Angiotensinergic Versus Nonangiotensinergic Hemodynamic Effects of Converting Enzyme Inhibition in Patients With Chronic Heart Failure

Assessment by Acute Renin and Converting Enzyme Inhibition

Wolfgang Kiowski, MD; Jens Beermann, MD; Peter Rickenbacher, MD; Ruedi Haemmerli, MD; Martin Thomas, MD; Felix Burkart, MD; Thomas Meinertz, MD

Background The contribution of nonangiotensinergic effects of converting enzyme inhibitors to their hemodynamic effects in patients with chronic heart failure is not clear. A comparison of the effects of renin and converting enzyme inhibition should help to clarify this issue.

Methods and Results Thirty-six patients with chronic heart failure (New York Heart Association class II or III) were randomly assigned to receive double-blind either intravenous placebo, the renin inhibitor remikiren, or the converting enzyme inhibitor enalaprilat followed by infusion of a second placebo infusion, the addition of remikiren to enalaprilat, or the addition of enalaprilat to remikiren, respectively. Systemic hemodynamics (Swan-Ganz and radial artery catheters) were measured before (rest and submaximal recumbent bicycle ergometry), during (rest), and at the end (rest and exercise) of each 45-minute single- or combination-infusion period. Placebo did not change hemodynamics or renin activity. Effective inhibition of the renin-angiotensin system by remikiren and enalaprilat was indicated by increases of plasma immunoreactive renin together with rapid and complete inhibition of renin activity after remikiren and an increase after enalaprilat (all P≤.05). Remikiren and enalaprilat rapidly and to a similar extent reduced resting blood pressure through a reduction of systemic vascular resistance, and these changes were significantly correlated to baseline plasma renin activity. Both compounds also decreased pulmonary artery, pulmonary capillary wedge, and right atrial pressures to a similar extent (P≤.05). During exercise, pulmonary capillary wedge and right atrial pressures were equally reduced and stroke volume index was increased with remikiren and enalaprilat (P≤.05 for both). The combination of converting enzyme with renin inhibition or vice versa did not cause additional hemodynamic changes.

Conclusions Specific renin inhibition in patients with chronic heart failure produces short-term hemodynamic effects that are almost indistinguishable from those of converting enzyme inhibition. This finding and the lack of additional effects of converting enzyme inhibition added to renin inhibition suggest that nonangiotensinergic effects of converting enzyme inhibitors do not play a significant role in their short-term hemodynamic effects in patients with chronic heart failure. (Circulation. 1994;90:2748-2756.)

Key Words: • renin • converting enzymes • remikiren • enalaprilat • heart failure

Angiotensin-converting enzyme inhibitors improve symptoms,1,2 prevent the progression of left ventricular dysfunction and dilatation,3,4 and reduce mortality5,6 in patients with chronic heart failure. Although their name implies that their mechanism of action relates to the inhibition of angiotensin-converting enzyme and a reduced formation of the vasoconstrictor peptide angiotensin II, it is well known that converting enzyme also cleaves other peptides, including vasodilating kinins.7 Accordingly, blockade of the enzyme also leads to reduced degradation of kinins8,9 and accumulation of kinins or vasodilating prostaglandins and therefore may contribute to the blood pressure and hemodynamic effects of angiotensin-converting enzyme inhibitors in normotensive10 and hypertensive humans11-13 and in patients with chronic heart failure,14,15 respectively. The development of potent and specific inhibitors of renin16-19 has provided the opportunity to study the effects of a reduction of angiotensin II formation independent of potential effects related to bradykinin accumulation. These compounds derived from the minimal sequence of angiotensinogen reacting with renin specifically inhibit renin as the rate-limiting enzyme in the cascade leading to formation of the vasoconstricting peptide angiotensin II.20,21 Angiotensinogen is the only known natural substrate for renin, and therefore renin inhibition does not lead to inhibition of bradykinin degradation.9,10 Thus, a comparison of the effects of angiotensin-converting enzyme with those of renin inhibition appears to be well suited to differentiate angiotensinergic from nonangiotensinergic effects of converting enzyme inhibition.22 To further
clarify this issue, we compared the short-term hemodynamic changes induced by the angiotensin-converting enzyme inhibitor enalaprilat with those of the renin inhibitor remikiren\(^1\) in patients with chronic heart failure. Because additive hemodynamic effects of angiotensin-converting enzyme and renin inhibitors have also been described,\(^24-26\) we studied also the effects of adding enalaprilat to remikiren and vice versa.

**Methods**

**Patients**

Three female and 33 male patients (age range, 37 to 75 years; mean age, 57.5±9.7 years) with chronic heart failure of more than 3 months' duration and dyspnea according to New York Heart Association class II (n=11) or III (n=25) despite therapy with digoxin (n=24), diuretics (n=36), or angiotensin-converting enzyme inhibitors (n=20) participated in the study. Seventeen patients had underlying coronary artery disease with previous myocardial infarctions, but none had angina at the time of study. Nineteen patients had underlying idiopathic dilated cardiomyopathy. Angiotensin-converting enzyme inhibitor therapy was discontinued for 2 weeks in the respective patients, and the diuretic was withheld on the morning of the hemodynamic study in all. To be included in the study, patients had to have a reduced left ventricular ejection fraction determined by either contrast or radionuclide ventriculography (range, 9% to 45%; mean, 27.3±9.1%) and a pulmonary artery wedge pressure during right heart catheterization at rest and during exercise of more than 12 and 20 mm Hg, respectively, or a reduced cardiac index at rest (<2.5 L·min\(^{-1}\)·m\(^{-2}\)).

The study protocol was approved by the respective hospitals' ethical committees on the use of human subjects in clinical investigations, and written informed consent was obtained from all subjects before the study.

**Hemodynamic Measurements**

Systemic hemodynamics were measured invasively using standard techniques.\(^27\) In short, a flow-guided Swan-Ganz thermodilution catheter was inserted percutaneously under local anesthesia (lidocaine 1%), and the tip was advanced under fluoroscopic guidance to the pulmonary artery for measurement of right atrial, systolic, diastolic, and mean pulmonary pressures and pulmonary capillary wedge pressure. Thermodilution cardiac output was determined by injecting 10 mL of ice-cold saline into the right atrium, and the average of two consecutive measurements varying less than 10% was calculated. Systolic, diastolic, and mean arterial pressures were measured directly from the radial or brachial artery, which was cannulated under local anesthesia with an 18-gauge catheter (Abbocath-T, Abbott). Systemic vascular resistance (dyne·s\(^{-1}\)·cm\(^{-5}\)) was calculated by dividing mean arterial pressure by cardiac output. Heart rate was measured from the ECG, which was monitored throughout the study.

**Hormone Determinations**

Arterial blood for measurement of renin was drawn into precooled tubes containing EDTA, immediately placed on ice, centrifuged at 4°C, and frozen at -70°C until assaying. All samples from a subject were analyzed in duplicate in the same assay to avoid interassay variability. For the determination of plasma renin activity, the trapping methodology of Poulsen and Jørgensen\(^28\) as modified by Nussberger et al\(^29\) was used. Immunoactive renin was measured with an immunoradiometric assay (Diagnosics Pasteur). The monoclonal antibody used does not crossreact with inactive prorenin but crossreacts fully with active renin even when inhibited.\(^30\) Remikiren interferes slightly in this assay, but interference was less than

**Fig 1.** Diagram depicting sequence of interventions and measurements.

10% at 10 nM, a plasma concentration that is 10 times higher than the IC\(_{50}\) measured in the plasma assay.\(^31\)

**Randomization and Drug Administration**

Patients were randomized per center in groups of three to one of the following groups (Fig 1). One group received a placebo infusion followed by confusion of a second placebo. The second group received the renin inhibitor remikiren followed by confusion of the angiotensin-converting enzyme inhibitor enalaprilat. The third group received enalaprilat followed by confusion of remikiren.

All infusions were freshly prepared, and doses were adjusted to the patients' weight by the respective hospitals' pharmacies. Drug concentrations were calculated so that identical volumes of the two infusions were infused for each patient using constant-speed infusion pumps (Perfusor, B. Braun). Treatment was started with a slow intravenous bolus injection administered over 5 minutes and followed by a constant-rate infusion until the end of the study. Eighty minutes after the start of the first infusion, the second infusion was started in an identical way, starting with a slow intravenous injection followed by confusion of both compounds for the remainder of the study. Placebo infusions consisted of 0.9% saline. Remikiren was given as a 0.3 mg/kg intravenous bolus followed by infusion at a rate of 0.1 mg/kg per hour. This dosage regimen was chosen based on previous studies in volunteers showing rapid, complete, and long-lasting renin inhibition after similar intravenous doses.\(^32\) Enalaprilat was administrated as a 9 μg/kg intravenous bolus followed by infusion of 1.5 μg/kg per hour. This dosage regimen was chosen based on the manufacturer's recommendation and published data showing that similar doses induced rapid hemodynamic changes and complete inhibition of angiotensin-converting enzyme.\(^33-36\)

**Study Protocol**

All studies were performed in the morning with the patients recumbent and comfortably resting after a light breakfast. The studies were performed in a quiet, air-conditioned room at an ambient temperature of 20° to 22°C and lasted approximately 4 to 5 hours. The sequence of assessments is depicted schematically in Fig 1. After completion of instrumentation, the patients were allowed to rest for 60 minutes. Subsequently, resting pressure, heart rate, and cardiac output were measured, and blood was withdrawn for hormone determinations. The subjects then underwent recumbent bicycle ergometry with a load adjusted to 60% of the patients' previously determined physical work capacity. Measurements during exercise started at the beginning of the third minute and were always obtained in exactly the same order. Patients were then allowed to rest for 30 minutes, after which hemodynamic measurements were repeated to ensure that baseline values had been reached again. Then, measurements of pressures, heart rate, cardiac output, and hormones were obtained as indicated in Fig 1 during the first drug infusion. Forty-five minutes after starting the first drug infusion, patients repeated
TABLE 1. Baseline Characteristics of the Three Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo+Placebo</th>
<th>Remikiren+Enalaprilat</th>
<th>Enalaprilat+Remikiren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.6±9.6</td>
<td>59±8.2</td>
<td>55±10.1</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/2</td>
<td>11/1</td>
<td>12/0</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.8±0.4</td>
<td>2.6±0.5</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>29.8±10.5</td>
<td>25.3±8.5</td>
<td>26.6±8.2</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133.7±22.6</td>
<td>127.8±24.2</td>
<td>135.7±18.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.3±12.6</td>
<td>78.5±15.1</td>
<td>78.5±6.8</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>18.7±11.6</td>
<td>22.2±14.5</td>
<td>19.3±9</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.54±0.67</td>
<td>2.50±0.82</td>
<td>2.40±0.51</td>
</tr>
<tr>
<td>Plasma renin activity, ng</td>
<td>1.8±1.6</td>
<td>2.3±1.6</td>
<td>1.6±1.6</td>
</tr>
</tbody>
</table>

the exercise test using the same workload. Subsequently, with the first infusion continuing, patients were allowed to recover from the exercise test for 30 minutes after which hemodynamic measurements were assessed immediately before starting the second infusion. Measurements of pressures, heart rate, cardiac output, and hormones were then repeated during the combined infusions in the same sequence as during the first single infusion, followed after 45 minutes by a final assessment of exercise hemodynamics.

Statistical Analysis

Results are expressed as mean±SD. ANOVA was used to assess differences in baseline variables among the three study groups, and two-way profile analysis of repeated measures was used to assess the effects of enalaprilat, remikiren, and placebo on hemodynamic and hormonal changes. The unpaired Student’s t test and linear regression analysis were used as appropriate. A two-tailed P<.05 was considered to indicate a significant difference. All calculations were performed using the STATVIEW IV (Abacus Inc) statistical program.

Results

Baseline characteristics of the three study groups are depicted in Table 1. There were no significant differences in hemodynamic or hormonal parameters among the groups assigned to the three different regimens. Two patients were withdrawn from the study. One patient developed symptomatic hypotension 15 minutes after enalaprilat was started during the first infusion period. Rapid infusion of 0.9% saline reversed hypotension, and the patient recovered without sequelae. Technical problems necessitated termination of the study at the end of the first infusion before the repeat exercise test in the other patient who was randomized to placebo infusions.

Hormonal Responses

The time course and magnitude of changes in plasma renin activity and total, immunoreactive renin concentration during infusion of either placebo, remikiren, or enalaprilat are summarized in Table 2. Placebo did not change either parameter. Renin inhibition by remikiren and angiotensin-converting enzyme inhibition by enalaprilat both resulted in an increase of immunoreactive plasma renin concentration. In addition, remikiren induced a significant, rapid (eg, within 5 minutes), and persisting reduction of plasma renin activity to almost undetectable levels in all patients, whereas enalaprilat significantly increased plasma renin activity.

The effects of adding remikiren to enalaprilat and vice versa in comparison to the effects of a second placebo infusion are depicted in Fig 2. Placebo did not change either hormone measurement, but plasma renin activity decreased rapidly and significantly when remikiren was added to enalaprilat (from 2.12±2.12 to 0.08±0.02 ng/min per hour after 45 minutes), and immunoreactive renin increased significantly from 85.6±128 to 165±216 pg/mL. The addition of enalaprilat to remikiren did not change either hormone measurement significantly.

Hemodynamic Responses to Renin and Angiotensin-Converting Enzyme Inhibition

The time course of hemodynamic changes for resting mean arterial, mean pulmonary artery, and pulmonary

TABLE 2. Resting Plasma Renin Activity and Plasma Immunoreactive Renin Concentration Before and at the End of the First Infusion in the Three Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Remikiren</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 5 min</td>
<td>15 min</td>
</tr>
<tr>
<td>PRA, ng angiotensin L·mL⁻¹·h⁻¹</td>
<td>1.82±1.63</td>
<td>1.80±1.64</td>
</tr>
<tr>
<td>Immunoreactive renin, pg/mL</td>
<td>64±71</td>
<td>63±76</td>
</tr>
</tbody>
</table>

PRA indicates plasma renin activity.

*P<.05, †P<.01 by repeated-measures ANOVA; note that baseline value for PRA is different from that given in Table 1 for the enalaprilat group since one subject was withdrawn from the study due to symptomatic hypotension.
capillary wedge pressures during infusion of placebo, remikiren, or enalaprilat is depicted in Fig 3. Resting and exercise hemodynamic measurements before and at the end of each single infusion are summarized in Table 3.

Placebo did not change any hemodynamic parameter at rest or during exercise, attesting to the reproducibility of the methods used and the adequacy of the study design. In contrast, both remikiren and enalaprilat significantly reduced resting blood pressure, pulmonary artery, and pulmonary capillary wedge pressure within 5 minutes after the respective infusions were started.

As detailed in Table 3, the pattern and magnitude of resting hemodynamic changes were almost identical for remikiren and enalaprilat, although some hemodynamic changes, although numerically similar, were significant compared with baseline measurements for one compound but not for the other (eg, right atrial pressure and cardiac index). However, none of these differences between remikiren and enalaprilat reached statistical significance. Both drugs caused a marked reduction in peripheral vascular resistance. As shown in Fig 4, the reduction in systemic vascular resistance was significantly correlated to pretreatment plasma renin activity for either drug. Likewise, the decrease in diastolic arterial pressure correlated with pretreatment plasma renin activity for both remikiren \( (r=0.59, P<0.05) \) and enalaprilat \( (r=0.85, P<0.01) \).

As would be expected from preload and afterload reducing therapy, cardiac filling pressures, eg, pulmonary capillary wedge and right atrial pressures, were significantly and similarly lowered during exercise in patients administered remikiren or enalaprilat (Table 3). Heart rate during exercise was lower, although not statistically significant, after remikiren and enalaprilat, and stroke volume index was significantly increased with both compounds. Interestingly, systolic and diastolic blood pressures were reduced only by remikiren but not by enalaprilat during exercise. Systemic vascular resistance during exercise decreased numerically but not statistically significant \( (P=0.062) \) after remikiren and was unchanged after enalaprilat.

**Hemodynamic Responses to Combined Renin and Angiotensin-Converting Enzyme Inhibition**

Thirty minutes after the end of the exercise test at the end of the first infusion period, resting hemodynamic parameters were unchanged compared with the last resting measurements obtained immediately before the exercise test, indicating hemodynamic stability. Adding the second to the first placebo infusion did not cause hemodynamic changes at rest or during exercise. Also, neither the addition of enalaprilat to remikiren nor the addition of remikiren to enalaprilat resulted in systematic hemodynamic effects for any measured or calculated variable at rest or during exercise. This lack of additional effect is illustrated in Fig 5 by unchanged mean values for mean arterial blood, pulmonary capillary wedge, and right atrial pressures and systemic vascular resistance (all three treatment groups) and in the plot of systemic vascular resistance values at the end of the single-infusion period versus those at the end of the combined-infusion period (Fig 6; active treatment groups only). It is evident that the regression line for the relation for both groups combined was almost superimposable on the line of identity (broken line). This also held true when the two active treatment groups were considered separately (slopes statistically not different from that of the line of identity) or when percent changes of systemic vascular resistance from baseline were compared instead of absolute values (enalaprilat first: \( y=94 \times 0.94x, r=0.82, P<0.001 \); remikiren first: \( y=3.7 \times 1.05x, r=0.86, P<0.001 \)).

**Discussion**

This double-blind, randomized, and placebo-controlled study provides evidence that the mechanism of immediate action of angiotensin-converting enzyme inhibitors in patients with chronic, stable heart failure predominantly reflects reduction of angiotensin II levels and not effects related to reduced degradation of va-

---

**Table 2. Continued**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Enalaprilat</th>
<th>Remikiren</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5 min</td>
<td>15 min</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>1.1±0.88</td>
<td>1.4±1.4</td>
<td>2.07±2.21</td>
</tr>
<tr>
<td>33±34</td>
<td>37±41</td>
<td>80±125</td>
</tr>
</tbody>
</table>

**Fig 2.** Bar graph of sequential determinations of plasma renin activity and immunoactive renin in the three study groups during the second combined-infusion period. Values are mean±SD. *P<0.05, **P<0.01 for repeated-measures ANOVA. Al indicates angiotensin I.

**Fig 3.** Bar graph of sequential hemodynamic measurements in the three study groups during the first single-infusion period. Note the lack of hemodynamic changes in the group given placebo. Values are mean±SD. **P<0.01 for repeated-measures ANOVA. PCWP indicates pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; and BP, blood pressure.
TABLE 3. Hemodynamic Parameters at Rest and During Exercise in the Three Treatment Groups Before and at the End of the First Infusion

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Remikiren</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>45 min</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>82.3±12.7</td>
<td>117.6±14.0</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>138.3±20.4</td>
<td>171.1±27.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.8±13.5</td>
<td>86.8±15.4</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>40.2±16.5</td>
<td>69.3±18.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>19.9±11.8</td>
<td>40.3±13.8</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>7.7±5.8</td>
<td>16.9±7.9</td>
</tr>
<tr>
<td>Cardiac index, L.min⁻¹.m⁻²</td>
<td>2.54±0.7</td>
<td>4.31±1.4</td>
</tr>
<tr>
<td>Stroke volume index, mL.beat⁻¹.m⁻²</td>
<td>31.3±9.1</td>
<td>37.7±13.0</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne·s⁻¹·cm⁻⁵</td>
<td>1616±696</td>
<td>1139±766</td>
</tr>
</tbody>
</table>

*P<.05, †P<.01 by repeated-measures ANOVA including all measurements up to the 45th minute of infusion; ‡P<.05 for paired comparison with baseline exercise values.

Sodilating kinins and/or accumulation of sodilating prostaglandins. This conclusion is based on the following considerations.

Remikiren and enalaprilat given alone resulted in short-term hemodynamic changes that were almost identical; systemic vascular resistance at rest decreased by 16% with either compound, left ventricular filling pressures were reduced by 24% and 25%, and diastolic arterial pressures decreased by 11% and 12%, respectively, without increases in heart rate. Accordingly, cardiac index increased as a result of afterload reduction by 14% and 8% with remikiren and enalaprilat, respectively. Because hemodynamics remained remarkably stable in patients assigned to placebo infusions, the similarity of changes in patients randomized to remikiren and enalaprilat alone and in combination is unlikely due to chance. Further support for this contention comes from results obtained during combination therapy. Thus, addition of enalaprilat to remikiren did not result in additional hemodynamic changes as would be expected if nonangiotensinergic effects of converting enzyme inhibition had been of importance. This is borne out not only by unchanged mean hemodynamic values but also by the close relation between individual systemic vascular resistance values at the end of the single-infusion period and those of the combined-infusion period. If enalaprilat would have had an additive effect, the slope of the regression line should have been significantly smaller than that of the line of identity. This, however, was not the case. In addition, the main hemodynamic changes, eg, reductions in blood pressure and systemic vascular resistance, were significantly correlated with the pretreatment activity of the renin-angiotensin system for both the renin inhibitor re-

**FIGURE 4.** Scatterplot of pretreatment plasma renin activity and changes of systemic vascular resistance in patients randomized to receive remikiren or enalaprilat. Changes in systemic vascular resistance reflect those obtained at the end of the first single-drug infusion period.

**FIGURE 5.** Bar graph of sequential hemodynamic measurements in the three study groups during the second combined-infusion period. Note the lack of effect of the addition of enalaprilat (E) to remikiren (R+E) and of remikiren (R) to enalaprilat (E+R). Values are mean±SD.
mikiren and for enalaprilat. Although such a correlation at least in theory might be expected for a specific renin inhibitor such as mikiren and has been described in an experimental model of ovine heart failure\(^{37}\) and in human hypertension,\(^{38}\) its existence for the angiotensin-converting enzyme inhibitor might be taken as evidence that interference with the renin-angiotensin system was the major determinant of the hemodynamic effects of enalaprilat.\(^{39}\) However, it must be kept in mind that correlations cannot prove a causal relation, although they are well compatible with it. Finally, angiotensin II type 1 receptor blockade by specific receptor antagonists also resulted in hemodynamic changes comparable to those of captorpril in a rat model of heart failure.\(^{40}\) No direct comparison of hemodynamic effects has been studied in humans, but the magnitude of hemodynamic changes after administration of the angiotensin II type 1 receptor antagonist losartan in patients with chronic heart failure appears to be of similar magnitude compared with published data regarding converting enzyme inhibitors.\(^{41}\)

The acceptance of this interpretation of the present data relies to a major degree on the assumption that complete blockade of the renin-angiotensin system was induced by either drug. The renin inhibitor used in this study is a transition-state renin substrate analogue with a high affinity for human renin, little or no affinity for other aspartyl proteases, and virtually no effect on angiotensin-converting enzyme in animals\(^{42}\) or humans.\(^{43}\) In the present study, plasma renin activity was rapidly reduced to almost undetectable levels after administration of remikiren in all subjects. In agreement with the known regulatory mechanisms governing renin release, immunoreactive renin increased after remikiren due to interruption of negative feedback control of plasma renin by reduced angiotensin II levels.\(^{44}\) This effect persisted throughout the period of drug administration, confirming the potency of this renin inhibitor when administered intravenously in humans.\(^{32,44}\)

Enalaprilat also caused biochemical changes compatible with blockade of the renin-angiotensin system; plasma renin activity and immunoreactive renin increased as expected from a loss of negative feedback control of plasma renin by reduced angiotensin II levels, but incompleteness of converting enzyme blockade is more difficult to determine without measurement of converting enzyme activity or plasma angiotensin II concentrations. However, indirect evidence suggests that enalaprilat caused complete blockade of the renin-angiotensin system. Thus, renin inhibition by remikiren after enalaprilat completely suppressed elevated plasma renin activity but did not cause additional hemodynamic effects as has been described when blockade of the renin-angiotensin system by a converting enzyme inhibitor alone was incomplete\(^{45}\) or when enalaprilat-induced hyperreninemia caused blood pressure to become partially renin dependent. Also, intravenous infusion without preceding bolus injection of a much lower dosage of enalaprilat, eg, 0.25 mg/hr, inhibited plasma angiotensin-converting enzyme activity already by approximately 60% after 1 hour.\(^{46}\) Thus, it appears reasonable to assume that the present dosage regimen using an approximately three times more initial bolus (9 μg/kg or 0.675 mg for a 75-kg patient) followed by a low-dose infusion resulted in complete angiotensin-converting enzyme inhibition. Finally, hemodynamic and hormonal changes in this study closely resemble findings in other studies of enalaprilat using higher doses.\(^{35,39,46}\)

Our findings are in contrast to some others in experimental animals and humans. Thus, data obtained in normotensive healthy volunteers,\(^{10}\) hypertensive patients,\(^{11}\) and normotensive\(^{47}\) and hypertensive\(^{48}\) animals suggest a role of non-angiotensin-mediated effects of angiotensin-converting enzyme inhibitors. The difference between these observations and the present findings is probably best explained by the fact that chronic heart failure is characterized by neurohormonal activation in many patients\(^{49,50}\) and, in particular, by increased activity of the renin-angiotensin system in patients.

### Table 3. Continued

<table>
<thead>
<tr>
<th>Enalaprilat</th>
<th>45 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Rest</td>
</tr>
<tr>
<td>75.3±20.8</td>
<td>111.5±24.9</td>
</tr>
<tr>
<td>135.8±15.5</td>
<td>166.3±31.3</td>
</tr>
<tr>
<td>73.8±10.4</td>
<td>81.9±12.3</td>
</tr>
<tr>
<td>38.1±17.8</td>
<td>65.8±11.2</td>
</tr>
<tr>
<td>19.9±9.7</td>
<td>35.6±5.7</td>
</tr>
<tr>
<td>20.4±9.6</td>
<td>42.1±11.1</td>
</tr>
<tr>
<td>6.7±2.8</td>
<td>14.6±4.9</td>
</tr>
<tr>
<td>2.40±0.5</td>
<td>4.22±1.4</td>
</tr>
<tr>
<td>33.8±10.9</td>
<td>37.9±13.8</td>
</tr>
<tr>
<td>1564±513</td>
<td>1008±403</td>
</tr>
</tbody>
</table>

![Fig 6. Scatterplot of individual systemic vascular resistance (SVR) values at the end of the first single-infusion period versus those at the end of the combined-infusion period in patients randomized to receive either remikiren or enalaprilat first. Note the similarity of the regression line to that of the theoretical line of identity (broken line). When the active treatment groups were considered separately, the corresponding regression lines were also not statistically different from the line of identity (enalaprilat first: y=-68+1.01·x, r=.92, P<.001; remikiren first: y=329+0.85·x, r=.84, P<.001).](http://circ.ahajournals.org/)

---

Kiowski et al  Renin Inhibition in Chronic Heart Failure 2753

---

Downloaded from http://circ.ahajournals.org/ by guest on November 17, 2017
administered diuretics.\textsuperscript{51} This activation of the renin-angiotensin system might lead to a dominance of angiotensin-mediated effects as observed in this study and might explain, at least in part, the different results obtained in normotensive\textsuperscript{10,16} or hypertensive\textsuperscript{13,52} humans.

However, contrasting results have also been described in patients with heart failure. Thus, aspirin counteracted the systemic arterial vasodilation of angiotensin-converting enzyme inhibition with enalapril,\textsuperscript{15} and indomethacin attenuated the forearm vasodilator effects\textsuperscript{34} of captopril in patients with heart failure. These short-term findings, therefore, are compatible with a role of bradykinin-mediated release of vasodilating prostaglandins for the short-term hemodynamic response to angiotensin-converting enzyme inhibition in human heart failure and are not easily reconciled with our results. However, one obvious difference is the investigation of a regional vascular bed, eg, the forearm circulation in one of the studies\textsuperscript{34} compared with the systemic circulation in the present investigation. Thus, it is conceivable that the vascular bed of the forearm, which mostly supplies skeletal muscle, behaves differently from other vascular beds, which may override any potential effect seen in the human forearm. Accordingly, when an integrated approach is chosen, such as the measurement of systemic hemodynamic changes in this study, a regional difference might go undetected. However, even if this were so, the relevance of such regional differences would have to be determined in the presence of almost identical systemic hemodynamic changes.

Although the human forearm\textsuperscript{14} may not be representative for other vascular beds in patients with heart failure, the reduction by aspirin of enalapril-induced systemic vascular resistance changes\textsuperscript{35} is more difficult to reconcile with the present data. Theoretically, the present data cannot exclude the possibility that angiotensin-converting enzyme inhibitors have a dual mode of action and that the contribution of each to the total effect depends on the prevailing activity of the renin-angiotensin system and/or the blood pressure level. Thus, non-angiotensin-mediated effects might be of no major importance when the renin-angiotensin system is already completely blocked and blood pressure is reduced, a situation presented in this study by patients receiving remikiren first followed by enalaprilat. Counterregulatory mechanisms might mask additional non-angiotensin-dependent vasodilation in this situation, but we did not observe additional vasodilation at any time after the addition of enalaprilat to remikiren, and heart rate did not increase. Alternatively, activation of bradykinin and/or prostaglandin effects may require longer than the time span allowed in this study, but other studies in humans appear to argue against this explanation.

Thus, the present results in patients with heart failure appear to be best explained by a predominance of renin-angiotensin system inhibition over any putative non-angiotensin-mediated short-term hemodynamic effect.

This was a short-term study, and the results obviously cannot be extrapolated to long-term therapy as suggested, eg, by greater blood pressure-lowering effects of the converting enzyme inhibitors cilazapril\textsuperscript{53} and lisinopril\textsuperscript{54} during prolonged compared with short-term therapy in animals. However, results from short-term studies in humans suggesting an involvement of nonangiotensinergic mechanisms in the hemodynamic effects of angiotensin-converting enzyme inhibitors\textsuperscript{14,15} also should not be extrapolated to long-term therapy since nonangiotensinergic effects—if they exist—may be only transient and therefore of unknown relevance for long-term hemodynamic effects. Thus, trials using long-term renin inhibition or angiotensin II type 1 receptor blockade will be needed to solve this question eventually. Long-term data certainly would be interesting for renin inhibitors since they should also allow better delineation of the relation between decreases of angiotensin II levels and improvement of symptoms, but they may not be available soon because the oral bioavailability of renin inhibitors currently under investigation is very low. However, demonstration of similar hemodynamic efficacy compared with angiotensin-converting enzyme inhibition, as in the present study, should encourage the pursuit of this potentially new therapeutic modality.

There is little other information regarding the hemodynamic effects of renin inhibition in patients with heart failure, but the magnitude and the pattern of short-term hemodynamic changes at rest in this study are very similar to that described in an open study with enalkiren\textsuperscript{45} in a comparable patient population. No other comparative trials have been published so far, and there are no data for comparison of the effects of remikiren to other renin inhibitors during exercise. However, the results are fully compatible with a beneficial hemodynamic effect of remikiren during physical stress. Although it is not clear whether the greater blood pressure reduction during exercise by remikiren represents a true difference or a chance finding, it is of interest that remikiren decreased blood pressure more than, eg, cilazapril, in an animal model of cyclosporin-induced hypertension.\textsuperscript{26} No data are available regarding the effects of long-term renin inhibition on symptoms and exercise tolerance in human heart failure. If beneficial effects could be shown during long-term therapy, then renin inhibition might offer some advantages over angiotensin-converting enzyme inhibition. Thus, elevated kinin or prostaglandin levels have been implicated in the pathogenesis of certain side effects of angiotensin-converting enzyme inhibitors, such as cough and angioneurotic edema.\textsuperscript{56-58} Because renin inhibitors do not influence these systems, such effects might be avoided.

In conclusion, our results demonstrate that specific renin inhibition in patients with chronic heart failure produces short-term hemodynamic effects that are almost indistinguishable from those of converting enzyme inhibition, suggesting that nonangiotensinergic effects of converting enzyme inhibitors do not play a significant role in their short-term hemodynamic effects in patients with chronic heart failure. Evaluation of long-term renin inhibition is needed to document the clinical effects of specific reductions of angiotensin II.

Acknowledgment

This work was supported by an educational grant from F. Hoffman-LaRoche and Co, Basal, Switzerland.

References

1. Dzau VJ, Colucci WS, Williams GH, Curburn G, Meggs L, Hollenberg NK. Sustained effectiveness of converting-enzyme inhi-


Angiotensinergic versus nonangiotensinergic hemodynamic effects of converting enzyme inhibition in patients with chronic heart failure. Assessment by acute renin and converting enzyme inhibition.

W Kiowski, J Beermann, P Rickenbacher, R Haemmerli, M Thomas, F Burkart and T Meinertz

Circulation. 1994;90:2748-2756
doi: 10.1161/01.CIR.90.6.2748

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/6/2748

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/