Effects of the Angiotensin II Antagonist Valsartan on Blood Pressure, Proteinuria, and Renal Hemodynamics in Patients with Chronic Renal Failure and Hypertension

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Abstract. Angiotensin II receptor antagonists have become clinically available for the treatment of arterial hypertension. Presently, there is little information about their effects on BP, proteinuria, and renal function in patients with moderate or advanced renal failure. This study examines the effects of the angiotensin II antagonist Valsartan (80 mg/d) on proteinuria and glomerular permselectivity in patients with chronic renal failure during a 6-mo treatment, using a double-blind, randomized, placebo-controlled study (treatment group [V-group]: n = 5, age 57 ± 7 yr, serum creatinine 365 ± 122 µmol/L; placebo group [P-group]: n = 4, age 62 ± 11 yr, serum creatinine 346 ± 61 µmol/L). Study parameters included BP, 24-h proteinuria, GFR, and effective renal plasma flow (ERPF) as determined by inulin and para-aminohippurate clearance. Changes in glomerular permselectivity were assessed by measuring the fractional clearances of neutral dextrans by HPLC gel-permeation chromatography. Valsartan lowered the mean arterial pressure on average by 13 ± 7 mmHg during the 6-mo treatment (P < 0.05). GFR and ERPF remained almost unchanged. However, after 6 mo of Valsartan treatment, proteinuria was reduced by 396 ± 323 mg/24 h (26 ± 18%) and albuminuria by 531 ± 499 mg/24 h (41 ± 21%) with regard to baseline values (P < 0.05). In the P-group, both proteinuria and albuminuria increased slightly with time (by 30 ± 43% and 30 ± 54%, respectively, NS). The fractional clearances of high molecular weight dextrans >66 Å were significantly reduced after 6 mo of Valsartan treatment (P < 0.05), indicating a reduction of the glomerular shunt volume by 54 ± 20% (P < 0.05) according to the model of Deen et al. (Am J Physiol 249: 347–389, 1985). The mean pore size radius of the glomerular membrane remained unchanged. This effect was independent of glomerular hemodynamic changes. Valsartan persistently lowered proteinuria in patients with chronic renal failure. Although GFR and ERPF remained nearly stable, this effect could be attributed to an improvement in glomerular permselectivity.

Renal disease is the most important cause of secondary hypertension and is prevalent in about five to 10 out of 100 patients (1). Although the mechanisms that cause elevated BP in various conditions of glomerular or tubular disease are not completely understood, an activated renin-angiotensin-aldosterone system as related to body fluid and sodium status seems to be an important underlying pathogenetic factor (2,3). It has been clearly shown in prospective studies that poor BP control is a main risk factor for the progression of renal disease (4,5). On the other hand, strict control of BP in these patients is appropriate to slow down the decline in renal function.

During the past decade, angiotensin-converting enzyme inhibitors (ACEI) have become successful and widespread agents in the treatment of arterial hypertension, lowering BP by inhibiting the conversion of angiotensin I to angiotensin II (AngII). Prospective multicenter studies on patients with diabetic nephropathy and nondiabetic renal disease demonstrated an antiproteinuric, especially antialbuminuric, effect of ACEI (6–9). ACE inhibitors also protected from hypertension-induced glomerular sclerosis in animal models (10,11). By lowering transglomerular hydraulic pressure, proteinuria was reduced (10,12). But another specific, nonhemodynamic effect on glomerular permselectivity has also been described (11,13,14). Changes in the glomerular sieving coefficient have been specifically measured by the clearance of neutral dextrans (11,15). Thereby, ACE inhibition or AngII receptor inhibition (in animals) resulted in a partial restoration of glomerular size selectivity (8,11,15).

The clinical use of ACEI is sometimes complicated by side effects such as dry cough and, rarely, angioneurotic edema (16,17). Most of these side effects are due to the inhibition of Bradykinin degradation (18,19).

AngII type 1 receptor antagonists are a class of drugs derived from imidazole-5-acetic acid. Losartan is the most widely studied receptor antagonist up to now and is comparable to ACEI in BP lowering effect in patients with essential hypertension (20,21). No severe clinical side effects of losartan or Valsartan (a nonheterocyclic AngII antagonist) have been re-
ported thus far (20,22–24). Direct blocking of the AngII type 1 receptor binding site by AngII antagonists may provide the advantage of a more specific blocking of AngII action by additionally inhibiting the AngII generation caused by tissue enzymes (e.g., chymase or chymostatin-sensitive AngII-generating enzyme) (25).

Although there is an increasing number of reports about the potency of AngII receptor antagonists to lower BP in essential hypertension (20,22), there is not much information about their antihypertensive and antiproteinuric effects in patients with arterial hypertension and impaired renal function. Only Gansevoort et al. (26) have described BP lowering effects and influence on renal function in these patients by losartan. Therefore, we started a prospective, randomized, placebo-controlled double-blind study using the AngII antagonist Valsartan in hypertensive patients with advanced renal failure to investigate the antiproteinuric effect of Valsartan and the underlying effects on renal hemodynamics and glomerular size selectivity. We followed an A-B study design observing a run-in period of 3 mo and a treatment phase of 6 mo with repeated follow-up examinations to document the effect of Valsartan or placebo treatment compared with baseline. The placebo group was included to discriminate the effects of Valsartan from changes based on the spontaneous course of renal disease.

Materials and Methods
Patients and Study Design

Nine patients of mean age of 59 ± 9 yr with hypertension (mean arterial pressure [MAP] 113 ± 7 mmHg) and moderate renal failure (serum creatinine 357 ± 94 μmol/L) were enrolled in the study. The underlying renal diseases were IgA nephropathy (n = 2), autosomal dominant polycystic kidney disease (proteinuria >500 mg/24 h, with a significant portion of glomerular proteinuria [type V] according to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, n = 2), benign nephrosclerosis (not due to diabetic nephropathy, n = 3), membranous glomerulonephritis (n = 1), and mesangiolipoproliferative glomerulonephritis (n = 1) (Table 1).

Inclusion criteria were: (1) arterial hypertension, sitting diastolic BP <105 mmHg, and systolic BP <180 mmHg at visit 4 (Figure 1); (2) stable renal insufficiency with a serum creatinine between 200 and 600 μmol/L; (3) stable proteinuria of at least 500 mg/24 h; (4) no increase of serum creatinine over 30% within 6 mo before the trial; and (5) no history of heart failure, malignancy, or any disorders requiring immunosuppressive therapy.

Main efficacy parameters of the study were the reduction in proteinuria and the changes in renal hemodynamics and glomerular perme selectivity. Secondary parameters were the changes in BP, electrolyte excretion, and metabolic patterns. A 3-mo baseline period was compared with a 6-mo Valsartan or placebo treatment phase.

The trial started with the 3-mo run-in period (Figure 1). BP control was maintained by concomitant antihypertensive drugs including: β-blockers, α-blockers, calcium antagonists, clonidine, and minoxidil. ACE inhibitors were withdrawn 4 wk before the onset of the trial and substituted with another antihypertensive drug if necessary. Furosemide treatment was allowed if necessary and continued throughout the study. Concomitant medication was not changed unless marked changes in BP were registered (e.g., dose reduction of concomitant antihypertensives in two patients of the V-group after the onset of Valsartan treatment, and additional treatment with urapidil in one patient of the P-group due to increasing BP) (Table 1). After the run-in period, a randomized, double-blind treatment was started (n = 5 in the verum group [V] receiving Valsartan and n = 4 in the placebo group [P]). All patients were given 80 mg of Valsartan or placebo once a day in the morning. The trial treatment phase lasted 6 mo with repeated examinations every 4 wk (Figure 1). By repeated measurements over a 9-mo period, statistical power was increased by reducing the effect of short-term variations. The allocation of the patients to the P- or V-group was revealed to the physician and the patients only after all patients had completed the trial.

The trial started with 10 patients, and nine patients completed the trial. One patient in the V-group dropped out due to an accelerated increase in serum creatinine that did not respond to drug discontinuation. Reference values concerning parameters of glomerular size selectivity were evaluated by additionally investigating a group of 10 healthy volunteers (age 24 ± 2 yr) with inulin and dextran clearances. The study was approved by the ethics committee of the Heinrich Heine University.

Parameters Measured

BP was determined according to Riva Rocci by two measurements in the sitting position after 5 min at rest. All measurements were made by the same investigator on the patient’s dominant arm between 8 a.m. and 11 a.m. MAP was calculated as:

\[
\text{Systolic pressure} \times 2 \times \text{Diastolic pressure} \div 3
\]

Effective renal plasma flow (ERPF) and GFR were measured according to the clearance of sodium para-aminobiphenyl (PAH) (Merck & Co.) and inulin (Inuest 25%, Laevosan, Linz, Austria). Briefly, the following procedure was used: After a bolus infusion of 6.5 g of PAH and 2.5 g of inulin, a constant dose of PAH (4 g/h) and inulin (dose-dependent on plasma creatinine concentration, i.e., between 1.5 and 0.1 g/h) was infused over 2.5 h. Dextran 40 (Thomae-dextr 40, Delta-Pharma, Pfullingen, Germany) and Dextran 70 (Longasteril 70, Fresenius, Bad Homburg, Germany) were mixed and given each at a dose of 50 mg/kg body wt over 15 min after the PAH and inulin bolus injection. After an equilibration period of 30 min, five exactly timed serum samples were drawn every 30 min, and two 1-h urine samples were collected by spontaneous voiding. Diuresis was promoted by drinking tea or tap water. GFR and ERPF were calculated as the inulin or PAH urine clearance averaged for the two collection periods and corrected for body surface area.

Laboratory Methods

Inulin was measured by the colorimetric determination of fructose (resorcin method) after hydrolytic cleavage of inulin in plasma and urine. PAH was determined by a diazo reaction of the PAH amino group with sodium nitrite yielding a red color complex (colorimetric determination [ΔE] at 546 nm, method according to Smith et al. [27]).

The interassay coefficient of variation was 6.8 ± 5.1% for the inulin clearance method and 7.9 ± 7.0% for the PAH method (n = 10).

Fractional dextran concentrations were determined by HPLC-gel permeation chromatography (Perkin Elmer, Überlingen, Germany) on a BIO-Gel TSK 30× L column (Bio-Rad, Munich, Germany). Dextrans were isolated and purified from plasma and urine after deproteinization and ethanol extraction. Molecular size-related quantification was performed by software area integration using a data slice modus between 23 and 73 Å. The colloid osmotic pressure in the plasma (necessary for the calculation of the glomerular pressure
Table 1. Clinical data of the patients enrolled in the study*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Gender</th>
<th>MAP, Run-In (mmHg)</th>
<th>Serum Creatinine, Run-In (μmol/L)</th>
<th>Proteinuria, Run-In (mg/d)</th>
<th>Underlying Renal Disease</th>
<th>Concomitant Antihypertensive Drugs</th>
<th>Change during Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>78</td>
<td>179</td>
<td>M</td>
<td>108</td>
<td>328</td>
<td>955</td>
<td>Benign nephrosclerosis</td>
<td>Bisoprolol, doxazosin</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>80</td>
<td>160</td>
<td>F</td>
<td>117</td>
<td>197</td>
<td>1800</td>
<td>Membranous GN</td>
<td>Metoprolol, urapidil,</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>felodipin</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>63</td>
<td>174</td>
<td>M</td>
<td>118</td>
<td>504</td>
<td>823</td>
<td>Autosomal dominant polycystic kidney disease</td>
<td>Urapidil</td>
<td>Dose reduced, then withdrawn</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>82</td>
<td>171</td>
<td>M</td>
<td>116</td>
<td>337</td>
<td>4020</td>
<td>IgA nephropathy</td>
<td>Clonidin</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>84</td>
<td>162</td>
<td>F</td>
<td>100</td>
<td>411</td>
<td>763</td>
<td>Benign nephrosclerosis</td>
<td>Metoprolol</td>
<td>Dose reduced</td>
</tr>
<tr>
<td>Total</td>
<td>57 ± 7</td>
<td>78 ± 8</td>
<td>169 ± 8</td>
<td>F = 2, M = 3</td>
<td>112 ± 8</td>
<td>365 ± 122</td>
<td>1672 ± 1113</td>
<td></td>
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</tr>
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<td>Placebo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>66</td>
<td>67</td>
<td>168</td>
<td>M</td>
<td>123</td>
<td>378</td>
<td>1910</td>
<td>Benign nephrosclerosis</td>
<td>Metoprolol, urapidil,</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nifedipin, minoxidil</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>85</td>
<td>178</td>
<td>M</td>
<td>119</td>
<td>389</td>
<td>755</td>
<td>IgA nephropathy</td>
<td>Urapidil</td>
<td>No</td>
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<tr>
<td>8</td>
<td>50</td>
<td>92</td>
<td>168</td>
<td>F</td>
<td>115</td>
<td>244</td>
<td>560</td>
<td>Autosomal dominant polycystic kidney disease</td>
<td>Urapidil, nifedipin,</td>
<td>Dose of urapidil increased</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>bisoprolol</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>103</td>
<td>178</td>
<td>M</td>
<td>110</td>
<td>338</td>
<td>3049</td>
<td>Mesangio proliferative GN</td>
<td>Nitrendipin, urapidil</td>
<td>No</td>
</tr>
<tr>
<td>Total</td>
<td>62 ± 11</td>
<td>87 ± 15</td>
<td>173 ± 6</td>
<td>F = 1, M = 3</td>
<td>117 ± 6</td>
<td>346 ± 61</td>
<td>1276 ± 1217</td>
<td></td>
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</tr>
</tbody>
</table>

* There was no significant difference between the groups regarding age, mean arterial pressure, or serum creatinine in the run-in period. Values are given as mean ± SD. MAP, mean arterial pressure; GN, glomerulonephritis.
<table>
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<tr>
<th>Week:</th>
<th>-12</th>
<th>-8</th>
<th>-4</th>
<th>0</th>
<th>+1</th>
<th>+4</th>
<th>+8</th>
<th>+12</th>
<th>+16</th>
<th>+20</th>
<th>+24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>run in period</td>
<td>treatment phase: Valsartan 80 mg or placebo</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Blood pressure, body weight**
- **Blood pressure:**
  - ▲
  - +
  - ●
  - ●
  - ●
  - ●
  - ●
  - ●
  - ●
  - ●

**Lab. parameters**
- □
- □
- □
- □
- □
- □
- □
- □
- □
- □

**Renal function tests**
- +
- +
- +
- +

*Figure 1. Investigation schedule. □ = Clinical biochemistry (Serum: sodium, potassium, chloride, urea, creatinine, bicarbonate, uric acid) and 24-h urine (total protein, albumin); △ = Hematology (RBC, WBC, hemoglobin, hematocrit, platelets) and 24-h urine (sodium, potassium); + = Renal function tests (inulin clearance, para-aminohippurate clearance, dextran clearance).*

The clearance of neutral dextrans was used to characterize the size selectivity of the glomerular membrane. According to a well established physiologic model by Deen et al. (28), the properties of the glomerular membrane can be described by the parameters $r_0$ (mean pore radius), $\omega_0$ (fraction of volume flux through shunts if plasma proteins were absent), and $K_f$ (ultrafiltration coefficient).

Using this model, changes in membrane permeability and glomerular hemodynamics can be evaluated. The sieving function $\theta$ of the basal membrane for a dextran fraction of a definite molecular size is:

$$\theta = \frac{U/P_{\text{dextran}}}{U/P_{\text{ulin}}}. $$

A two-parameter pore structure can be defined with size-selective pores of a definite diameter and a shunt pathway ($\omega_0$) that has negligible size selectivity (isoporous model with shunt). Assuming Poiseille flow through parallel pores of radius $r_0$, the following equation is valid (which can be further resolved with clinically measurable parameters):

$$\frac{8\eta K_f}{r_0^2} = fS \frac{P}{T}.$$

where $\eta$ is viscosity of the glomerular filtrate, $K_f$ is glomerular ultrafiltration coefficient, $r_0$ is pore radius of the isoporous membrane, $f$ is the fraction of capillary surface area occupied by pores, $S$ is the total glomerular capillary surface area, and $l$ is pore length.

For large molecules passing the glomerular membrane almost unrestricted, the additional shunt pathway ($\omega$, fraction of total filtrate volume) is calculated as follows:

$$\omega = \frac{1}{1 + \left(\frac{1 - \omega_0}{\omega_0}\right)\frac{\Delta P - \Pi_0}{\Pi_0} \frac{\eta_0}{\eta_\text{pl}}}.$$

where $\omega_0$ is the fraction of volume flux through shunts if plasma proteins were absent, $\Delta P$ is transmural hydraulic pressure, $\Pi_0$ is colloid osmotic pressure in glomerular plasma, and $\eta_\text{pl}$ is the viscosity of plasma and saline.

**Calculations**

GFR and ERPF were calculated by the ratio of urine excretion and plasma concentration of inulin/PAH under constant infusion as:

$$\text{Clearance} = \frac{U \times V}{T \times P},$$

where $U$ is urine concentration, $V$ is urine volume (ml), $T$ is time (min), and $P$ is plasma concentration. The results were averaged for two 1-h urine sampling periods and corrected for standard body surface area of 1.73 m².

Renal blood flow (RBF) was calculated as:

$$\text{RBF} = \frac{\text{ERPF}(1 - \text{Hct})}{\text{Eff}},$$

where Hct is hematocrit.

The filtration fraction (FF) was calculated as:

$$\text{FF} = \frac{GFR}{\text{ERPF}} \times 100.$$

Renovascular resistance (RVR) was calculated as:

$$\text{RVR} = \frac{\text{MAP}}{\text{RBF}}$$

and corrected for SI units:

$$\text{RVR} = 133.2 \times \frac{\text{MAP}}{\text{RBF}} \times 60.$$
\( \Delta P \) cannot be directly measured and was assumed to be 45 mmHg in our hypertensive patients according to previous studies and micropuncture results (29). To make sure that the changes of the sieving properties measured in our study were mediated by size-selective changes in the barrier function of the glomerular membrane and not by a reduction in glomerular hydraulic pressure, we performed serial calculations for \( \Delta P \) values between 37.5 and 47.5 mmHg. Computed data for \( r_0 \) and \( w_0 \) were optimized using a nonlinear fitting.

**Statistical Analyses**

Statistical analyses were performed using the ANOVA function (one-way, repeated measurement) to test for changes within the groups over time. Differences between two measurements within one group were tested by \( t \) test for dependent samples. To control for significance against the spontaneous course of renal disease, the data of the V-group were compared with results measured in the placebo group, using a multivariate model with repeated measurement (MANOVA). 0-Hypothesis (no differences between the samples) was rejected with \( P < 0.05 \). The statistical disadvantage of a small number of patients was compensated for by a repeated measurement design. Repeated examinations were made at least four times in each patient, so that in the V-group \( \geq 20 \) and in the P-group \( \geq 16 \) single measurements for each parameter could be evaluated. It has been shown in statistical analysis that the sample size needed is inversely correlated to the number of repeated measures in the ANOVA model (30). In this way, we could fulfill the requirements of an adequate sample size. All values are given as mean \( \pm \) SD, except in the figures, where mean \( \pm \) SEM is depicted.

**Results**

**Blood Pressure**

After 1 wk of Valsartan treatment, BP (MAP) decreased from 112 \( \pm \) 8 mmHg (MAP) to 97 \( \pm \) 1 mmHg in the V-group \( (P < 0.01) \). BP remained on this lower level throughout the observation period (MAP over 6 mo: 99 \( \pm \) 2 mmHg, \( \Delta \text{MAP} = 13 \pm 7 \text{ mmHg}, P < 0.01 \)). During Valsartan therapy, our clinical BP target (MAP \(<97 \text{ mmHg}, \text{approximately} <130/80 \text{ mmHg} \) was reached in three of five patients, whereas two patients still had a MAP up to 103 mmHg. In the P-group, BP initially decreased from 117 \( \pm \) 5 to 108 \( \pm \) mmHg after 1 wk \( (P < 0.05) \) and remained somewhat lower than baseline values for up to 3 mo (placebo effect, compliance?). MAP returned to near baseline levels (113 \( \pm \) 7 mmHg) after 6 mo of follow-up (NS from baseline value). Average BP reduction over 6 mo was significantly different between the V-group and the P-group according to MANOVA \( (P < 0.05) \) (Figure 2).

**Serum Potassium and Urinary Electrolyte Excretion**

Baseline serum potassium concentrations in the V-group increased from 4.4 \( \pm \) 0.4 mmol/L to 4.9 \( \pm \) 0.5 mmol/L after 3 mo of Valsartan treatment \( (P < 0.05) \) and remained almost unchanged then. There was no change in serum potassium values in the P-group \( (4.2 \pm 0.4 \text{ mmol/L} \text{ versus} 4.1 \pm 0.3 \text{ mmol/L} \text{ after 6 mo}). \text{The effect of Valsartan treatment on serum potassium turned out to be significant between groups (MANOVA,} P < 0.05 \text{, V-group versus P-group). During the entire trial, the absolute and fractional urinary excretion rates of sodium and potassium did not change significantly either within or between the groups (Table 2).}

**Blood Count, Serum Creatinine, and Blood Urea Nitrogen**

Hemoglobin and hematocrit slightly decreased over 6 mo of Valsartan treatment \( (P < 0.05) \), whereas no such change was

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**Figure 2.** Change in mean arterial pressure (MAP) during 6 mo of treatment with 80 mg/d Valsartan (V-group, \( n = 5 \)) or placebo (P-group, \( n = 4 \)) in patients with renal failure. Values are given as mean \( \pm \) SEM. Changes versus run-in phase are indicated by asterisks, \(*P < 0.05\). Differences between study groups during the treatment phase are tested by multivariate ANOVA (MANOVA) and indicated by brackets.
Table 2. Changes in hematology, blood biochemistry, and urinary electrolyte excretion during treatment with Valsartan (80 mg; n = 5) or placebo (n = 4)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (80 mg)</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Run-In Phase</td>
<td>Treatment Phase</td>
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<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC (10\textsuperscript{12}/L)</td>
<td>4.0 to 5.7</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.0 to 18.0</td>
<td>12.1 ± 1.0</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>32.0 to 52.0</td>
<td>36.0 ± 3.0</td>
</tr>
<tr>
<td>WBC (10\textsuperscript{3}/L)</td>
<td>4.0 to 10.0</td>
<td>6.0 ± 1.2</td>
</tr>
<tr>
<td>Plt (10\textsuperscript{9}/L)</td>
<td>150 to 400</td>
<td>254 ± 87</td>
</tr>
<tr>
<td><strong>Biochemistry (serum)</strong></td>
<td></td>
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</tr>
<tr>
<td>sodium (mmol/L)</td>
<td>135 to 145</td>
<td>141 ± 1</td>
</tr>
<tr>
<td>potassium (mmol/L)</td>
<td>3.5 to 5.0</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>calcium (mmol/L)</td>
<td>2.2 to 2.8</td>
<td>2.4 ± 0.7</td>
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<tr>
<td>phosphate (mmol/L)</td>
<td>0.8 to 1.6</td>
<td>1.2 ± 0.4</td>
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<tr>
<td>chloride (mmol/L)</td>
<td>94 to 110</td>
<td>106 ± 2</td>
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<tr>
<td>creatinine ((\mu)mol/L)</td>
<td>44 to 106</td>
<td>366 ± 122</td>
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<tr>
<td>urea (mmol/L)</td>
<td>2.5 to 7.5</td>
<td>19.3 ± 5.4</td>
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<tr>
<td>bicarbonate (mmol/L)</td>
<td>22 to 28</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>uric acid ((\mu)mol/L)</td>
<td>178 to 416</td>
<td>426 ± 135</td>
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<tr>
<td><strong>Urinary electrolyte excretion</strong></td>
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<td></td>
</tr>
<tr>
<td>sodium (mmol/24 h)</td>
<td>100 to 260</td>
<td>188 ± 89</td>
</tr>
<tr>
<td>potassium (mmol/24 h)</td>
<td>25 to 100</td>
<td>72 ± 31</td>
</tr>
<tr>
<td>FE\textsubscript{sodium} (%)</td>
<td>0.9 to 2.5</td>
<td>5.6 ± 3.0</td>
</tr>
<tr>
<td>FE\textsubscript{potassium} (%)</td>
<td>12 to 24</td>
<td>64.8 ± 33.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Repeated measurements were averaged for the run-in and treatment phase. Values are given as mean ± SD. RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; Plt, platelet; FE, fractional excretion.

\textsuperscript{b} \(P < 0.05\), differences between run-in and treatment phase were tested within each group by ANOVA.

\textsuperscript{c} \(P < 0.05\), differences between groups were tested by MANOVA.

observed in the P-group. The amount of blood drawn for study purposes or other reasons was the same for both groups.

Serum creatinine concentrations were not significantly different between both groups at study entry. Within the V-group, serum creatinine slightly increased by 7 ± 6\% from 366 ± 122 \(\mu\)mol/L in the run-in period to 392 ± 135 \(\mu\)mol/L during treatment (ANOVA, \(P < 0.05\)). Some spontaneous increase was also observed in the P-group; thus, the course of serum creatinine did not differ between the groups according to multivariate testing. For blood urea nitrogen, a similar trend as for serum creatinine could be observed (Table 2).

**Renal Hemodynamics**

In the V-group baseline, GFR was 20 ± 7 ml/min in the run-in period and averaged 18 ± 6 ml/min for the three measurements during the treatment phase (NS). In the P-group, GFR changed from 19 ± 5 to 21 ± 8 ml/min, respectively (NS) (Figure 3).

Baseline ERPF in the run-in phase was 97 ± 30 ml/min in the V-group and 100 ± 37 ml/min in the P-group (NS). During treatment, ERPF was almost stable in the V-group (96 ± 30 ml/min), whereas there was some spontaneous decrease in the P-group (\(P < 0.05\), after 1 wk, NS after 3 and 6 mo). RBF decreased slightly over time from 152 ± 47 to 140 ± 47 ml/min in the V-group and from 143 ± 53 to 129 ± 55 ml/min in the P-group. The trend between the groups concerning ERPF and RBF was not significantly different during the entire observation period.

FF increased from 20 ± 3\% to 24 ± 2\% (\(P < 0.01\)) during the treatment period in the P-group. A small but significant decrease from 20 ± 3\% to 17 ± 4\% (\(P < 0.05\)) was observed after 1 wk of Valsartan treatment. But the values returned to near baseline levels thereafter (19 ± 3\%, ANOVA, NS). The significant difference between the groups (MANOVA, \(P < 0.05\)) was predominantly due to the increase of FF over time in the P-group. Renovascular resistance showed a similar trend as FF in the V-group (difference between groups: MANOVA, \(P = 0.052\)) (Figure 3).

**Proteinuria**

Proteinuria significantly dropped from 1672 ± 1113 to 1276 ± 1217 mg/24 h after 6 mo of Valsartan treatment (\(P < 0.05\)). During this time, a steady decrease of proteinuria was observed. However, in the P-group proteinuria tended to increase by 30 ± 43\% over 6 mo (from 1568 ± 1152 to 2055 ± 1971 mg/24 h after 6 mo, NS). Thereby, the between-group treatment effect of Valsartan treatment was significant from 3 to 6 mo (MANOVA, \(P < 0.05\)) (Figure 4).
With regard to albuminuria, the effect of Valsartan was even more marked. Albuminuria decreased by 41 ± 21% (from 1300 ± 1269 to 769 ± 906 mg/24 h) during 6 mo of treatment ($P < 0.05$), reaching stable values after 3 mo. In the P-group, albuminuria increased slightly but not significantly with time (from 1016 ± 1116 to 1339 ± 1990 mg/24 h, NS). The between-group effect was also clearly significant (MANOVA, $P < 0.05$) (Figure 4).

Fractional albumin excretion was reduced by Valsartan treatment from 51 ± 60 µg/ml to 36 ± 49 µg/ml after 6 mo (i.e., -34 ± 11%, $P < 0.05$). In the P-group, fractional albumin excretion did not change (37 ± 37 µg/ml versus 41 ± 42 µg/ml).

**Changes in Glomerular Permeability**

**Glomerular Sieving Coefficient.** All patients investigated (including those with autosomal dominant polycystic kidney disease) had evidence of glomerular barrier dysfunction when comparing dextran sieving coefficients with those of the healthy control group (Figure 5). The sieving coefficients for dextrans with radii of ≥58 Å were clearly increased in the study groups compared with healthy control subjects ($P < 0.05$). After 6 mo of Valsartan treatment, the differences in the fractional dextran clearances between the V-group and the control group became smaller ($P < 0.05$), indicating a partial restoration of membrane function.

During Valsartan therapy, the slope of the sieving curve became particularly steeper in the high molecular range above 60 Å. This effect gradually increased after 1, 12, and 24 wk of Valsartan application. After 6 mo of treatment, the fractional clearance of dextran fractions from 66.1 to 73.2 Å was significantly reduced by 51 ± 31% compared with the run-in period ($P < 0.05$). In contrast, the P-group did not show any directed changes of the sieving coefficients with time. The difference in the sieving coefficients for larger molecules after 6 mo of Valsartan treatment also became significant between the groups (MANOVA, $P < 0.05$).
Calculated Mean Pore Size Radius and Shunt Volume.

The mean glomerular pore size radius ($r_0$) was unaffected by Valsartan treatment. It was 52.5 ± 4.8 Å before treatment and 50.8 ± 4.7 Å after 6 mo (NS). In the P-group, we found a similar situation (55.1 ± 6.9 Å versus 55.3 ± 5.9 Å, NS). These values did not significantly differ from those of the healthy control group (54.4 ± 3.0 Å).

However, the glomerular shunt volume ($\omega_0$) was significantly increased in both the V-group (0.0025 ± 0.0020) and the P-group (0.0027 ± 0.0013) compared with healthy control subjects (0.00059 ± 0.00027) ($P < 0.01$).

When treating with Valsartan, a decrease in glomerular permeability could be attributed to a reduction of glomerular shunt volume. $\omega_0$ decreased significantly by 54 ± 20% (from 0.0025 ± 0.0020 to 0.0015 ± 0.0017) in the V-group ($P < 0.05$), whereas it remained almost unchanged in the P-group (from 0.0027 ± 0.0013 to 0.0025 ± 0.0009, NS) (Figure 5).

The calculated data for $r_0$ and $\omega_0$ were reevaluated on the basis of an assumed decrease of glomerular hydraulic pressure by BP lowering. Within wide variations of the glomerular pressure differences (between 37.5 and 47.5 mmHg), there were only minor changes in the calculated pore radii and shunt volumes. The data are presented in Figure 5. Based on the mathematical model of restricted and unrestricted glomerular transport, it is obvious that the mean pore radius and shunt volume are not very sensitive to changes of assumed $\Delta P$ values. An assumed additional drop of the glomerular hydraulic pressure by Valsartan from 45 mmHg to 40 or 37.5 mmHg by this method did not significantly change the calculated membrane parameters as compared with an unchanged pressure gradient.

Discussion

Our results demonstrate a significant and sustained BP lowering effect of Valsartan in patients with advanced renal failure. Compared to previous studies with Valsartan in patients with essential hypertension (23,31–33), the degree of BP lowering was comparable. With regard to our own experiences and some prior studies with Valsartan, the substance was as effective as ACE inhibitor treatment (34) in patients with renal failure. In our study, BP reduction with Valsartan reached a maximum after 1 wk and remained almost unchanged over the following months. Tachyphylaxis did not seem to occur. A notable decrease of MAP in the P-group was interpreted as a study bias due to a better patient compliance with regard to concomitant drug intake during the closely monitored study. The fact that additional antihypertensive medication had to be lowered due to a marked BP decrease in two patients of the verum group but in neither case of the placebo group further underscores the efficacy of Valsartan. It was well tolerated with no adverse events noted. BP lowering was smooth, and no acute events of hypotension were observed. In addition, no episodes of dry cough were reported.

The elevation of serum potassium levels is a side effect of the renin-angiotensin-aldosterone system blockade by angiotensin receptor antagonists that was reported even in hypertensive patients with normal renal function (35). This may limit the use of angiotensin receptor antagonists, especially in pa-
patients with renal failure. We also found an increase in serum potassium values during Valsartan therapy. In most cases, the increase was only small or moderate and did not cause drug discontinuation in any of our patients. It is recommended, however, to introduce dietary education in patients with serum potassium levels in the upper range and to perform a close follow-up after initiation of therapy.

Hemoglobin and hematocrit were reduced with Valsartan therapy without signs of hemolysis. Similar results have been reported with ACE inhibitors. A decrease in circulating erythropoietin concentrations has been observed in kidney transplant recipients with ACE inhibitor therapy (36,37), but there are no definite explanations about the underlying mechanism at present.

Deterioration of the renal excretory function is a severe problem observed during ACE inhibitor treatment and can be deduced from changes in renal hemodynamics on the basis of a decrease of transmembranous glomerular pressure (38-40). Preexisting chronic renal failure generally enhances this problem. A relevant deterioration of GFR is clinically observed in patients with preswitched renal artery stenosis or dehydration but seems to be minor without such conditions. Only few data on AngII antagonist treatment in chronic renal failure exist and reveal only minor changes in clearance parameters (26). In this study, Valsartan treatment was accompanied by only a slight increase in serum creatinine and urea concentrations over 6 mo, which did not differ significantly from the course of the P-group.

We did not find major changes in renal hemodynamics in the V-group. Our findings only indicated some minor changes. A small initial drop in GFR and FF could be observed after 1 wk of Valsartan therapy, but this decrease reversed later in the treatment period. Renovascular resistance showed a similar profile with only a small initial decrease. An increase in ERPF, which has been attributed to vasodilation in patients with essential hypertension (24) or in renal disease with only slightly reduced GFR (>60 ml/min) (26), could not be observed in our patients. It is possible that the change in ERPF and FF is blunted in patients with advanced renal failure (GFR approximately 20 ml/min in our patients). Moderate volume
overload in advanced renal failure may also produce some limited changes in renal hemodynamics. A significant finding was a clear decrease of urinary protein excretion. A 20 to 40\% reduction of total protein and albumin excretion was found during 6 mo of Valsartan treatment. The decrease of albumin excretion was more marked, and the effect on fractional albumin excretion indicated a potential change in glomerular permeability, as no significant effect on GFR was noted. Prospective multicenter studies in patients with diabetic nephropathy have demonstrated an antiproteinuric, especially antialbuminuric, effect of ACEI (6–8). Although the nephroprotective effect of ACEI has been clearly demonstrated in these patients, the benefits for nondiabetic nephropathy are less validated. However, actual studies (e.g., the “REIN” study) also demonstrate the benefits for the latter indication with a significant improvement in GFR reduction for ACEI treatment (ramipril) versus placebo (0.5 versus 0.9 ml/min per month)(9).

It is thought that proteins have an intrinsic nephrotoxicity. Experiments with proximal tubular cells gave evidence for a protein concentration-dependent release of free radicals and the activation of the NFκB gene as a promoter for the release of proinflammatory cytokines. Renal interstitial inflammation and fibrosis may be the consequences. Similar results compared to ACEI treatment with regard to protein excretion have been found by Gansevoort and coworkers, using losartan in only moderate renal failure (26). In another study of this group comparing the effects of losartan on proteinuria to that of enalapril or placebo, the authors concluded that the reduction of proteinuria is indeed only mediated by AngII inhibition (34). Whether the more specific blockade of the renin-angiotensin system by AngII receptor antagonists may be advantageous due to the fact that AngII produced via the pathway of tissue-specific enzymes (e.g., chymases or CAGE) is also inhibited is currently under debate (25). It is also unclear whether it is favorable that bradykinin levels (acting as a vasodilator) are not elevated during AngII receptor antagonist treatment.

By lowering systemic BP, Valsartan may probably have reduced transglomerular hydraulic pressure and decreased glomerular proteinuria in our patients in this way (10,12). Inhibition of AngII should also reduce postglomerular vascular resistance by vasodilation of the efferent arteriole. The fact that we measured FF only initially reduced by Valsartan (after 1 wk) and then values near to baseline does not exclude a possible change in glomerular hydraulic pressure. AngII receptor inhibition can influence hydraulic pressure and glomerular capillary surface area (by mesangial cell relaxation) in an opposite way, thereby leaving single nephrone FF unchanged. However, infusion experiments with AngII in isolated rat kidneys also showed that by the contraction of mesangial cells, nonselective glomerular pores can be opened (41). This finding indicates that besides a reduction of hydraulic glomerular pressure, AngII antagonism can also influence structural membrane properties.

To investigate whether the decrease of proteinuria could only be a consequence of systemic BP lowering and glomerular hemodynamic changes or whether some structural changes in the glomerular sieving properties had taken place, we measured the fractional clearances of neutral dextrans with different size. With this method, the permeolselectivity of the glomerular basement membrane can be assessed without being influenced by changes in GFR or tubular function. Although the sieving coefficient of small dextran molecules was not affected by Valsartan, a clear improvement (i.e., decrease in sieving coefficients) could be found for higher weight dextran molecules >66 Å. This greatly resembles the way in which ACE inhibitors (e.g., enalapril) affected the sieving coefficients, especially of large pores (with radii >56 Å), in cases of diabetes or human IgA nephropathy (42,43). We also applied the so-called “isoporous model with shunt” developed by Deen et al. (28) to discriminate between the influence of Valsartan on mean pore radius of the glomerular membrane and a change in the so-called “shunt pathway.” This model assumes that the major portion of the glomerular wall functions as an isoporous membrane, but that a small fraction of the glomerular filtrate passes through shunt pores that are unable to discriminate among macromolecules of different size. The mean pore radius ($r_0$) of the membrane was not changed by Valsartan, but the shunt ($\omega_0$), which is responsible for the unrestricted passage of macromolecules, was significantly reduced by 54 ± 20\%. According to the model of Deen et al., changes of $\omega_0$ reflect alterations of unrestricted membrane transport. Changes in hydraulic transmembrane pressure ($\Delta P$) cannot directly be measured in human experiments. However, assuming a given $\Delta P$ value without direct measurement has been justified in several animal experiments (11,29) and in human glomerulonephritis by the observations of Myers et al. (44), who demonstrated that variations in $\Delta P$ do not markedly influence the calculation of membrane parameters related to the pore structure. In our study, we made additional computations assuming that Valsartan may have decreased $\Delta P$ due to the systemic BP reduction and/or by Vas afferens/Vas efferens dilation. Even when considering a simultaneous drop of the glomerular capillary pressure from 47.5 or 45 to 37.5 mmHg during Valsartan treatment, the results of the calculated membrane parameters did not significantly change, underscoring the clear effect of Valsartan on membrane permeolselectivity. Experimental work in hypertensive rats showed that glomerular hydraulic pressure could be lowered at most by 10 mmHg with the AngII antagonist irbesartan (12). Therefore, our findings indicate that besides some potential influence on glomerular hydraulic pressure, AngII antagonism in moderate renal failure improves structural membrane properties. This will explain the marked decrease of urinary protein excretion with only minor changes in GFR and FF in our study.

In animal studies with Munich-Wistar rats following kidney ablation, a preservation of near to normal sieving coefficients under AngII blockade was found in contrast to a deterioration in an untreated control group (15). For other AngII antagonists (e.g., losartan, saralasin), a reduction in proteinuria has also been found in animal studies (Munich-Wistar rats) with models of hypertension or subtotal nephrectomy (12,14,45,46). In these studies it could also be shown that reduced proteinuria was accompanied by a protection of the glomeruli from segmental sclerosis as assessed by histopathology. The fact that
AngII may also act as a growth factor on mesangial cells may be one theoretical explanation. Other therapeutic regimens leading to a similar reduction in systemic and intrarenal BP (e.g., reserpine/hydralazine/hydrochlorothiazide versus ACEI or AngII receptor antagonist) were not accompanied by comparable structural benefits (14,15).

Our findings with the AngII antagonist Valsartan show a sustained reduction in BP and proteinuria even in patients with advanced renal failure. A preserved excretory renal function together with functional benefits in glomerular permselectivity may recommend this new class of antihypertensive agents as a “nephroprotective alternative” to ACE inhibitors, and thus warrants additional long-term studies.

Acknowledgment

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References

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