Maximally Recommended Doses of Angiotensin-Converting Enzyme (ACE) Inhibitors Do Not Completely Prevent ACE-Mediated Formation of Angiotensin II in Chronic Heart Failure

Ulrich P. Jorde, MD; Pierre V. Ennezat, MD; Jay Lisker, BA; Vanarani Suryadevara, MD; Jason Infeld, MD; Sonja Cukon, MD; Adam Hammer, BA; Edmund H. Sonnenblick, MD; Thierry H. Le Jemtel, MD

Background—The added benefits of angiotensin II type I receptor (AT1) blockers (ARBs) to ACE inhibition suggests that recommended doses of ACE inhibitors provide only partial inhibition of ACE in chronic heart failure (CHF). Accordingly, the level of ACE inhibition was assessed by the pressor response to angiotensin (Ang) I in patients who had been treated with recommended doses of ACE inhibitors.

Methods and Results—Forty-two patients with CHF receiving 40 mg/d of a long-acting ACE inhibitor or 150 mg of captopril were studied. Radial artery systolic pressure (RASP, mm Hg) was monitored noninvasively. The pressor response to ascending doses of Ang I was evaluated in all patients before and after administration of the ARB valsartan. The pressor response to Ang I before and after valsartan was also reevaluated in 11 patients after the dose of ACE inhibitor was doubled for 1 week. RASP increased linearly with significantly ascending doses of Ang I despite treatment with ACE inhibitors. The pressor response to Ang I was blunted significantly by valsartan. Ang I–induced increase in RASP did not correlate with duration of ACE inhibitor therapy. After the dose of ACE inhibitors was doubled, the pressor response to Ang I was no longer different from that noted after valsartan.

Conclusions—Recommended doses of ACE inhibitors do not fully inhibit ACE in CHF. The level of ACE inhibition achieved is not related to duration of ACE inhibitor therapy. Greater ACE inhibition is also achieved at twice the recommended doses of ACE inhibitors. (Circulation. 2000;101:844-846.)

Key Words: angiotensin • heart failure • enzymes

Angiotensin (Ang) II type 1 receptor (AT1) blockade (ARB) improves hemodynamic parameters and functional capacity in patients with CHF treated with recommended doses of ACE inhibitors.1,2 The added benefits of ARB suggest continued Ang II formation despite ACE inhibitor therapy. Several mechanisms may be responsible for continuous Ang II formation despite ACE inhibition. Recommended doses of ACE inhibitors may result in incomplete ACE inhibition when the renin-angiotensin system (RAS) is markedly activated.3 Alternatively, enzymatic pathways other than ACE may contribute to Ang II formation.4

The aim of the present study was to determine the level of ACE inhibition achieved by maximally recommended doses of ACE inhibitors. The level of ACE inhibition was assessed by the pressor response to ascending doses of Ang I.5 The pressor response to Ang I depends on conversion of Ang I to Ang II. In the intravascular space, conversion to Ang II is mediated exclusively by circulating and endothelium-bound ACE.6,7 Thus, the pressor response to Ang I reflects ACE activity within the vascular lumen and thereby the level of inhibition achieved by ACE inhibitors.

Accordingly, the pressor response to Ang I has been assessed in 42 patients treated with maximally recommended doses of ACE inhibitors for periods ranging from 3 to 120 months. To assess the complete inhibition of ACE, the pressor response to Ang I was measured before and after administration of an ARB (valsartan).8 In 11 patients, the pressor response to Ang I was also evaluated after treatment with twice the maximally recommended doses of ACE inhibitors.

Methods

Patient Population

Study subjects were 26 men and 16 women with CHF who had been receiving maximally recommended doses of ACE inhibitors for ≥3 months. The daily dose of long-acting ACE inhibitor was 40 mg.
these patients, 22 were treated with fosinopril, 10 with lisinopril, and 6 with enalapril. The remaining 4 patients received 150 mg/d of captopril. Other medications included furosemide in 88% of patients, digoxin in 71%, β-adrenergic blockade in 47%, and spironolactone in 5%. Mean age and ejection fraction were 59 years and 32%, respectively. Twenty-seven patients had coronary artery disease, 15 had hypertension, and 12 were diabetic. NYHA functional class was III in 30 patients and II in 12.

The radial artery waveform was recorded continuously with a Colin Pilot Monitor 9200 (Colin Instruments Corp). Data were stored on a notebook computer using TDA program version 2 from Colin. Analysis of the changes in radial artery systolic pressure (RASP, mm Hg) was subsequently performed by an investigator (J.L.) blinded to dose of Ang I, dosing sequence, study design, and date.

**Drug Administration**

**Ang I**

Ascending doses of Ang I were administered intravenously to increase RASP by >20 mm Hg. The first dose was 10 ng/kg, and provided that RASP did not increase >10 mm Hg, the subsequent doses were 100 and 200 ng/kg. When RASP increased by >10 mm Hg, a second and last dose of 50 ng/kg was administered. The pressor response to Ang I was evaluated 12 hours after administration of fosinopril or lisinopril, 6 hours after administration of enalapril, or 3 hours after administration of captopril. Five patients similarly treated for CHF who were not enrolled in the study received ascending doses of Ang I at 3-day intervals. The pressor responses to Ang I were extremely reproducible ($r=0.97$, $P<0.001$) during this period of time.

**Valsartan**

Once the pressor response to ascending doses of Ang I had been obtained and RASP had returned to baseline, 80 mg of valsartan was orally administered in all patients. Two hours later, the pressor response to identical doses of Ang I was measured.

**ACE Inhibitors**

The dose of ACE inhibitor was increased to 80 mg/d for 1 week in the last 11 patients who experienced a RASP increase >10 mm Hg after 10 ng/kg of Ang I or >25 mm Hg after 200 ng/kg. Six patients received fosinopril and 5 lisinopril. At the end of the week, the pressor response to identical doses of Ang I was measured before and after valsartan.

**Statistical Analysis**

Values are expressed as mean±SEM. Repeated-measures ANOVA and Scheffe’s test were used for multiple comparisons between groups. Significance was accepted at $P<0.05$.

**Results**

In 34 patients receiving the maximally recommended dose of ACE inhibitors, the mean increases in RASP after 3 ascending doses of 10, 100, and 200 ng/kg of Ang I are depicted in Figure 1. RASP increased linearly with ascending doses of Ang I. The increases in RASP were significantly lower after valsartan: 1.8±0.5 versus 5.0±1.0, 4.6±0.9 versus 11.7±1.4, and 8.5±1.0 versus 18.0±1.7 mm Hg for the 10-, 100-, and 200-ng/kg doses of Ang I, respectively (Figure 1). Increases in RASP were also significantly lower after valsartan in 8 patients who received doses of Ang I of only 10 and 50 ng/kg: 3.5±0.7 versus 14.5±1.2 and 9.6±1.2 versus 29.3±2.3 mm Hg, respectively.

Increment in RASP at the highest dose of Ang I administered (50 and 200 ng/kg in 8 and 34 patients, respectively) was not related to duration of ACE inhibitor therapy and nature of the ACE inhibitor. The pressor response to Ang I was evaluated in patients receiving twice the maximally recommended dose of ACE inhibitor for 1 week. Compared with that noted on maximally recommended doses of ACE inhibitors, the pressor response to Ang I was significantly blunted by the doubled dose of ACE inhibitors and was similar to the pressor response after valsartan (Figure 2).

**Discussion**

Three lines of evidence support the conclusion that ACE inhibition is incomplete in patients with CHF treated with maximally recommended doses of ACE inhibitors and that this is due to an inadequate dose of medication. First, the rise in blood pressure in response to Ang I indicates persistent Ang II formation. Second, the blunting of the rise in blood pressure by acute ARB provides further evidence of incomplete ACE inhibition. Last, the Ang I–induced rise in blood pressure was blunted to a similar extent either by doubled doses of ACE inhibitors or by acute ARB.
During long-term ACE inhibition, plasma Ang II levels may increase and exceed baseline values in patients with hypertension or CHF. Increased levels of Ang II observed during therapy with ACE inhibitors have been attributed to increased activity of ACE or to non–ACE-mediated formation of Ang II. Non–ACE-mediated formation of Ang II occurs in the extravascular space, whereas Ang II is generated by ACE entirely in the intravascular space. The blood pressure response to Ang I depends on intravascular formation of Ang II and therefore reflects the level of ACE inhibition. The fact that merely doubling the dose of ACE inhibitor completely blocks the response to Ang I, as does administration of the ARB (valsartan), suggests that incomplete inhibition of ACE is not due to a secondary tissue ACE.

The level of ACE inhibition achieved in the interstitium cannot be ascertainment from the present study. However, experimental findings suggest that ACE inhibition is achieved at a lower dose of ACE inhibitors in the intravascular space than in the interstitial space. Thus, doses of ACE inhibitors that incompletely inhibit circulating ACE are unlikely to completely inhibit interstitial ACE.

Increasing plasma Ang II levels and attenuation of the antiremodeling effects of ACE inhibitors with time suggest that as in hypertension, an escape from ACE inhibition may also occur in CHF. The lack of relationship between the pressor response to Ang I and the duration of ACE inhibitor therapy argues against time being a major determinant of escape from ACE inhibition. The pressor response to Ang I needs to be serially measured in patients receiving high doses of ACE inhibitors to further characterize escape from ACE inhibition in CHF.

The clinical correlates of incomplete inhibition of ACE in CHF are currently unknown. Addition of ARB to recommended doses of ACE inhibitors relieves symptoms. Further studies are needed to assess whether increasing the dose of ACE inhibitors above that currently recommended will result in improvement in symptoms and survival in CHF.
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_Circulation_. 2000;101:844-846
doi: 10.1161/01.CIR.101.8.844

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 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/101/8/844

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