Effects of ACE Inhibitors on Cardiac Angiotensin II and Aldosterone in Humans: “Relevance of Lipophilicity and Affinity for ACE”

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BACKGROUND
Angiotensin-converting enzyme (ACE) inhibitors differ in their lipophilic/hydrophilic index that determines their tissue bioavailability and affinity to ACE, which may result in major differences in the degree of blockade of cardiac ACE. We evaluated the hypothesis that in patients with chronic heart failure (CHF) and activated cardiac renin–angiotensin–aldosterone system (RAAS), lipophilic ACE inhibitors with high affinity for ACE (perindopril and quinapril) will cause marked blockade of cardiac angiotensin (Ang) II and aldosterone generation, but not a hydrophilic ACE inhibitor with low affinity for ACE (lisinopril).

METHODS
Patients were randomized to receive perindopril (8 mg/day), quinapril (40 mg/day), or lisinopril (20 mg/day) for 3–4 weeks before cardiac catheterization. The coronary sinus–aortic root gradients for Ang I and II, and aldosterone were determined.

RESULTS
A total of 19 patients completed the study. Compared to a healthy control group, all three ACE inhibitors decreased circulating Ang II and aldosterone to a similar extent. There were only minor differences between the three ACE inhibitors for the Ang II gradient between the coronary sinus and aortic root. The gradient for aldosterone tended to be positive in the quinapril group and absent/negative in the lisinopril and perindopril groups. Despite the lowest pulmonary capillary wedge pressure (PCWP), gradients between the coronary sinus and aortic root for Ang II and aldosterone were actually the highest in the quinapril group.

CONCLUSIONS
These findings do not support the concept that a hydrophilic ACE inhibitor is less effective in blocking the cardiac RAAS as compared to lipophilic ACE inhibitors.

Keywords: ACE inhibitors; blood pressure; cardiac aldosterone; cardiac angiotensin II; chronic heart failure; hypertension

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ACE inhibitors with low affinity to ACE. In animal models of cardiac infarction–induced cardiac remodelling, lipophilic ACE inhibitors with high affinity for cardiac ACE resulted in better prevention of remodelling as compared to hydrophilic ACE inhibitors with low affinity to ACE. For example, in rats with cardiac volume overload induced by aorto-caval shunt, the increase in cardiac Ang II and cardiac remodelling were significantly attenuated by quinapril, a lipophilic ACE inhibitor with high affinity to ACE, but not by enalapril, a hydrophilic ACE inhibitor with low affinity to ACE, despite similar effects on general hemodynamics.

In this study, we evaluated the hypothesis that in patients with CHF and activated cardiac RAAS, lipophilic ACE inhibitors with high affinity for ACE (perindopril and quinapril) will cause marked blockade of cardiac Ang II and aldosterone generation, but a hydrophilic ACE inhibitor with low affinity for ACE (lisinopril) will not. Patients scheduled for coronary angiography were randomized to receive perindopril, quinapril, or lisinopril at clinically equivalent doses and the coronary sinus–aortic root gradient was determined.

METHODS

This study was designed and executed as a prospective single-blind trial. Laboratory personnel performing assays for Ang I and II and aldosterone as well as study staff responsible for statistical analyses were blinded to the treatment allocation.

Patients (age 21–75 years) with ischemic CHF (NYHA class I–III) and ejection fraction <40% on radionuclide ventriculography referred for cardiac catheterization were eligible for this study. Excluded were patients hemodynamically unstable, with known allergy to ACE inhibitors, requiring combination therapy with an ACE inhibitor and angiotensin receptor blocker or aldosterone receptor blocker, or with a serum potassium >5.1 mmol/L. A control group comprised of 12 healthy age-matched individuals.

Eligible patients had their ACE inhibitor, angiotensin receptor blocker, and spironolactone discontinued 3–4 weeks before the procedure. They were then randomized to treatment with perindopril 8 mg/day, quinapril 40 mg/day, or lisinopril 20 mg/day. Doses of ACE inhibitors used in this study were chosen as the highest recommended doses in clinical practice. Patients previously taking high doses of ACE inhibitors or angiotensin receptor blockers were switched directly to the ACE inhibitor they were randomized to at the above doses. Those on low-to-medium doses of an ACE inhibitor or angiotensin receptor blocker were switched to the clinically equivalent dose of the ACE inhibitor they were randomized to, and this dose was titrated up four times for 2–3 days. Patients naive to treatment with a blocker of the RAS were started on perindopril 2 mg/day, lisinopril 5 mg/day, or quinapril 10 mg/day, and this dose was titrated up four times for 2–3 days.

Cardiac catheterization was performed in the morning, with patients in a fasting state at the end of the dosing interval. Hemodynamic measurements including pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), right atrial pressure, and cardiac output were performed using a Swan–Ganz catheter inserted into a femoral or jugular vein. Cardiac output was determined in triplicate by the temperature-dilution technique. After the right heart catheterization was completed, a 6F Goodale-Lubin catheter was placed into the coronary sinus through a brachial vein, and a Judkins catheter was placed at the root of the aorta through a femoral artery. Blood was sampled at the coronary sinus and aortic root within 2 min of each other.

Healthy individuals were asked to fast after midnight, and in the morning blood samples for biochemical assays were taken from a peripheral vein after a 30-min rest in the supine position.

Plasma renin activity (PRA) and plasma aldosterone were measured by radioimmunoassay as previously described. Plasma Ang I and II were measured by radioimmunoassay after separation using high-pressure liquid chromatography as previously described.

Based on the findings from Mizuno et al. to detect a positive aldosterone gradient for lisinopril vs. quinapril of 20 pg/ml with s.d. 22, 20 patients/group would give 82% power. An interim analysis showed opposite gradients to the ones expected and a low likelihood (<1%) that the original hypothesis would be confirmed. The study was stopped at this point. All values are expressed as mean ± s.e.m. Analysis of variance was used to analyze results of hemodynamic or hormonal measurements. Hormonal levels at the aortic root and coronary sinus within each group were compared with paired t-test. Statistical significance was defined as P < 0.05.

RESULTS

A total of 19 patients were recruited and completed the study. Their demographic data are shown in Table 1. The majority of patients were males. There were no significant differences in age and body mass index between the three treatment groups. The majority of patients were taking a β-blocker and approximately half of them also a loop diuretic.

Hemodynamics

BP was in the normal range, and there were no significant differences in BP between the three groups (Table 1). Heart failure was well controlled with drug therapy; cardiac index was in the normal range and PCWP was only modestly elevated. There were modest (nonsignificant) differences in PCWP between the three groups.

Circulating RAAS

As compared to healthy individuals, in patients with CHF treated with an ACE inhibitor and β-blocker, PRA was higher although the increase did not reach statistical significance (P = 0.09; Table 1). Consistent with ACE inhibition, in patients with CHF, plasma Ang I was significantly increased (P < 0.05), whereas Ang II and aldosterone were significantly decreased (P < 0.001 and P < 0.01, respectively) as compared to healthy individuals. There were no significant differences in PRA,
plasma Ang I, Ang II, and aldosterone levels between the three treatment groups.

Cardiac RAAS
There were no significant differences in PRA and Ang I between samples from the coronary sinus and aortic root for any treatment group (Table 1).

There were no significant differences for Ang II or aldosterone levels in the coronary sinus and aortic root in any of the three treatment groups (Table 1). When data from the three groups were pooled together, there was a trend ($P = 0.10$) for an increase in Ang II in the coronary sinus as compared to the aortic root, but gradients for Ang II did not differ between the three groups (Figure 1).

The gradient for aldosterone between the coronary sinus and aortic root tended to be positive in the quinapril group and negative in the other groups (Figure 1), but the gradients did not differ significantly between the three groups.

Interactions within the RAAS
As expected, gradients between the coronary sinus and aortic root for PRA and Ang I showed a positive correlation with each other ($r = 0.54$, $P = 0.028$). Similarly, gradients between the coronary sinus and aortic root for Ang II and aldosterone positively correlated with each other ($r = 0.60$, $P = 0.017$).

**Table 1 | Baseline characteristics and parameters of the circulating and cardiac RAAS of healthy subjects and patients with CHF**

<table>
<thead>
<tr>
<th></th>
<th>Controls ($n = 12$)</th>
<th>Lisinopril ($n = 6$)</th>
<th>Perindopril ($n = 8$)</th>
<th>Quinapril ($n = 5$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 4</td>
<td>65 ± 4</td>
<td>58 ± 3</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>5/7</td>
<td>5/1</td>
<td>8/0</td>
<td>5/0</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28 ± 2</td>
<td>34 ± 2</td>
<td>26 ± 2</td>
<td></td>
</tr>
<tr>
<td>Loop diuretic (yes/no)</td>
<td>0/12</td>
<td>3/3</td>
<td>4/4</td>
<td>2/3</td>
</tr>
<tr>
<td>β-Blocker (yes/no)</td>
<td>0/12</td>
<td>6/0</td>
<td>7/1</td>
<td>4/1</td>
</tr>
<tr>
<td><strong>BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>128 ± 6/79 ± 5</td>
<td>113 ± 5/72 ± 2</td>
<td>119 ± 9/72 ± 7</td>
<td></td>
</tr>
<tr>
<td>Cl (ml/min/m²)</td>
<td>2.5 ± 0.3</td>
<td>2.6 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>11 ± 3</td>
<td>17 ± 2</td>
<td>8 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>Parameters of the circulating and cardiac RAAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (aortic root/peripheral vein) (ng/ml/min)</td>
<td>2.6 ± 0.2</td>
<td>6.6 ± 4.2</td>
<td>3.6 ± 0.8</td>
<td>9.5 ± 6.1</td>
</tr>
<tr>
<td>PRA (coronary sinus) (ng/ml/min)</td>
<td>6.0 ± 3.7</td>
<td>4.9 ± 0.8</td>
<td>10.5 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Angl (aortic root/peripheral vein) (pg/ml)</td>
<td>8.9 ± 0.5</td>
<td>71 ± 56*</td>
<td>31 ± 23*</td>
<td>132 ± 89*</td>
</tr>
<tr>
<td>Angl (coronary sinus) (pg/ml)</td>
<td>69 ± 46</td>
<td>26 ± 13</td>
<td>142 ± 112</td>
<td></td>
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<tr>
<td>Angll (aortic root/peripheral vein) (pg/ml)</td>
<td>4.5 ± 0.5</td>
<td>2.1 ± 0.5*</td>
<td>1.8 ± 0.4*</td>
<td>2.6 ± 0.7*</td>
</tr>
<tr>
<td>Angll (coronary sinus) (pg/ml)</td>
<td>2.5 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>3.7 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Aldosterone (aortic root/peripheral vein) (pg/ml)</td>
<td>128 ± 28</td>
<td>62 ± 11*</td>
<td>54 ± 8*</td>
<td>75 ± 13</td>
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<tr>
<td>Aldosterone (coronary sinus) (pg/ml)</td>
<td>53 ± 14</td>
<td>51 ± 8</td>
<td>87 ± 18</td>
<td></td>
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</tbody>
</table>

*Values are means ± s.e.m. In the controls, blood was only obtained from a peripheral vein.

Ang, angiotensin; BP, blood pressure; Cl, cardiac index; CHF, chronic heart failure; PCWP, pulmonary capillary wedge pressure; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system.

* $P = 0.01$ for Ang II: lisinopril vs. control, $P = 0.003$ for Ang II: perindopril vs. control, $P = 0.03$ Ang II: quinapril vs. control, $P = 0.05$ for aldosterone: lisinopril vs. control, $P = 0.02$ for aldosterone: perindopril vs. control.

**DISCUSSION**
In this prospective single-blind trial, we tested the hypothesis that in patients with mild CHF, differences in cardiac tissue affinity and/or lipophilicity between ACE inhibitors result in significant differences in blockade of the cardiac RAAS, as assessed from the Ang II and aldosterone gradients between the coronary sinus and aortic root.

As compared to a control group of healthy individuals, all three ACE inhibitors decreased circulating Ang II and aldosterone to a similar extent consistent with equivalent blockade of the circulating RAAS.
In patients without blockers of the RAAS, Neri Serneri et al. reported that cardiac Ang II generation shows a positive correlation with left ventricular end diastolic pressure and negative correlation with left ventricular ejection fraction. In their study, the gradient for Ang II between the coronary sinus and aortic root was negative (−1.1 ± 1.6 pg/min/g) in healthy controls, and it increased progressively to 1.4 ± 2.3, 2.5 ± 4.1, 8.9 ± 5.8, and 11.3 ± 3.1 pg/min/g in patients with ischemic CHF NYHA class I–IV, respectively. In this study, in patients with mild CHF and only a modest increase in PCWP, one would expect an Ang II gradient between the coronary sinus and the aortic root of 2–3 in the absence of an ACE inhibitor. A gradient for Ang II ranging from 0.4 to 1.1 in our study is consistent with blockade of most Ang II production by the heart. There were no significant differences between the three ACE inhibitors for the Ang II gradient between the coronary sinus and aortic root.

Mizuno et al. showed a positive correlation between cardiac aldosterone generation and left ventricular end diastolic pressure and a negative correlation between cardiac aldosterone generation and left ventricular ejection fraction. A positive gradient for aldosterone between the coronary sinus (92 ± 9 pg/ml) and aortic root (71 ± 8 pg/ml) in the placebo group was absent after treatment with the ACE inhibitor perindopril (4 mg/day). In our study, aortic root aldosterone levels were significantly lower as compared to the control subjects and similar to those reported by others in patients on an ACE inhibitor, consistent with a high degree of blockade of the circulating RAAS by the three ACE inhibitors. The strong positive correlation between the gradients for aldosterone and Ang II between the coronary sinus and aortic root indicates that cardiac aldosterone production appears to be mostly Ang II driven. Nonetheless, the gradient for aldosterone tended to be positive in the quinapril group and absent/negative in the lisinopril and perindopril groups, the latter consistent with the study by Mizuno et al. Despite the lowest PCWP, gradients between the coronary sinus and aortic root for Ang II and aldosterone were actually the highest in the quinapril group. Perindopril and quinapril have fairly similar lipophilicity and affinity for ACE, and this tendency for lower inhibition of cardiac Ang II and aldosterone generation in the quinapril group likely reflects a chance finding.

Altogether, from these findings in patients with mild CHF of ischemic origin, it appears unlikely that even at only medium high doses the hydrophilic ACE inhibitor lisinopril is less effective for blockade of coronary overflow of Ang II and aldosterone than lipophilic blockers such as perindopril or quinapril. Whether similar blockades would be obtained in patients with more severe CHF requires further study. As limitation of the study one should consider the modest sample size (see Methods), with potential imbalances between the treatment groups.

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Disclosure: The authors declared no conflict of interest.

References:


