Differentiated Response of the Sympathetic Nervous System to Angiotensin-Converting Enzyme Inhibition in Hypertension

Mats Johansson, Mikael Elam, Bengt Rundqvist, Graeme Eisenhofer, Hans Herlitz, Gert Jensen, Peter Friberg

Abstract—Hypertension with renal artery stenosis is associated with both an activated renin-angiotensin system and elevated sympathetic activity. Therefore, in this condition it may be favorable to use a therapeutic modality that does not reflexly increase heart rate, renin secretion, and sympathetic nervous activity. The purpose of the present study was to assess overall, renal, and muscle sympathetic activity after short-term administration of an angiotensin-converting enzyme inhibitor (enalaprilat) and a nonspecific vasodilator (dihydralazine) to hypertensive patients with renal artery stenosis. Forty-eight patients undergoing a clinical investigation for renovascular hypertension were included in the study. An isotope dilution technique for assessing norepinephrine spillover was used to estimate overall and bilateral renal sympathetic nerve activity. In 11 patients simultaneous intraneural recordings of efferent muscle sympathetic nerve activity were performed. Thirty minutes after dihydralazine administration, mean arterial pressure fell by 15%, whereas plasma angiotensin II, muscle sympathetic nerve activity, heart rate, and total body norepinephrine spillover increased (P<0.05 for all). In contrast, after enalaprilat administration a fall in arterial pressure similar to that for dihydralazine was followed by decreased angiotensin II levels and unchanged muscle sympathetic nerve activity, heart rate, and total body norepinephrine spillover, whereas renal norepinephrine spillover increased by 44% (P<0.05). Acute blood pressure reduction by an angiotensin-converting enzyme inhibitor provokes a differentiated sympathetic response in patients with hypertension and renal artery stenosis, inasmuch that overall and muscle sympathetic reflex activation are blunted, whereas the reflex renal sympathetic response to blood pressure reduction is preserved. (Hypertension. 2000;36:543-548.)

Key Words: hypertension, renovascular □ sympathetic nervous system □ renin-angiotensin system

Renovascular hypertension is a condition associated with both an activated renin-angiotensin system and elevated sympathetic nerve activity.1-2 Previous data, obtained in experimental models, indicate a positive interaction between the renin-angiotensin and the sympathetic nervous systems.3 Therefore, in renovascular hypertension it may be favorable to use a therapeutic modality that does not reflexly further increase heart rate, renin secretion, and sympathetic nervous activity. It is well known that certain drugs used in cardiovascular medicine affect various indices of sympathetic activity. For example, sympathetic activity increases in response to nonspecific vasodilators, whereas therapy with angiotensin-converting enzyme (ACE) inhibitors has demonstrated reduced peroneal sympathetic activity.4 Thus, it appears that vasodilators and ACE inhibitors produce different sympathetic nerve responses; the effects of the latter could be due to either a direct-acting central mechanism5,6 or a reduction of angiotensin II (Ang II) facilitatory effects on norepinephrine (NE) release in peripheral sympathetic nerve endings.7,8

The aim of the present study was to assess the effect of short-term ACE inhibition on the adrenergic drive in patients with hypertension and renal artery stenosis. Given that animal experiments indicate different effects on renal nerve activity and heart rate in response to Ang II,9 we also wanted to explore whether there is regional differentiation in the sympathetic response to ACE inhibition and nonspecific vasodilation, with the latter used as a positive control test.

Patients were divided into 2 groups given either a single dose of the ACE inhibitor enalaprilat or a single dose of the nonspecific vasodilator dihydralazine, in an attempt to reduce blood pressure to a similar extent. In this model, the former drug prevents Ang II production and the latter increases Ang II plasma concentrations. The degree of sympathetic activity was estimated by means of NE isotope dilution and direct recordings of sympathetic nerve traffic in the peroneal nerve.

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Baseline Data for Patients With Hypertension and Renal Artery Stenosis Given Either Enalaprilat or Dihydralazine

<table>
<thead>
<tr>
<th></th>
<th>Enalaprilat (n=27)</th>
<th>Dihydralazine (n=21)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±3</td>
<td>55±2</td>
<td>0.45</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>14/13</td>
<td>10/11</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±1</td>
<td>26±1</td>
<td>0.67</td>
</tr>
<tr>
<td>Chromium-Erda, clearance, mL/min · 1.73 m²</td>
<td>66±6</td>
<td>68±7</td>
<td>0.79</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>188±4</td>
<td>177±4</td>
<td>0.06</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>89±4</td>
<td>85±2</td>
<td>0.42</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76±4</td>
<td>69±3</td>
<td>0.23</td>
</tr>
<tr>
<td>Renal plasma flow, mL/min</td>
<td>413±47</td>
<td>480±56</td>
<td>0.36</td>
</tr>
<tr>
<td>Arterial Ang II, pg/mL</td>
<td>30±8</td>
<td>34±9</td>
<td>0.75</td>
</tr>
<tr>
<td>Arterial plasma renin, ng</td>
<td>7±2</td>
<td>8±2</td>
<td>0.89</td>
</tr>
<tr>
<td>Arterial NE, pmol/mL</td>
<td>4.32±0.44</td>
<td>3.36±0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Total body NE clearance, mL/min</td>
<td>1890±224</td>
<td>1579±113</td>
<td>0.65</td>
</tr>
<tr>
<td>Total body NE spillover, pmol/min</td>
<td>7458±739</td>
<td>5843±846</td>
<td>0.14</td>
</tr>
<tr>
<td>Renal NE spillover, pmol/min†</td>
<td>1156±130</td>
<td>1553±284</td>
<td>0.44</td>
</tr>
<tr>
<td>MSA, bursts/min‡</td>
<td>56±3</td>
<td>51±6</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Values represent numbers in each group and mean±SEM.

* Differences between the 2 treatment groups.
† Both kidneys combined.
‡ Muscle sympathetic nerve activity (MSA) was measured in 11 patients.

Methods

Subjects

The local ethical and isotope committees at Sahlgrenska University Hospital approved the studies, and all subjects gave their consent to participate in the study.

The study group comprised patients with hypertension undergoing a clinical investigation for renovascular hypertension, involving renal vein blood sampling for assessment of plasma renin activity (PRA) (Table). The present study population represents a subset of patients referred to in previous publications. All patients had hypertension and renal artery stenosis ≥50% according to angiography. Overall, 57 patients were examined. Nine patients were excluded because of vagal reactions during the catheterization procedure, and therefore 48 patients were included in the study.

Catheterization

Subjects were studied in the morning in a catheterization laboratory. Subjects refrained from smoking and coffee drinking 12 hours before the study. All patients were hospitalized 4 days before catheterization, and while they were inpatients they were kept on a low salt diet (40 mmol/24 h). Diuretics and calcium channel blockers were given during the hospital stay, but other antihypertensive medications were withdrawn 2 days before the investigation. The proportion of patients medicated with calcium channel blockers and diuretics did not differ between the 2 intervention groups. Calcium channel blockers were used by 83% of the patients in the enalaprilat group and by 70% in the dihydralazine group. Diuretics were taken by 65% of the patients in the enalaprilat group and by 70% in the dihydralazine group. No antihypertensive drugs were given for the 12 hours preceding the investigation. A cannula was introduced percutaneously into a left radial artery for blood pressure monitoring and blood sampling. Both renal veins were catheterized via femoral veins, and the renal vein catheters were positioned under fluoroscopic control, with their positions confirmed by means of oxygen saturation.

Infusions

Para-aminobenzozoic acid (PAH) (Merck Sharp & Dohme), with dosing depending on estimated glomerular filtration rate, and tracer doses of 1,2,3,4,5,6-[3H]NE (40 to 60 Ci/mmol, New England Nuclear) were infused into a peripheral vein. An infusion rate of 1.0 to 1.5 µCi/min of [3H]NE was used.

Sympathetic Nerve Recordings

Multunit postganglionic sympathetic nerve activity was recorded with a tungsten microelectrode, with a tip diameter of a few micrometers, inserted into a muscle-innervating fascicle of the peroneal nerve at the fibular head. A reference electrode was inserted subcutaneously 1 to 2 cm from the recording electrode. Details regarding the recording technique and the criteria for muscle sympathetic nerve activity have been described previously. The number of muscle sympathetic nerve activity bursts in the mean voltage neurogram, which occur in bursts strictly coupled to the cardiac rhythm, were counted by inspection of the mean voltage neurogram. Total muscle sympathetic nerve activity is the cumulative burst area per minute (arbitrary units) in the mean voltage neurogram and is presented as percentage of prestimulus control.

Two independent laboratory colleagues, who were not part of the study and had no knowledge of the study protocol, performed the analysis. For interindividual comparisons of baseline activity, muscle sympathetic nerve activity is presented as burst frequency (bursts per minute) calculated from a 5-minute resting period and during a 60-second period starting 6 minutes after enalaprilat or dihydralazine administration. Total muscle sympathetic nerve activity was determined for each individual during successive 60-second periods up to 8 minutes after enalaprilat or dihydralazine administration. Muscle sympathetic nerve activity recordings were available for 11 of 11 subjects up to 6 minutes and for 9 of 11 patients at 8 minutes.

Experimental Protocol

Patients were divided into 2 groups given intravenously either a single dose of 1.25 mg enalaprilat (n=27) or a single dose of 6.25 mg dihydralazine (n=21) during 3 minutes. All blood samples were taken simultaneously from a radial artery and both renal vein(s) at steady state, at least 30 minutes after the [3H]NE and PAH infusions were started. Sampling was performed at baseline and 30 minutes after drug administration. Samples were collected into ice-chilled tubes containing heparin or EDTA and glutathione, including a renin inhibitor for the Ang II tubes. Plasma was separated by centrifugation and stored at −80°C until assayed for catecholamines, PRA, and Ang II. Renal plasma flow was derived from total infusion clearance of PAH corrected for renal fractional extraction, and separate renal plasma flow was assessed by gamma camera renography.

Of the 11 patients in whom muscle sympathetic nerve activity was recorded in addition to measurements of NE spillover, 6 received enalaprilat and 5 dihydralazine. Muscle sympathetic nerve activity was measured at baseline and continuously up to 8 minutes after drug administration. In 5 patients to whom enalaprilat was administered, muscle sympathetic nerve activity was recorded up to 30 minutes after drug administration.

Assays

Catecholamines were extracted from plasma (1 mL) and samples of infusedate (10 µL) with the use of alumina adsorption and separated by high-performance liquid chromatography. Timed collection of [3H] eluate leaving the electrochemical cell permitted separation of [3H]NE for subsequent counting by liquid scintillation spectrometry. Interassay coefficients of variation were 4.6% for endogenous NE and 3.2% for [3H]NE.
PRA was measured according to Giese et al., with the use of radioimmunoassay for angiotensin I (Ang I). EDTA was added to inhibit ACE. The interassay coefficient of variation for the renin analysis was 8.8%. The reference values are 0.2 to 2.0 ng Ang I per milliliter per hour. Ang II was assayed according to Kappelgaard et al. and Morton and Webb. Bestatin was used to specifically inhibit aminopeptidase B and leucine aminopeptidase. The interassay coefficient of variation was 5.1%. The radioactive recovery for 125I-Ang II was 87% and the biological recovery 82% in duplicate determinations.

Calculations
Renal NE spillover was estimated with the use of Fick’s principle corrected for the fractional extraction across the kidney, as follows:

\[
\text{Renal NE spillover} = \left( \frac{\text{NE}_v - \text{NE}_a}{\text{I} \times \text{Ex}} \right) \times \text{RPF}
\]

where \( \text{NE}_v \) and \( \text{NE}_a \) are the concentrations (pmol/mL) of NE in arterial and renal venous plasma, and RPF and Ex are renal plasma flow and fractional extraction of \( [\text{H}] \text{NE} \) across the kidney.

Total body NE spillover was measured by the radiotracer method and calculated according to the following formula:

\[
\text{Total body NE spillover} = \frac{\text{I}}{\text{SA}_A}
\]

where \( \text{I} \) is the infusion rate of tritium-labeled NE in disintegrations per minute (dpm/min), and \( \text{SA}_A \) is the specific activity of NE in arterial plasma (dpm/pmol). \( \text{SA}_A \) is calculated as follows:

\[
\text{SA}_A = \frac{[\text{H}] \text{NE} \times \text{NE}}{\text{NE}_v}
\]

where \( [\text{H}] \text{NE} \) is the plasma concentration of tritium-labeled NE (dpm/mL) and \( \text{NE} \) is the plasma concentration of NE (pmol/mL).

Statistical Methods
Results are expressed as mean±SEM values. Student’s \( t \) tests for paired and unpaired observations were used. Parameters not normally distributed were transformed logarithmically before the parametric test. If a nonnormal distribution was retained, the Wilcoxon signed rank test for paired comparisons and the Mann-Whitney \( U \) test for unpaired comparisons were used. We assessed the relation between 2 variables by calculating the rank correlation coefficient according to Spearman. Effects of enalaprilat and dihydralazine on total muscle sympathetic nerve activity over time were compared with an ANOVA for repeated measurements, with time after drug administration as within-subjects factor and drug as between-group factor. Statistical significance was defined as \( P<0.05 \).

Results
Patients treated with enalaprilat showed a trend toward higher blood pressure and higher arterial NE plasma concentrations compared with patients treated with dihydralazine (Table). The differences, however, were not statistically significant.

Arterial pressure decreased (\( P<0.01 \)) to a similar extent after enalaprilat and dihydralazine, whereas heart rate increased only after dihydralazine and remained unchanged after enalaprilat administration (Figure 1, top panel). Renal plasma flow increased to a similar extent after both enalaprilat and dihydralazine administration (Figure 1; \( P<0.01 \) for both).

PRA increased after both enalaprilat and dihydralazine stimulation, with a more pronounced increase for the former drug (348% increase after enalaprilat versus 134% increase after dihydralazine). As expected, plasma Ang II concentrations decreased by 68% after enalaprilat, whereas dihydralazine administration resulted in a 73% increase. The magnitude of the blood pressure reduction was correlated with the preintervention PRA (\( r=0.53, P<0.01 \)) in enalaprilat-treated patients, whereas no correlation was found in the dihydralazine group.

Arterial plasma NE concentrations increased after dihydralazine (from 3.36±0.39 to 5.03±0.68 pmol/mL; \( P<0.01 \)), whereas they remained unchanged after enalaprilat administration (4.32±0.44 before and 4.56±0.37 pmol/mL after enalaprilat). Total body NE spillover increased by 48% (\( P<0.01 \)) after dihydralazine, whereas no change was seen after enalaprilat administration (Figure 1). Renal NE spillover increased by 44% after enalaprilat (\( P<0.01 \); Figure 1, bottom panel) and tended to increase after dihydralazine administration (\( \approx 15\% \)). There was no correlation between the change in plasma flow and the change in renal NE spillover in either the enalaprilat or the dihydralazine group.

Muscle sympathetic nerve activity measured at baseline and 6 minutes after dihydralazine increased from 51±6 to 59±7 bursts per minute (\( P<0.05 \)), whereas it remained unchanged after enalaprilat administration, at 56±3 before...
sympathetic nerves to facilitate NE release. This mechanism inhibits sympathetic nerve activity, there are several possibilities.

Kidneys, is overridden by ACE inhibition. This implies that baroreceptor control of the general sympathetic outflow, except to the fall in mean arterial pressure. This suggests a role for renal sympathetic nerve activity, increased with hypertension and renal artery stenosis. Renal NE spill-over, an index of renal sympathetic nerve activity, increased after enalaprilat administration. In contrast, simultaneously recorded muscle sympathetic nerve activity, heart rate, and total body NE spillover remained unchanged despite a 14% fall in mean arterial pressure. This implies that baroreceptor control of the general sympathetic outflow, except to the kidneys, is overridden by ACE inhibition.

Although the present study cannot delineate the specific mechanism responsible for the differentiated effect of ACE inhibition on sympathetic nerve activity, there are several possibilities. First, Ang II acts presynaptically in sympathetic nerves to facilitate NE release. This mechanism may explain the inhibited sympathetic response after enalaprilat since blood pressure reduction was accompanied by a fall in Ang II plasma concentrations. However, directly recorded muscle sympathetic nerve activity increased after dihydralazine, whereas no change was seen after enalaprilat administration. This is consistent with a central site of action.

Enalaprilat can reach cerebral tissue through regions without an intact blood-brain barrier and thus directly reduce the activity of the tissue-bound renin-angiotensin system. A reduced circulating level of Ang II, crossing the blood-brain barrier, is another effect of ACE inhibition. Matsumara et al found a blunted baroreflex inhibition of heart rate when Ang II was infused into the vertebral artery compared with intravenous infusion of Ang II, indicating a central effect. Furthermore, inhibition of ACE causes accumulation of bradykinin and increased formation of prostaglandin and nitric oxide, which also may affect central sympathetic outflow.

Although there is some disagreement as to whether Ang II modulates baroreceptor reflex control of heart rate by changing the sensitivity or resetting the reflex control of heart rate to a higher blood pressure level, the latter mechanism is now generally accepted. Consequently, the arterial pressure increase due to infusion of Ang II is followed by a modest bradycardia, contrasting with a marked bradycardia in response to infusion of phenylephrine. When an ACE inhibitor is administered, plasma concentrations of Ang II fall and the baroreflex curve resets to a lower arterial pressure. A resetting of the baroreflex control of heart rate provides an explanation for the lack of heart rate increase after enalaprilat administration in the present study.

Unchanged heart rate and arterial plasma NE concentrations after enalaprilat, in conjunction with an increase of both these variables after dihydralazine administration, are in agreement with the findings of Herlitz et al. Moreover, Ligtenberg et al recently reported a blunted muscle sympathetic nerve response to short-term treatment with enalaprilat compared with the calcium channel blocker amloidipine. Rongen et al reported reduced blood pressure and unchanged total body NE spillover and heart rate after a 1-week treatment of losartan in healthy subjects. Thus, the present findings of unchanged overall and muscle sympathetic nerve activity after short-term ACE inhibition are in agreement with previous results.

The novel findings of a differentiated sympathetic response pattern after enalaprilat in patients with renal artery stenosis corroborate the results of animal experiments. In conscious rabbits, Kumaga and Reid found that both an ACE inhibitor and an angiotensin type I receptor antagonist decreased arterial pressure and increased renal sympathetic nerve activity, whereas heart rate was unchanged. Thus, Ang II resets the baroreflex control of heart rate, leaving the control of renal nerve activity unaffected. In contrast, DiBona et al found decreased renal sympathetic nerve activity after intravenous angiotensin type I receptor blockade, suggesting that endogenous Ang II tonically influences renal baroreflex control in rats on a low or normal but not on a high sodium diet. These contrasting results in animal studies may be due to different experimental approaches. DiBona et al used infusions of methoxamine after losartan administration to restore arterial pressure to baseline values before measuring renal sympathetic nerve activity. Experimental data indicate that arterial baroreceptor activity may respond to constriction and stiffening of aortic smooth muscle, leaving arterial pressure unaffected. Hence, arterial baroreceptors may have been activated by methoxamine, although arterial pressure and filling pressure of the left heart were similar to baseline values.

![Figure 2. Repeated measurements of total muscle sympathetic nerve activity (MSA) during successive 60-second periods before and after enalaprilat (n=6) or dihydralazine (n=5) administration. Total MSA is the cumulative burst area per minute (arbitrary units) in the mean voltage neurogram and is presented as percentage of prestimulus control. Total MSA increased after dihydralazine (P<0.01, repeated ANOVA), whereas no change followed enalaprilat administration.](https://hyper.ahajournals.org/doi/figure/10.1161/01.HYP.83.4.546)
In agreement with Noll et al., who found unchanged muscle sympathetic nerve activity in conjunction with reduced diastolic blood pressure after oral short-term administration of captopril to healthy subjects, we found unchanged muscle sympathetic nerve activity after intravenous administration of enalaprilat, suggesting resetting of the baroreflex control of muscle sympathetic nerve activity to lower blood pressures. This notion is further supported by the findings of Matsukawa et al., who examined muscle sympathetic nerve activity in healthy subjects during equipotent infusions of Ang II and phenylephrine. They found a dose-dependent reduction of muscle sympathetic nerve activity after Ang II that was smaller than during the infusion of phenylephrine.

When the effects of dihydralazine and enalaprilat are compared, it is important to consider the effects on hemodynamics. The former drug is a vasodilator that preferentially dilates arterial blood vessels, whereas the latter also dilates capacitance vessels, thereby reducing the filling pressures of the heart. Hence, it is conceivable that enalaprilat exerts a more pronounced unloading effect on cardiac low-pressure baroreceptors than dihydralazine. Unloading of cardiac low-pressure baroreceptors preferentially activates renal sympathetic nerve activity with little effect on abdominal or peripheral sympathetic outflows. In support of this contention, we have found that short-term enalaprilat administration to healthy subjects causes a slight reduction in mean arterial pressure, whereas left ventricular filling pressure is markedly reduced (M. Johansson et al., unpublished data, 1999).

**Study Limitations**

Regional plasma flow affects NE spillover measurements, and an increase in plasma flow may increase regional NE spillover by a washout effect. In the present study, renal plasma flow increased by only 17% after enalaprilat, whereas renal NE spillover showed a 44% increase. Moreover, there was no correlation between the change in renal NE spillover and the change in renal plasma flow after enalaprilat administration, and therefore a major washout effect on renal NE spillover by increased renal plasma flow after enalaprilat administration seems unlikely. Furthermore, reduced blood flow and glomerular filtration rate in stenotic kidneys may have affected the estimation of renal sympathetic nerve activity by the isotope dilution method. However, we obtained similar results by analyzing the material after excluding stenotic kidneys (renal NE spillover increased by 46% in nonstenotic kidneys after enalaprilat; \( P = 0.01 \)). Although the isotope dilution method has its limitations, we advocate that it is the best method available for providing an index of efferent renal sympathetic nerve activity in humans.

To keep blood pressure under control, treatments with a calcium channel blocker and/or diuretics (80% and 69% of the study population, respectively) were sustained during the examination. These treatments may have affected both the baseline values for sympathetic nerve activity and the response to the drug intervention. Moreover, treatment with diuretics is known to activate the renin-angiotensin system. Although the results of long-term treatment with calcium channel blockers on sympathetic activity have been variable, there is a possibility of sympathetic reflex activation as a response to the vasodilatory effect of these drugs. However, total body NE spillover did not differ among patients treated or not treated with diuretics or a calcium channel blocker. Hence, an important drug or drug withdrawal effect on overall sympathetic nerve activity seems unlikely.

The design of the present study did not mimic completely the clinical situation of long-term treatment with ACE inhibitors, but the results may still have clinical implications because of the effects of reduced salt and water excretion by increased renal sympathetic nerve activity.

In conclusion, the blood pressure reduction after short-term administration of an ACE inhibitor to hypertensives with renal artery stenosis is associated with lack of overall and muscle sympathetic reflex activation but preserved reflex increases in renal sympathetic activity. These data thus suggest a differentially regulated sympathetic outflow in this condition. Moreover, the concomitant reduction of Ang II plasma concentrations does not support a stimulatory effect of endogenous Ang II on renal sympathetic nerve activity in these patients.

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