Renal Damage after Myocardial Infarction Is Prevented by Renin-Angiotensin-Aldosterone-System Intervention


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Recently, it was shown that myocardial infarction aggravates preexistent mild renal damage that is elicited by unilateral nephrectomy in rats. The mechanism behind this cardiorenal interaction likely involves the renin-angiotensin-aldosterone-system and/or vasoactive peptides that are metabolized by neutral endopeptidase (NEP). The renoprotective effect of angiotensin-converting enzyme inhibition (ACEi) as well as combined ACE/NEP inhibition with a vasopeptidase inhibitor (VPI) was investigated in the same model to clarify the underlying mechanism. At week 17 after sequential induction of unilateral nephrectomy and myocardial infarction, treatment with lisinopril (ACEi), AVE7688 (VPI), or vehicle was initiated for 6 wk. Proteinuria and systolic BP (SBP) were evaluated weekly. Renal damage was assessed primarily by proteinuria, interstitial α-smooth muscle actin (α-SMA) staining, and the incidence of focal glomerulosclerosis (FGS). At start of treatment, proteinuria had increased progressively to 167 ± 20 mg/d in the entire cohort (n = 42). Both ACEi and VPI provided a similar reduction in proteinuria, α-SMA, and FGS compared with vehicle at week 23 (proteinuria 76 ± 6 versus 77 ± 4%; α-SMA 60 ± 6 versus 77 ± 3%; FGS 52 ± 14 versus 61 ± 10%). Similar reductions in systolic BP were observed in both ACEi- and VPI-treated groups (33 ± 3 and 37 ± 2%, respectively). Compared with ACEi, VPI-treated rats displayed a significantly larger reduction of plasma (41 ± 5 versus 61 ± 4%) and renal (53 ± 6 versus 74 ± 4%) ACE activity. It is concluded that both ACEi and VPI intervention prevent renal damage in a rat model of cardiorenal interaction. VPI treatment seemed to provide no additional renoprotection compared with sole ACEi after 6 wk of treatment in this model, despite a more pronounced ACE-inhibiting effect of VPI.


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Materials and Methods

Experimental Protocol

Male Wistar rats (320 to 350 g; n = 75) were housed under standard conditions with free access to food and drinking water. Rats received a standard chow diet that contained 19% protein (diet #1324; Altromin, Lage, Germany). Animal experiments were approved by the institutional animal ethics committee.

At week −2, all 75 rats underwent right unilateral nephrectomy under anesthesia with 2.0% isoflurane in O2. Male Wistar rats (320 to 350 g; n = 75) were housed under standard conditions with free access to food and drinking water. Rats received a standard chow diet that contained 19% protein (diet #1324; Altromin, Lage, Germany). Animal experiments were approved by the institutional animal ethics committee.

At week 0, rats were intubated, ventilated (ALV, Hoek Loos, The Netherlands), and anesthetized using 2.0% isoflurane in O2. MI was induced by ligation of the left anterior descending coronary...
artery as described previously (24). Of these 75 rats, 30 died within 24 h after MI surgery and were excluded from the study. Seventeen weeks after MI, rats were stratified for proteinuria as a measure for renal damage and assigned to one of the following treatment groups: (1) vehicle (n = 12), (2) lisinopril 5 mg/kg per d (ACEi; n = 16), and (3) AVE7688 21 mg/kg per d (VPI; n = 14). A 6-wk treatment period was initiated up to week 23, when the rats were killed. Lisinopril (Merck, Sharp & Dohme, Haarlem, The Netherlands) was administered through the drinking water in a concentration of 75 mg/L, providing a dosage of 5 mg/kg per d. AVE7688 (Sanofi-Aventis Pharma Deutschland, Frankfurt am Main, Germany) was mixed through the food at a concentration of 450 ppm, resulting in a dosage of 21 mg/kg per d. In a pilot experiment, these dosages resulted in comparable plasma ACEi.

At the end of the experiment, after measurement of functional cardiac parameters under 2.5% isoflurane anesthesia, laparotomy was performed and rats were exsanguinated by taking blood samples from the abdominal aorta for plasma measurements. The remaining kidney was flushed with saline, and the heart and the kidney were removed and weighed.

Functional Parameters

**BP and Urinary Measurements.** Systolic BP (SBP) was measured using tail-cuff plethysmography (IITC Life Science, Woodland Hills, CA) in trained awake, restrained rats. SBP was measured at baseline and regularly thereafter until the end of study. Measurements of water and food intake as well as 24-h urine collections for determination of urinary total protein excretion and urine production were performed weekly by placing the rats in metabolic cages.

**Urinary, Plasma, and Tissue Measurements.** Urinary total protein was analyzed using end-point measurement with TCA precipitation (Nephelometer Analyzer II; Dade Behring, Marburg, Germany). As a representation of renal function, creatinine clearance was calculated from urinary and plasma creatinine levels at baseline, at stratification, and at the end of the experiment. Creatinine was determined using standard kits (Roche Diagnostics, Basel, Switzerland) on a Hitachi 912 E analyzer (Hitachi, Mountain View, CA). Plasma and renal ACE activity were measured to evaluate the effect of treatment on ACEi using the conversion of hippuryl-His-Leu (Sigma, St. Louis, MO) by ACE to free His-Leu (25). Plasma renin activity was measured to investigate the activity of the RAAS by aRIA (Adaltis Italy SPA, Bologna, Italy), and pro-atrial natriuretic peptide (pro-ANP) was measured to investigate NEP inhibition using a sandwich enzyme immunoassay (Biomedica, Vienna, Austria).

Cardiac Function at the End of the Study

Under 2.5% isoflurane in O2 anesthesia, cardiac performance was measured with a pressure transducer catheter that was inserted through the right carotid artery (Micro-Tip 3French; Millar Instruments Inc., Houston, TX), connected to a personal computer that was equipped with an analog-to-digital converter and appropriate software (Millar Instruments). After a 3-min period of stabilization, left ventricular end diastolic pressure (LVEDP), left ventricular end systolic pressure (LVESP), and heart rate were recorded. Thereafter, the catheter was withdrawn into the aortic root to measure central SBP (SBPcentral). As a parameter of global myocardial contractility and relaxation, we determined the maximal rates of increase and decrease in left ventricular pressure (LVP) (systolic +dP/dtmax, and diastolic −dP/dtmax), which were normalized to left ventricular pressure change (i.e., LVESP − LVEDP) for individual rats.

**Histology**

**Kidney.** Kidneys were fixed by immersion for 48 h in a 4% buffered formaldehyde solution (Klinpath, Duiven, The Netherlands) after longitudinal bisection and subsequently embedded in paraffin according to standard procedures. An examiner who was blinded for the groups evaluated all sections.

**Mesangial Matrix Expansion, Focal Glomerulosclerosis, and Interstitial Fibrosis.** Sections of 3 μm were stained with periodic acid Schiff. The degree of mesangial matrix expansion (MME) and focal glomerulosclerosis (FGS) were assessed in 50 glomeruli by scoring semi-quantitatively on a scale of 0 to 4 (26). FGS was scored positive when MME and adhesion to Bowman’s capsule were present in the same quadrant. When one quadrant of the glomerulus was affected, a score of 1+ was assigned, two quadrants was scored as 2+, three quadrants as 3+, and four quadrants as 4+. Overall MME and FGS score is expressed in arbitrary units (AU) with a maximum of 200. Interstitial fibrosis (IF) was defined as expansion of the interstitial space, with or without the presence of atrophied and dilated tubules and thickened tubular basement membranes. The degree of IF was assessed in 30 interstitial fields at ×20 magnification by scoring semi-quantitatively on a scale of 0 to 5 as follows: 0, no IF; 1, 1 to 10%; 2, 10 to 25%; 3, 25 to 50%; 4, 50 to 75%; and 5, 75 to 100%. The score is given as AU with a maximum of 150.

**Intertitial and Glomerular α-Smooth Muscle Actin and Glomerular Surface Area.** α-Smooth muscle actin (α-SMA) was determined as a profibrotic marker and detected in paraffin-embedded sections by means of a mouse monoclonal α-SMA antibody (Sigma Chemical). First, the antibody was incubated for 60 min, and its binding was detected by sequential incubations with peroxidase-labeled rabbit anti-mouse and peroxidase-labeled goat anti-rabbit antibody (both from Dakopatts, DAKO, Glostrup, Denmark) for 30 min. The expression of interstitial α-SMA was measured by computerized morphometry. Therefore, 40 fields were scored at ×20 magnification in the cortical region; glomeruli and vessels were excluded from measurement along Bowman’s capsule and the vessel wall. Glomerular surface area, as a measure for glomerular hypertrophy, was measured using this procedure as well. For the expression of glomerular α-SMA, 40 glomeruli were scored at ×20 magnification. Total staining was expressed as percentage of total area surface.

**Intestinal Macrophage Number.** The number of interstitial macrophages was determined as an indication of the degree of inflammation. Therefore, a mouse monoclonal anti-rat monocye and macrophage IgG1 (ED-1; Serotec, Oxford, England) was used. First, the antibody was incubated for 60 min, and its binding was detected by sequential incubations with peroxidase-labeled rabbit anti-mouse and peroxidase-labeled goat anti-rabbit antibody (both from Dakopatts, DAKO) for 30 min. The expression of interstitial ED-1—positive cells per field was measured by computerized morphometry. Therefore, 40 fields were scored at ×20 magnification in the cortical region; glomeruli were excluded from measurement along Bowman’s capsule. The average score was calculated per cortical section.

**Glomerular Desmin.** Desmin, a marker for glomerular visceral epithelial cell damage, was detected using a mouse mAb (clone DE-R-11; Novocastra Laboratories Ltd, Newcastle, UK). For glomerular desmin staining, 30 glomeruli were scored semiquantitatively, by estimating the percentage of desmin-positive glomerular visceral epithelial cells (injured podocytes) in the outer cell layer of the
glomerular tuft from 0 to 5 as follows: 0, no staining; 1, 1 to 10%; 2, 10 to 25%; 3, 25 to 50%; 4, 50 to 75%; and 5, 75 to 100% staining. Desmin staining is presented in AU with a maximum of 150.

Heart.

Infarct Size. The heart was arrested in diastole in a cold 1-M KCl solution and weighed. The atria were dissected from the ventricles, and the right free wall was separated from the left ventricle and weighed. Two left ventricular midsagittal slices (of approximately 2 mm) were fixed in 4% buffered formaldehyde solution, embedded in paraffin, cut into 5-μm slices, and stained with 0.1% Sirius Red F3B (Klinipath, Duiven, The Netherlands) and 0.1% Fast Green FCF (Klinipath). Endo- and epicardial circumference of the left ventricle and of scar tissue was determined by means of a computerized planimeter (Image-Pro plus; Media Cybernetics Inc., Silver Spring, MD). MI size was expressed as the mean of the inner and outer percentage of scar tissue to the inner and outer total circumference of the left ventricle. All sections were evaluated by an examiner who was blinded for the groups.

Statistical Analyses

All data are presented as mean ± SEM. In general, differences between the groups were compared using a one-way ANOVA for parameters measured at one time point and an analysis of covariance for parameters with two repeated measurements before and after the treatment period. A general linear model for repeated measures was used to compare the change in proteinuria and change in SBP curves during the treatment phase (weeks 18 through 23). A Bonferroni post hoc test was used to identify the differences between groups. A paired samples t test was used to compare a parameter before and after treatment in one group. In all tests, P < 0.05 was considered statistically significant.

Results

Overall Condition

In the vehicle- and ACEi-treated groups, body weight remained stable during the treatment period, even as food intake and urine production (Table 1). In the VPI-treated group, body weight significantly decreased during this period, whereas food intake remained stable and water intake increased. Differences in urine production before and after treatment were not observed between groups. Water intake was significantly higher in the ACEi- and the VPI-treated groups compared with vehicle.

Effects of Treatment Regimens on Plasma and Renal ACE Activity, Levels of Renin, and Pro-ANP

At the end of the treatment period, plasma ACE activity was significantly lower (41 ± 5%) in the ACEi-treated group and in the VPI-treated group (61 ± 4%) compared with vehicle (Table 2). Renal ACE activity was significantly lower in the ACEi-treated group (53 ± 6%) and in the VPI-treated group (74 ± 4%) compared with vehicle (Table 2). Plasma and renal ACE activity was significantly more inhibited in the VPI- compared with the ACEi-treated group. Plasma renin activity was significantly and equally higher in both the ACEi- and the VPI-treated groups (Table 2) compared with vehicle. Pro-ANP levels were significantly higher in the VPI- compared with the ACEi-treated group (Table 2).

Cardiovascular Characteristics

Tail-cuff SBP remained stable from a baseline level of 134 ± 2 to 137 ± 3 mmHg at stratification. At the end of the treatment period, the groups that were treated with ACEi and VPI showed a significant reduction in SBP compared with stratification (33 ± 3 and 37 ± 2%, respectively), whereas SBP remained stable in the vehicle-treated group (Figure 1A). The BP-lowering effect was comparable in the ACEi- and VPI-treated groups. Intra-arterially measured SBP (at the end of the study) showed a comparable difference between vehicle and both treatment groups (20 ± 2 and 26 ± 3% lower in ACEi and VPI, respectively; Table 3).

MI size was comparable in all groups (Table 3). Total wet heart weight was significantly lower in the ACEi- and VPI-treated groups compared with the vehicle-treated group (Table 3). LVESP and LVEDP were significantly lowered in the ACEi- and VPI-treated groups compared with the vehicle-treated groups.

Table 1. Rat characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Time Point</th>
<th>VEH (n = 12)</th>
<th>ACEi (n = 16)</th>
<th>VPI (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>Stratification</td>
<td>523 ± 10</td>
<td>513 ± 9</td>
<td>530 ± 8</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>530 ± 11</td>
<td>525 ± 9</td>
<td>516 ± 7</td>
</tr>
<tr>
<td>Food intake (g)</td>
<td>Stratification</td>
<td>20 ± 2</td>
<td>18 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>18 ± 2</td>
<td>19 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Water intake (ml/d)</td>
<td>Stratification</td>
<td>31 ± 4</td>
<td>33 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>27 ± 4</td>
<td>35 ± 2</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>Urine production (ml/d)</td>
<td>Stratification</td>
<td>14 ± 2</td>
<td>18 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>15 ± 2</td>
<td>20 ± 1</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Total protein excretion (mg/d)</td>
<td>Stratification</td>
<td>180 ± 43</td>
<td>171 ± 31</td>
<td>163 ± 35</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>224 ± 45</td>
<td>54 ± 14</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per kg)</td>
<td>Stratification</td>
<td>4.0 ± 0.2</td>
<td>5.1 ± 0.2</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>3.7 ± 0.4</td>
<td>4.2 ± 0.3</td>
<td>3.4 ± 0.3</td>
</tr>
</tbody>
</table>

aACEi, angiotensin-converting enzyme inhibitor; VEH, vehicle; VPI, vasopeptidase inhibitor.

bP < 0.05 versus stratification.

cP < 0.05 versus VEH.

dP < 0.05 versus ACEi.
group (Table 3) and therefore were not different between ACEi and VPI. The maximal rate of left ventricular isovolumetric pressure development ($\frac{dP}{dt_{\text{max}}}$) was significantly higher in the ACEi- compared with the vehicle-treated group. A similar trend, although not statistically significant, was observed in the VPI-treated group (Table 3). The isovolumetric pressure decay ($-\frac{dP}{dt_{\text{max}}}$) was not affected by therapy.

### Renal Characteristics

Daily urinary total protein excretion increased in the entire cohort from a baseline level of $16 \pm 1$ to $167 \pm 20$ mg/d at stratification with comparable levels in all groups (Table 1). After a subsequent treatment period of 6 wk, proteinuria was significantly lower in the ACEi-treated group ($76 \pm 6\%$) and in the VPI-treated group ($77 \pm 4\%$) compared with the vehicle-treated group (Table 3). The isovolumetric pressure decay ($-\frac{dP}{dt_{\text{max}}}$) was not affected by therapy.

#### Table 2. Treatment effects at the end of the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VEH ($n=12$)</th>
<th>ACEi ($n=16$)</th>
<th>VPI ($n=14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ACE (nmol HisLeu/ml per min)</td>
<td>75 ± 6</td>
<td>45 ± 4$^b$</td>
<td>30 ± 4$^b,c$</td>
</tr>
<tr>
<td>Renal ACE (nmol HisLeu/ml per min)</td>
<td>28 ± 3</td>
<td>13 ± 2$^b$</td>
<td>7 ± 1$^b,c$</td>
</tr>
<tr>
<td>Plasma renin activity (ng AngI/ml per h)</td>
<td>11 ± 5</td>
<td>24 ± 2$^b$</td>
<td>25 ± 4$^b$</td>
</tr>
<tr>
<td>Pro-ANP (pmol/ml)</td>
<td>14 ± 1.5$^c$</td>
<td>5 ± 0.7$^b$</td>
<td>12 ± 1.1$^c$</td>
</tr>
</tbody>
</table>

$^a$AngI, angiotensin I; Pro-ANP, pro-atrial natriuretic peptide.  
$^bP < 0.05$ versus VEH.  
$^cP < 0.05$ versus ACEi.

### Figure 1

Effect of treatment with angiotensin-converting enzyme inhibitor (ACEi) and vasopeptidase inhibitor (VPI) on systolic BP (SBP; A) and proteinuria (B), given as change in SBP and change in proteinuria from stratification (week 17). *$P < 0.001$ versus vehicle (VEH).

At the end of the study, no significant differences were present in the wet weight of the remaining left kidney. Glomerular damage was investigated by measurement of glomerular surface area, FGS, MME, glomerular α-SMA staining, and glomerular desmin staining (Figure 2). Glomerular surface area was significantly smaller in ACEi- compared with the vehicle-treated group. VPI treatment did not affect glomerular surface area. FGS was significantly lower in ACEi- compared with the vehicle-treated group, and a trend toward a lower level was observed for the VPI-treated group ($P = 0.11$). Glomerular α-SMA staining was significantly lower after treatment with both ACEi and VPI compared with the vehicle-treated group.
Table 3. Cardiac parameters at the end of the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VEH (n = 12)</th>
<th>ACEi (n = 16)</th>
<th>VPI (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI size (%)</td>
<td>30 ± 3</td>
<td>24 ± 4</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>1.68 ± 0.06</td>
<td>1.40 ± 0.05b</td>
<td>1.38 ± 0.03b</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>321 ± 9</td>
<td>329 ± 10</td>
<td>340 ± 10</td>
</tr>
<tr>
<td>SBPcentral (mmHg)</td>
<td>115 ± 6</td>
<td>92 ± 2b</td>
<td>85 ± 4b</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>17 ± 3</td>
<td>12 ± 1b</td>
<td>11 ± 1b</td>
</tr>
<tr>
<td>LVESP (mmHg)</td>
<td>117 ± 6</td>
<td>94 ± 2b</td>
<td>87 ± 4b</td>
</tr>
<tr>
<td>+dP/dtmax (/s)</td>
<td>64 ± 5</td>
<td>81 ± 3b</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>−dP/dtmax (/s)</td>
<td>−85 ± 2</td>
<td>−86 ± 2</td>
<td>−82 ± 3</td>
</tr>
</tbody>
</table>

aLVEDP, left ventricular end diastolic pressure; LVESP, left ventricular end systolic pressure; MI, myocardial infarction; SBPcentral, central systolic BP.
bP < 0.05 versus VEH.

No significant differences in MME were observed after treatment with ACEi and VPI compared with vehicle. The level of desmin staining, as a measure for podocyte damage, was significantly lower after VPI treatment compared with both ACEi and vehicle. Interstitial damage was investigated by the measurement of IF, interstitial α-SMA staining, and interstitial ED-1 staining (Figure 2). A trend toward lower levels of IF was observed after treatment with ACEi (P = 0.2) and VPI (P = 0.2) compared with vehicle. A significant lower interstitial α-SMA staining was observed in both the ACEi- and the VPI-treated groups compared with the vehicle-treated group. A similar pattern was seen for the number of ED-1–positive cells.

**Discussion**

This study confirms our previous finding that MI induces enhanced progressive renal damage in unilateral nephrectomized rats (11). This detrimental cardiorenal interaction can be attenuated by treatment with either an ACE inhibitor or a VPI, with substantial beneficial effects on kidney and heart. It is interesting that the addition of NEP inhibition on top of ACEi (as offered by the VPI) was devoid of extra protection.

Several mechanisms have been hypothesized, including hemodynamic alterations, involvement of the RAAS and sympathetic nervous system, endothelial dysfunction, and inflammation (27), which also are thought to interact with each other. First, as far as the role of hemodynamics in explaining the observed cardiorenal interaction is concerned, reduced cardiac output after MI may lead to reduced renal perfusion, which in turn could lead to compensatory RAAS activation. This RAAS activation in turn can be detrimental to both heart and kidney. An elevated angiotensin II level is known to interact with cardiac function, leading to progressive cardiac function loss (28), and elevated angiotensin II levels may lead to progressive renal damage (29). It is interesting that RAAS intervention with either ACEi or angiotensin II receptor blocker can protect both heart and kidney (30,31). In our cardiorenal interaction model, ACEi therapy was effective in the prevention of enhanced renal damage that was caused by MI, because the level of proteinuria, interstitial and glomerular α-smooth muscle actin staining, glomerular surface area, and FGS incidence were significantly lower compared with those in the vehicle group. The level of renal inflammation (ED-1 staining) seemed to be significantly lower in the ACEi-treated group. It is interesting that cardiac contractility (+dP/dtmax) and LVEDP showed a more favorable outcome in the ACEi compared with the vehicle-treated group at the end of the study. In view of these findings, it is likely that the RAAS is of significant importance in this cardiorenal interaction model. It should be taken into account, however, that RAAS inhibition is invariably associated with BP reduction. Therefore, lowering BP by means of a calcium channel blocker would be an interesting strategy to allow further for a distinction between BP lowering per se and blockade of the RAAS.

Regarding VPI treatment, it has been postulated that natriuretic peptides act on both the heart and the kidneys by vasodilation, natriuresis, diuresis, decreased cell growth, inhibition of the sympathetic nervous system, and inhibition of the RAAS (32). In our previous study, we found a trend toward a decrease in natriuretic peptide levels in the group with combined cardiac and renal damage, whereas in the group with only cardiac damage, higher levels were observed (11). From this observation, we hypothesized a role for natriuretic peptides in the deteriorating effect of the cardiorenal interaction. However, no additional protective effect of VPI over ACEi on renal damage as measured as FGS, proteinuria, and interstitial and glomerular α-smooth muscle actin staining was observed in our study. Although VPI was more effective than ACEi in prevention of podocyte damage, this did not result in the expected augmented prevention of increased proteinuria or FGS (33). Overall, this leaves only a little evidence for a discernible beneficial effect of an increased level of natriuretic peptides beyond concurrent RAAS inhibition and associated BP reduction in this cardiorenal model with short-term pharmacologic intervention. Our study, however, does not exclude VPI still to have an important clinical contribution in both “renal” and “cardiac” patients, because VPI have proved to be effective in more isolated renal and cardiovascular disease (18–20,34).

Some caution is needed when interpreting the efficacy of ACEi versus VPI treatment. First, an important issue relates to finding equipotent dosages with respect to effects on BP and plasma ACE activity. Although we performed a pilot experiment to determine dosage levels that yield a comparably re-
Reduced level of plasma ACE activity with ACEi and VPI treatment in healthy rats, ACE activity was not reduced similarly by both treatment regimens in our study, although effects on BP were comparable. Besides this, no full dose-response relationships were established in our study. However, this would not change substantially the interpretation of the data, because the selected VPI dosage resulted in a larger reduction in ACE activity. The effects on proteinuria, α-SMA, and FGS were comparable. This might indicate a dissociation between the level of ACEi and antiproteinuric effect of these drugs. Second, despite the substantial increase in pro-ANP levels in the VPI compared with the ACEi-treated group, the NEP inhibiting component of the VPI may have insufficiently increased the levels of natriuretic peptides at the selected dosage to provide cardiorenal protection. Third, a VPI treatment period that is longer than 6 wk may be required for the beneficial cardiorenal protection.

Figure 2. Renal histologic characteristics. Representative photomicrographs and quantitative scoring of focal glomerulosclerosis (FGS) and mesangial matrix expansion (MME; A), interstitial and glomerular α-smooth muscle actin (α-SMA) staining (B), interstitial fibrosis (IF; C), glomerular desmin staining (D), and ED-1–positive cells (E). □, VEH; ■, ACEi; ■, VPI. *P < 0.05 versus VEH; †P < 0.05 versus VEH and ACEi. Magnifications: ×40 in A and D; ×20 in B, C, and E.
effects of ANP to develop. Taal et al. (18) showed that the VPI omapatrilat displayed favorable effects compared to the ACEi enalapril at a treatment duration of 32 wk in five-sixths nephrectomized rats, despite comparable efficacy in the short term. Further long-term studies are needed to clarify this issue.

Conclusion

Our results demonstrate the efficacy of RAAS-inhibiting therapy to prevent the enhanced progression of renal damage after MI in a model of mildly compromised renal dysfunction. This intervention is of potential clinical relevance, because it breaks a vicious circle: MI leading to cardiac dysfunction in turn leading to renal dysfunction triggering further cardiac dysfunction. This, however, will require changes in prescribing behavior of doctors who treat patients after MI. Patients are not regularly prescribed RAAS intervention after MI (35), whereas “cardiac” patients with compromised renal function are being approached with utmost care as far as RAAS intervention is concerned (36). This is in favor of the recent view that these drugs reduce long-term cardiovascular morbidity and mortality, apart from their direct effects on BP and proteinuria. Our study further indicates that RAAS intervention after MI may provide not only cardiac protection but also renal protection.

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