatment. In contrast, GFR was maintained with valsartan but increased by 8 ± 14 mL/min (P < .01) with amlodipine treatment (Fig. 1). The differences between treatment arms are statistically significant (valsartan vs amlodipine: P < .05). Consequently, valsartan did not change filtration fraction, whereas amlodipine increased it by 2.3% ± 3.0% (P < .001) with a significant difference between the two treatment regimens (P < .01). Changes in GFR and filtration fraction were only determined by allocation of treatment to valsartan or amlodipine, but were independent of changes in systolic and diastolic BP in an ANOVA.

These findings were mirrored by changes in the renal microcirculation. At similar fall of BP in the systemic circulation, valsartan increased the RE/RA ratio by 0.13 ± 0.25 (P < .01) and P Glo remained unchanged. Amlodipine increased the RE/RA ratio by 0.26 ± 0.26 (P < .001) and increased P Glo by 1.9 ± 4.3 mm Hg (P < .05) (Fig. 2). Compared to the valsartan group, the increase in the RE/RA ratio was greater in patients treated with amlodipine (P < .05) thereby explaining the disparate changes of P Glo across the treatment arms (P < .05).

Discussion

In the present study we have demonstrated disparate effects of the ARB valsartan and the calcium channel blocker amlodipine on renal hemodynamics despite similar BP control. RPF was maintained with either treatment. In contrast, at normal GFR at baseline, GFR further in-

### Table 2. Effect of treatment on systemic and renal hemodynamics, and on glomerular hydrostatic pressure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Val (n = 29)</th>
<th>P</th>
<th>Aml (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165 ± 14</td>
<td>&lt; .001</td>
<td>153 ± 17</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>102 ± 8</td>
<td>&lt; .001</td>
<td>95 ± 8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Renal plasma flow (mL/min)</td>
<td>504 ± 134</td>
<td>ns</td>
<td>517 ± 153</td>
<td>ns</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min/1.73 m²)</td>
<td>216 ± 19</td>
<td>&lt; .001</td>
<td>215 ± 20</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>filtration fraction (%)</td>
<td>23.1 ± 3.6</td>
<td>&lt; .001</td>
<td>23.0 ± 3.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>R₃ (dyne/cm²)</td>
<td>0.65 ± 0.34</td>
<td>&lt; .001</td>
<td>0.52 ± 0.20</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>P Glo (mm Hg)</td>
<td>103 ± 0.4</td>
<td>&lt; .001</td>
<td>104 ± 4.3</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*P < .05; †P < .01.
algorithms have also been studied by other research groups. For instance, nifedipine,23,24 amldopine,7,9 nitrendipine,24,25 and isradipine26,27 have been examined in humans. However, the results from these studies are not consistent: GFR increased in some studies8,23,25 but was maintained in others7,9,24,26,27; and RPF clearly increased with calcium channel blocker therapy in some studies9,25,26 but not in all.7,24,27 Again, results from these trials cannot be compared directly with each other, since clinical characteristics, sample size, and methods vary markedly across the trials.

We have therefore designed a randomized, parallel-group study in a homogenous cohort of hypertensive subjects without renal disease to compare directly the effects of the ARB valsartan with the dihydropyridine calcium channel blocker amldopine on renal hemodynamics. We are aware of only two studies directly comparing an ARB and a calcium channel blocker in 15 and 17 subjects, respectively.7,8 In our trial, we included 58 hypertensive subjects. However, the patient populations are quite different and therefore difficult to compare.

It is important to mention that despite titration of doses there was a numerical (but not statistically significant) difference between the antihypertensive effects of valsartan and amldopine in our study. This difference was found in systolic BP only and most probably results from our criterion for uptitration of doses of the study medication which was the achieved diastolic BP after 4 weeks of treatment. Nevertheless, changes in renal hemodynamic parameters were only dependent on treatment but not on changes in BP as indicated by the ANOVA. Of note, there was no difference in urinary sodium excretion as a measure of salt intake between the treatment groups; and, particularly in the valsartan group, there was no relation between the antihypertensive effect of treatment and urinary sodium intake.

In experimental models, the effects of ARB and calcium channel blockers have been elucidated in detail. Angiotensin II causes potent constriction of both the afferent and, even more, the efferent arterioles.10 Dihydropyridine calcium channel blockers uniformly increase the diameter of the afferent arteriole; however, amldopine did not dilate efferent arterioles in experimental models.6,28 A decrease in R\textsubscript{A} without changes in R\textsubscript{E} leads to an increase in P\textsubscript{Glo} and promotes glomerular hyperfiltration and proteinuria. Under certain conditions, glomerular hyperfiltration can even be found in early stages of human essential hypertension and is generally believed to be a first step in the development of hypertensive renal disease.16,29,30 Thus, an increase in GFR with calcium channel blockers at first glance suggests an amelioration of kidney function, but is in fact accompanied by an increase in P\textsubscript{Glo} and shear stress on the endothelium leading ultimately to proteinuria and glomerulosclerosis. In contrast, the renoprotective effect of ARB is thought to be mediated by a decrease in P\textsubscript{Glo} by predominantly dilating the efferent arteriole.31 Our data could provide a basis for the
recent finding that albuminuria in patients with diabetes mellitus type 2 is reduced with valsartan but not with amlodipine therapy. Of note, in our present study we have not measured albuminuria before and after treatment, as only patients with a negative dip stick result for albuminuria were included.

In contrast to experimental models, the human renal microcirculation cannot directly be examined. Therefore, Gomez has developed a model to calculate glomerular hemodynamic parameters from gross renal hemodynamic parameters and total serum protein concentration with some assumptions such as the presence of filtration dys-equilibrium along the glomerular capillaries. The filtration coefficient is estimated as 0.0406 mL · sec⁻¹ · mm Hg⁻¹ per kidney in this model. Recently, Black et al have shown that treatment with an angiotensin-converting enzyme inhibitor does not change total renal filtration surface area. The application of the Gomez formulas in our study clearly supports the data from experimental models. We have demonstrated that P Glo is maintained with valsartan but is increased with amlodipine. A similar finding resulted from a cross-over trial in renal transplant recipients treated with losartan and amlodipine. The ratio between R E and R A is shifted towards R E with either treatment, but this shift is more pronounced in subjects given amlodipine as compared with those given valsartan, promoting the previously mentioned increase in P Glo by amlodipine.

We are aware of the fact that the results from the Gomez formulas must not be overestimated. Like any other model using raw parameters and constants, the Gomez model does not provide any information that cannot be read from the raw parameters; in addition, it might even give false results, as is probably the case with the counter-intuitive increase in R A after amlodipine treatment. However, this model theoretically supports the experimental findings and might explain the underlying mechanism, in particular if the disparate pattern between treatment groups is compared in one double-blind, comparative study design. It is the only available method to determine glomerular hemodynamics in humans.

In summary, we have demonstrated a disparate pattern of intrarenal hemodynamics with the calcium channel blocker amlodipine causing glomerular hyperfiltration and the ARB valsartan maintaining GFR at a constant level. This disparate effect on GFR between the two antihypertensive agents was reflected by changes in P Glo with an increased P Glo for amlodipine. Clearly, our data do not provide evidence that calcium channel blockers have a negative impact on renal hemodynamics when combined with other antihypertensive agents, inasmuch as we only evaluated the effect of monotherapy. Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggest that if BP is well controlled (in most cases only by combination therapy), the negative effects of calcium channel blockers on cardiovascular events might be outweighed. However, our data provide evidence of pathogenetic mechanisms for the recent findings from clinical trials that demonstrated superiority of ARB over calcium channel blockers as the primarily chosen antihypertensive agents to delay the progression of renal disease.

Acknowledgments
We thank I. Fleischmann for excellent assistance in performing the experiments. We also thank O. Alter for performing laboratory measurements.

References


