Myocardial Uptake and Biochemical and Hemodynamic Effects of ACE Inhibitors in Humans

Christopher J. Zeitz, Duncan J. Campbell, John D. Horowitz

Abstract—There is little information on the processes affecting selective tissue ACE inhibition and the implications in human subjects. We compared intravenously administered ACE inhibitors, perindoprilat and enalaprilat, for myocardial drug uptake and effects on angiotensin and bradykinin peptides versus hemodynamic effects in 25 patients with stable angina and well-preserved left ventricular systolic function. Myocardial uptake was rapid and more efficient for perindoprilat than for enalaprilat (peak content at 26±3 and 30±4 seconds, 0.58±0.12% and 0.27±0.07% of the administered dose for perindoprilat and enalaprilat, respectively, P=0.04 for difference). Both drugs caused a decrease in angiotensin (Ang) II level, an increase in Ang I level, and reduction in Ang II/Ang I ratio in arterial and coronary sinus blood. Bradykinin (BK)-(1-9) and BK-(1-8) levels increased in arterial blood and BK-(1-8) levels increased in coronary sinus blood after drug administration. Perindoprilat and enalaprilat caused a small decrease in mean arterial pressure (−3±1%, P<0.05; and −4±1%, P<0.01, respectively) and LV+dP/dt (−5.8±1.7%, P<0.01 and −4.2±2.8%, P<0.05, respectively), whereas systemic vascular resistance index was unchanged. Despite relatively cardioselective uptake of perindoprilat, both drugs had similar effects on the cardiac metabolism of angiotensin and bradykinin and on cardiac function. Under resting conditions, both drugs exerted small negative inotropic effects. (Hypertension. 2003;41:482-487.)

Key Words: metabolism ■ hemodynamics ■ bradykinin ■ angiotensin ■ myocardium ■ enalapril

Angiotensin converting enzyme (ACE) inhibitors are of established benefit for the treatment of congestive cardiac failure and after acute myocardial infarction, particularly when systolic function is impaired.1,2 However, despite beneficial effects during long-term therapy, there is a surprising paucity of information regarding aspects of the acute effects of these drugs. There is considerable evidence from long-term administration of many ACE inhibitors in animal studies to indicate that these agents vary in their extent of inhibition of ACE activity in tissues such as the heart, relative to plasma,3,4 and it has been postulated that variable inhibition of tissue ACE may be of clinical importance. However, there are no previous data related to the uptake of ACE inhibitors into the human heart or to the relative extent of cardiac versus plasma ACE inhibition. It is possible, for example, that selective inhibition of intracardiac ACE activity might have a marked impact on the cardiovascular hemodynamic response to these compounds.

This study was therefore designed to (1) measure the time course and extent of myocardial drug uptake for two ACE inhibitors (perindoprilat and enalaprilat), (2) correlate uptake with changes in systemic and cardiac metabolism of angiotensin and bradykinin peptides, and (3) seek correlates between uptake, biochemical effects, and acute hemodynamic changes induced by these agents.

Methods

Patients were selected from those presenting for elective cardiac catheterization and coronary angiography for the investigation of chest pain. All cardioactive medications were withheld for at least 5 half lives before the research procedure. No patient received therapy with ACE inhibitors within the previous 3 months. The Queen Elizabeth Hospital Ethics of Human Research Committee approved the protocol, and written informed consent was obtained before the procedure in all cases. The protocol commenced at least 20 minutes after the last injection of nonionic contrast and was performed with the heart rate kept constant by atrial pacing at a rate just above the spontaneous rate. ACE inhibitors were injected intravenously as a bolus, as previously described for analogous myocardial drug uptake studies.5 Enalaprilat dosage was 2.5 mg and perindoprilat dosage was 1.25 mg; these doses reflect known relative potencies.6 Serial determination of pulmonary capillary wedge pressure and cardiac output was performed with a 7F Swan-Ganz catheter and instantaneous left ventricular (LV) pressure and its first derivative, dP/dt, with a 4F microtip catheter (Millar Instruments). A coronary sinus (CS) thermodilution catheter (Cordis) was used for serial blood sampling, thermodilution flow measurements, and atrial pacing.7 Paired arterial and CS blood samples were drawn for determination of plasma ACE activity and plasma concentrations of angiotensin (Ang) I and Ang II and blood concentrations of bradykinin-(1-7) [BK-(1-7)], BK-(1-8), and BK-(1-9) at baseline, 2, 5, and 10 minutes after drug injection. Paired blood samples for determination of perindoprilat and enalaprilat concentrations were drawn at 10, 20, 30, 45, 60, 90, 120, and 150 seconds and 3, 4, 5, 7.5, and 10 minutes.

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and CS blood flow was monitored to permit calculation of ACE inhibitor uptake into the myocardium.8

The assay of ACE inhibitor concentration was based on that reported by Jackson et al9 and modified for use with whole blood samples. Plasma ACE activity was measured as described by Johansen et al.10 Plasma angiotensin and blood bradykinin levels were measured by a high-performance liquid chromatography–based radioimmunoassay as previously described.11,12

All measures are quoted as mean±SEM. Drug effects on hemodynamic variables were analyzed by repeated-measures ANOVA, and change from baseline was determined by the Dunnett test. Drug effects on peptide levels were assessed on log-transformed data with t-test. The time course of drug uptake into the myocardium is shown in Figure 2. There was rapid uptake of perindoprilat into the heart, with peak drug uptake being observed at 21±2 seconds and peak myocardial drug content at 26±3 seconds,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perindoprilat</th>
<th>Enalaprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>72±4</td>
<td>71±4</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>182±8</td>
<td>184±7</td>
</tr>
<tr>
<td>QT interval, ms</td>
<td>394±9</td>
<td>393±7</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>157±6</td>
<td>150±8*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82±4</td>
<td>81±5</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>109±4</td>
<td>105±4*</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>10±1</td>
<td>9±1</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.5±0.1</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>LV+dP/dtmax, mm Hg/s</td>
<td>1480±80</td>
<td>1390±80*</td>
</tr>
<tr>
<td>SVRI, dynes·s/cm²/m²</td>
<td>3620±220</td>
<td>3610±200</td>
</tr>
<tr>
<td>CSBF, mL/min</td>
<td>102±10</td>
<td>109±13</td>
</tr>
<tr>
<td>CVRI, dynes·s/cm²/m²</td>
<td>110±15</td>
<td>106±11</td>
</tr>
<tr>
<td>LVSWI, g·m/m²/beat</td>
<td>45±3</td>
<td>40±2*</td>
</tr>
</tbody>
</table>

Data are mean±SEM; n=14 for perindoprilat and n=11 for enalaprilat. PCWP indicates pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; CSBF, coronary sinus blood flow; CVRI, coronary vascular resistance index; LVSWI, left ventricular stroke work index.

The majority of patients were hypertensive (in the absence of cardioactive medications), with no significant differences between groups. Patients received intravenous perindoprilat (n=14) or enalaprilat (n=11) in a nonrandom, unblinded fashion. No adverse events were recorded.

Both perindoprilat and enalaprilat caused a more rapid fall in mean arterial pressure than perindoprilat, with a corresponding small but statistically nonsignificant fall in cardiac index (Figure 1). Systemic vascular resistance index remained constant, with no indication of systemic vasoconstriction after either perindoprilat or enalaprilat. Two indexes of inotropic function were serially examined. At constant heart rate, perindoprilat and enalaprilat produced 6±2% and 4±3% decrease in LV+dP/dtmax, respectively (Figure 1). Both agents reduced LV stroke work index, by 6.0±3.2% for perindoprilat and by 6.4±2.5% for enalaprilat (Figure 1). There were no changes in either CS blood flow or coronary vascular resistance index (Table 2 and Figure 2).

The time course of drug uptake into the myocardium is shown in Figure 2. There was rapid uptake of perindoprilat into the heart, with peak drug uptake being observed at 21±2 seconds and peak myocardial drug content at 26±3 seconds,
being 0.58±0.12% (6.9±1.7 μg) of the injected dose, with marked hysteresis relative to peak hemodynamic effects. These values were unrelated to baseline patient characteristics such as LV ejection fraction, heart rate, extent of fixed coronary artery disease, or CS blood flow. The proportion of peak content persisting at 5 and 10 minutes after perindoprilat administration was 45% and 40%, respectively. Similarly, there was rapid uptake of enalaprilat into the heart, with peak uptake being observed at 19±3 seconds and peak myocardial drug content at 30±4 seconds, being 0.27±0.07% (5.0±1.5 μg) of the injected dose (P=0.04 versus perindoprilat), again with marked hysteresis between drug uptake and peak hemodynamic effect. The proportion of peak content persisting at 5 and 10 minutes after enalaprilat administration was 39% and 41%, respectively. There was no correlation between myocardial drug content and peak hemodynamic effect for either perindoprilat or enalaprilat.

Both ACE inhibitors produced marked suppression of plasma ACE activity in arterial and CS blood, from 93±10 U/L to <5 U/L within 2 minutes (P<0.0001) for perindoprilat and from 81±4 U/L to <5 U/L within 2 minutes (P<0.0001) for enalaprilat. This magnitude of effect was sustained for both drugs for at least 20 minutes.

The effects of ACE inhibition on plasma angiotensin peptide levels in arterial and CS blood are shown in Figure 3. At 2 minutes after drug administration, arterial plasma Ang II level was reduced by 46% and 71%, Ang I level was increased by ∼2-fold, and the Ang II/Ang I ratio was reduced by 62% and 90% by perindoprilat and enalaprilat, respectively. All changes in arterial plasma angiotensin peptide levels were statistically significant (P<0.01). The time course of change in CS plasma Ang II level for perindoprilat was different from that of enalaprilat. CS Ang II level was unchanged at 2 minutes after perindoprilat, then fell by 65% (P<0.01) at 5 minutes and was suppressed by 33% at 10 minutes. After enalaprilat, CS Ang II level was reduced by ∼40% at 2, 5, and 10 minutes, but this did not achieve statistical significance (P=0.11). CS Ang I level increased in parallel with the increase in arterial Ang I level (P<0.01), and the CS Ang II/Ang I ratio was reduced by a maximum of 80% to 90% by the two drugs (P<0.01). There was no significant change in transmyocardial concentration gradient for either Ang II or Ang I after drug administration.

The effects of ACE inhibition on bradykinin peptide levels in arterial and CS blood are shown in Figure 4. Perindoprilat and enalaprilat were without effect on arterial blood BK-(1-7) level, but BK-(1-8) level increased 1.9-fold for perindoprilat (P=0.07) and 3.1-fold for enalaprilat (P<0.01), BK-(1-9) level increased 2-fold for perindoprilat (P<0.01) and 2.8-fold for enalaprilat (P<0.01), and the BK-(1-7)/BK-(1-9) ratio was reduced by ∼60% for both perindoprilat (P=0.14) and enalaprilat (P<0.01). The levels of BK-(1-7) and BK-(1-9) were higher in CS than in arterial blood. CS blood BK-(1-7)
level was reduced by 55% by perindoprilat (P<0.01) and by 44% by enalaprilat (P<0.01); BK-(1-8) level increased 2.8-fold for perindoprilat (P<0.01) and 2.1-fold for enalaprilat (P<0.01), BK-(1-9) level was unchanged, and the BK-(1-7)/BK-(1-9) ratio was reduced by ≈46% for each drug (P<0.01 for perindoprilat, P=0.74 for enalaprilat).

Discussion

Perindoprilat and enalaprilat had similar effects on systemic hemodynamics and angiotensin and bradykinin peptide levels, indicating that the doses used were equivalent. Myocardial uptake of perindoprilat was more efficient than uptake of enalaprilat. However, despite the difference in efficiency of uptake, the two drugs had similar effects on cardiac metabolism of angiotensin and bradykinin peptides and on cardiac function. The major acute hemodynamic effect of both ACE inhibitors was negative inotropy; this rather than systemic vasodilation was the basis for the small decrease in arterial pressure with both agents.

The uptake of ACE inhibitors into the myocardium in humans has not been previously evaluated. Uptake of both agents into the heart was extremely rapid; more so than that of any other cardioactive agents previously assessed with this methodology. Theoretically, the major determinant of extent of myocardial drug uptake at matched heart rates should be lipid solubility. In the case of perindoprilat and enalaprilat, this would imply that the expected relative uptake should reflect the octanol:water partition coefficients for these agents. Indeed there is partial supportive evidence for this. Perindopril and enalapril have low lipophilicity, with perindopril more lipophilic than enalapril (partition coefficient 0.02 versus 0.01 at pH 7.4).13 Perindoprilat and enalaprilat have even lower lipophilicity (partition coefficient <0.001 at pH 7.4),13 although perindoprilat is likely to maintain superior lipophilicity to enalaprilat. Consistent with this, uptake of perindoprilat into the myocardium was more efficient than for enalaprilat.

As expected with the doses of perindoprilat and enalaprilat used, plasma ACE was inhibited by >90% in both arterial
and CS blood within 2 minutes of drug administration. ACE inhibition was associated with prompt increases in Ang I level, consequent to increased renin secretion. Most Ang I conversion occurs in vascular beds rather than in plasma, and the Ang II/Ang I ratio is a valid indication of ACE inhibition in vivo. Our data show that despite essentially complete inhibition of plasma ACE activity, the decrease in Ang II level was more modest, in part because of the increased Ang I level counteracting the effects of competitive ACE inhibition. There were similar changes in angiotensin peptide levels in arterial and CS blood. Moreover, despite the more efficient myocardial uptake of perindoprilat than enalaprilat, the two ACE inhibitors had similar effects on CS levels of angiotensin peptides. Animal studies show that the heart is a site of Ang I production and conversion to Ang II. Ang I production in the heart is primarily due to cardiac uptake of plasma renin, and approximately half of CS Ang I represents production in the heart. Approximately one third of CS Ang II is derived from de novo production in the cardiac vascular bed from conversion of either arterial Ang I or locally produced Ang I. The changes in CS angiotensin peptides therefore represent both changes in arterial angiotensin peptide levels and changes in cardiac production and conversion of Ang I. Our data indicate equivalent inhibition of ACE in the systemic and coronary vascular beds and support the findings of Zisman et al, who used radiolabeled Ang I infusion to demonstrate ACE to be the major pathway of Ang II formation in the human coronary vascular bed.

This is the first report of the rapid changes in arterial bradykinin peptide levels caused by acute ACE inhibition in humans. The levels of bradykinin peptides in arterial blood are determined in large part by their metabolism in the pulmonary vascular bed. The increase in BK-(1-9) level and decrease in BK-(1-7)/BK-(1-9) ratio indicate an important role for ACE in pulmonary metabolism of BK-(1-9). The maximum decrease in BK-(1-7)/BK-(1-9) ratio was only 60%, indicating that non-ACE kininases, such as neutral endopeptidase, also participate in BK-(1-9) conversion to BK-(1-7). BK-(1-8) is the carboxypeptidase metabolite of BK-(1-9). Whereas BK-(1-9) is an agonist for mainly the type 2 bradykinin (B2) receptor, BK-(1-8) is an agonist of the type 1 bradykinin (B1) receptor. BK-(1-8) is not metabolized by ACE, and the increase in arterial BK-(1-8) levels is most likely a consequence of carboxypeptidase-mediated metabolism of the elevated BK-(1-9) levels.

The levels of BK-(1-7) and BK-(1-9) in CS blood were higher than in arterial blood. BK-(1-9) level in CS blood was maintained after ACE inhibition, whereas BK-(1-7) level fell, with a corresponding reduction in the BK-(1-7)/BK-(1-9) ratio. These data raise the possibility that BK-(1-9) formation in the heart may result in bradykinin peptide spillover into CS blood and that ACE inhibition may have a cardioselective effect on bradykinin metabolism. However, there is a need for caution in the interpretation of the bradykinin peptide levels measured in CS blood because of possible artifactual generation of BK-(1-9) caused by activation of plasma prekallikrein as blood was drawn through the long CS catheter. The relatively high CS BK-(1-9) level measured in this study may have been due in part to BK-(1-9) formation in the catheter, and the fall in CS BK-(1-7) level and BK-(1 to 7)/BK-(1-9) ratio may represent inhibition of BK-(1-9) metabolism by plasma ACE in the catheter. In contrast to BK-(1-7) and BK-(1-9), the baseline CS level of BK-(1-8) was similar to arterial levels, suggesting that CS BK-(1-8) was primarily formed in the coronary vasculature rather than in the catheter. Moreover, the increase in CS BK-(1-8) levels after ACE inhibition provides direct evidence that ACE inhibition increased kinin levels in the coronary vascular bed. The similar 2.8- and 2.1-fold increases in CS BK-(1-8) levels for perindoprilat and enalaprilat, respectively, and the similar changes in CS angiotensin peptide levels indicate minor differences between the two ACE inhibitors in inhibition of cardiac ACE.

It is well recognized that the chronic antihypertensive effects of ACE inhibitors are due to reduction in systemic vascular resistance without change in cardiac output. Both reduced Ang II levels and increased BK-(1-9) levels have been implicated in the hypotensive response to ACE inhibition, and our peptide measurements provide support for both possibilities. The failure of ACE inhibition to produce vasodilation in our study was not anticipated, particularly given that many of our subjects were hypertensive with systemic vascular resistance index at the upper limit of the normal range. The acute hypotensive response to ACE inhibition is dependent on the extent of activation of the renin-angiotensin system. Ang II levels in our subjects were at the lower limit of the normal range, suggesting that Ang II made little contribution to control of systemic vascular resistance in our subjects, and may thus explain the lack of vasodilation in response to ACE inhibition. The hypotensive response to acute intravenous administration of ACE inhibitor is poorly correlated with the response to long-term oral therapy, and it is likely that any vasodilator action of ACE inhibition was delayed beyond the 10-minute period of observation in our study.

There are previous reports of a negative inotropic effect of acute ACE inhibition in man. Foul et al reported that intracoronary administration of enalaprilat produced reduction in cardiac index, ejection fraction, and end-systolic stress/end systolic volume ratio in patients with dilated cardiomyopathy. Haber et al also reported reduction in stroke work index after intracoronary enalaprilat in hypertensive subjects. However, Friedrich et al found no evidence of negative inotropic effect of intracoronary enalaprilat in subjects with either aortic stenosis or dilated cardiomyopathy. In the present study, a negative inotropic effect of ACE inhibition was evident for two different agents, with effects on LV+dp/dtmax and LV stroke work index being noted in the absence of changes in heart rate or marked changes in loading conditions. Our findings and those of others indicate that a negative inotropic effect is only seen with intravascular administration of ACE inhibitor.

We observed an effect of acute ACE inhibition on cardiac function without a detectable effect on systemic vasculature resistance. This may have been due in part to the efficiency of cardiac uptake of the ACE inhibitor. Similar to the systemic hemodynamic effects, there was no change in CS blood flow or coronary vascular resistance after either perindoprilat or enalaprilat. It is possible that any coronary vasodilator effect...
of ACE inhibition was obscured by decreased stroke work, resulting in decreased myocardial oxygen demand.

ACE inhibitors are not in routine use as intravenous agents. Indeed, the only previous large-scale study with intravenously administered ACE inhibitor was the CONSENSUS II study.28 This study of the effects of intravenously administered enalaprilat during the acute phase of myocardial infarction was terminated, in part because of possible adverse effects caused by early hypotensive reactions among elderly patients. Our findings suggest that the negative inotropic effect of intravenous ACE inhibitor may have contributed to the hypotensive reactions seen in the CONSENSUS II study.

Perspectives

Perindoprilat and enalaprilat had similar effects on systemic hemodynamics and angiotensin and bradykinin peptide levels, indicating that the doses used were equivalent. Despite marked ACE inhibition, no vasodilatation was evident during the first 10 minutes after drug administration. Rather, the hypotensive response was due to a negative inotropic effect of these compounds. Despite more efficient cardiac uptake of perindoprilat than enalaprilat, the two drugs had similar effects on angiotensin and bradykinin metabolism in the heart and similar negative inotropic effects, suggesting that the difference in efficiency of drug uptake was not a major determinant of cardiac response to these compounds under resting conditions. The negative inotropic effect indicates that intravenous administration of ACE inhibitor may be contraindicated, particularly in situations of impaired myocardial contractility.

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References

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