Elevated Plasma Aldosterone Levels Despite Complete Inhibition of the Vascular Angiotensin-Converting Enzyme in Chronic Heart Failure

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Background—Plasma aldosterone levels are elevated in patients with chronic heart failure (CHF) taking angiotensin-converting enzyme (ACE) inhibitors. Elevated aldosterone levels may reflect incomplete inhibition of the vascular converting enzyme during long-term ACE inhibition. We simultaneously measured plasma aldosterone levels and the degree of inhibition of the vascular converting enzyme in patients with CHF.

Methods and Results—Thirty-four subjects with CHF receiving the maximum recommended doses of ACE inhibitors for a duration of 3 to 105 months were studied. The pressor response to exogenous angiotensin I (AI) was measured and normalized for the pressor response to angiotensin II (AII) to assess inhibition of the vascular converting enzyme (AII/AI ratio). Aldosterone levels were determined by solid-phase radioimmunoassay. Eleven of the 34 subjects had plasma aldosterone levels above the upper limit of normal, ie, >15.0 ng/dL. Seven of these 11 subjects (64%) had an AII/AI ratio ≤0.05, indicating complete inhibition of the vascular converting enzyme. In the entire cohort, the AII/AI ratio did not correlate with the duration of ACE inhibitor therapy.

Conclusions—Plasma aldosterone levels are elevated in patients with CHF during long-term ACE inhibitor therapy despite complete inhibition of the vascular converting enzyme. Complete inhibition of the vascular converting enzyme does not obviate the need for aldosterone receptor blockade in patients with CHF. (Circulation. 2002;106:1055-1057.)

Key Words: heart failure ■ angiotensin ■ aldosterone
Clinical Characteristics of 34 Subjects

<table>
<thead>
<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>52.2 ± 10.5</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>25/9</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27.6 ± 8.8</td>
</tr>
<tr>
<td>NYHA FC II/III, n</td>
<td>16/18</td>
</tr>
<tr>
<td>V̇O₂ (n=12), mL·kg⁻¹·min⁻¹</td>
<td>18.1 ± 6.2</td>
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<tr>
<td>Pathogenesis, ICM/DCM</td>
<td>16/18</td>
</tr>
<tr>
<td>Diabetes, +/−</td>
<td>12/22</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>13.4 ± 9.3</td>
</tr>
<tr>
<td>Serum sodium, mmol/L per liter</td>
<td>138 ± 3.4</td>
</tr>
<tr>
<td>Serum potassium, mmol/L per liter</td>
<td>4.4 ± 0.36</td>
</tr>
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LVEF indicates left ventricular ejection fraction; NYHA FC, New York Heart Association functional class; V̇O₂, maximal oxygen consumption; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; ena, enalapril; fos, fosinopril; lis, lisinopril; tran, trandolapril; and cap, captopril.

Plasma Aldosterone Levels

Ten milliliters of venous blood was drawn from subjects resting supine for 20 minutes after insertion of an 20-gauge angiocath into a superficial vein of the opposite forearm between 10 and 12 AM and before administration of AI and AII. Samples were frozen immediately at −70°C. Solid-phase radioimmunoassay was used for determination of plasma aldosterone (Diagnostics Product Cooperation). The intra- and interassay coefficients were <10%.

Statistical Analysis

Associations between continuous variables were determined with univariate linear regression analysis (SPSS 10.1 software). Associations between categorical variables were determined with χ² analysis. A 2-tailed probability value <0.05 was used to infer statistical significance.

Results

Clinical characteristics, laboratory values, and background medications are summarized in the Table.

The AII/AI ratio ranged from 0.01 to 0.33 (median 0.037; mean 0.067). Twenty-three of the 34 subjects had an AII/AI ratio <0.05, which indicated complete inhibition of the vascular converting enzyme. The AII/AI ratio was unrelated to the duration of ACE inhibitor therapy, which ranged from 3 to 105 months (Figure 1).

Plasma aldosterone levels ranged from 2.5 to 42.1 ng/dL (median 9.7; mean 13.4 ng/dL). Twenty-three of the 34 subjects had a normal plasma aldosterone level, ie, ≤15.0 ng/dL. The remaining 11 subjects had elevated plasma aldosterone levels. Seven of these 11 subjects (64%) had an AII/AI ratio ≤0.05, which indicated complete inhibition of the vascular converting enzyme. Plasma aldosterone level and AII/AI ratio did not correlate (Figure 2) and were unrelated to the type of ACE inhibitor used. Plasma aldosterone levels were unrelated to serum potassium and sodium concentrations or diuretic doses.

Discussion

The present data clearly indicate that plasma aldosterone levels are elevated in patients with CHF, even when treatment with ACE inhibitors results in complete inhibition of the vascular converting enzyme. The data also suggest that the degree of inhibition of the vascular converting enzyme is independent of the duration of ACE inhibitor therapy.

Determination of residual ACE activity, direct measurement of circulating AI and AII, and the pressor response to AI are the methods used to estimate the degree of inhibition of the converting enzyme during ACE inhibitor therapy. Determination of ACE activity varies with substrate and assay conditions and thus may not always accurately reflect the
degree of converting enzyme inhibition. Measurement of circulating AII is technically challenging, and its relevance in assessing the degree of inhibition of the converting enzyme has been questioned. In contrast, the pressor response to AI, when normalized by the pressor response to AII, provides a reproducible functional bioassay to quantify the activity of the circulating and endothelium-bound converting enzyme.

Inhibition of the vascular converting enzyme as assessed by the pressor response to AI was complete in 7 of 11 (64%) patients with elevated plasma aldosterone levels. Continuous aldosterone formation in patients with complete inhibition of the vascular converting enzyme may be attributable to AII generation via non-ACE pathways or AII-independent stimuli of aldosterone production, such as intravascular depletion, potassium, corticotropin, endothelin, and catecholamines. Within the narrow range of potassium concentrations allowed in patients who were per protocol in a euolemic state, plasma aldosterone levels did not correlate with serum potassium concentrations. Although we did not measure catecholamine levels, it is of note that aldosterone levels were elevated in 9 of 29 (31%) of the patients receiving both β-blockers and ACE inhibitors.

Our findings are concordant with previously reported observations in patients with hypertension, in whom the plasma AII/AI ratio and plasma aldosterone do not correlate, and in patients with CHF, in whom plasma aldosterone levels do not seem to correlate with the activity of the renin-angiotensin system. Incomplete inhibition of the vascular converting enzyme was not related to the duration of ACE inhibitor therapy. This finding, albeit collected in a cross-sectional study, contrasts with results reported by other investigators who noted an increase in AI/AII conversion over time. The disparity between previous reports and ours cannot be readily explained. Although differences in methodology may be in part responsible for the divergent results, our findings suggest that factors other than time might contribute to ACE escape, which thus seems to be a more complex phenomenon than initially thought.

In summary, plasma aldosterone levels are elevated in patients with CHF, even when long-term ACE inhibitor therapy results in complete inhibition of the vascular converting enzyme. AII-independent stimuli of aldosterone production may account for this finding, and complete ACE inhibition does not obviate the need for aldosterone receptor blockade in patients with CHF.

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References

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