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Addition of Angiotensin II Receptor Blockade to Maximal Angiotensin-Converting Enzyme Inhibition Improves Exercise Capacity in Patients With Severe Congestive Heart Failure

Glenn Hamroff, MD; Stuart D. Katz, MD; Donna Mancini, MD; Ira Blaufarb, MD; Rachel Bijou, MD; Rajoo Patel, MD; Guillaume Jondeau, MD; Maria-Teresa Olivari, MD; Sylvia Thomas, MS, RPh; Thierry H. Le Jemtel, MD

Background—Incomplete suppression of the renin-angiotensin system during long-term ACE inhibition may contribute to symptomatic deterioration in patients with severe congestive heart failure (CHF). Combined angiotensin II type I (AT₁) receptor blockade and ACE inhibition more completely suppresses the activated renin-angiotensin system than either intervention alone in sodium-depleted normal individuals. Whether AT₁ receptor blockade with losartan improves exercise capacity in patients with severe CHF already treated with ACE inhibitors is unknown.

Methods and Results—Thirty-three patients with severe CHF despite treatment with maximally recommended or tolerated doses of ACE inhibitors were randomized 1:1 to receive 50 mg/d losartan or placebo for 6 months in addition to standard therapy in a multicenter, double-blind trial. Peak aerobic capacity (V̇O₂) during symptom-limited treadmill exercise and NYHA functional class were determined at baseline and after 3 and 6 months of double-blind therapy. Peak V̇O₂ at baseline and after 3 and 6 months were 13.5 ± 0.6, 15.1 ± 1.0, and 15.7 ± 1.1 mL · kg⁻¹ · min⁻¹, respectively, in patients receiving losartan and 14.1 ± 0.6, 14.3 ± 0.9, and 13.6 ± 1.1 mL · kg⁻¹ · min⁻¹, respectively, in patients receiving placebo (P < 0.02 for treatment group–by-time interaction). Functional class improved by at least one NYHA class in 9 of 16 patients receiving losartan and 1 of 17 patients receiving placebo.

Conclusions—Losartan enhances peak exercise capacity and alleviates symptoms in patients with CHF who are severely symptomatic despite treatment with maximally recommended or tolerated doses of ACE inhibitors. (Circulation. 1999;99:990-992.)

Key Words: angiotensin • heart failure • trials • exercise

Marked elevation of angiotensin II, norepinephrine, and aldosterone plasma levels and progression of left ventricular dilatation in patients with congestive heart failure (CHF) treated with recommended doses of ACE inhibitors suggests that long-term ACE inhibition may only partially suppress the activated renin-angiotensin system.¹–³ Mild activation of the renin-angiotensin system in sodium-depleted normotensive volunteers is more completely suppressed by combined administration of losartan, an angiotensin II type I (AT₁) receptor antagonist, and captopril, an ACE inhibitor, than by either intervention alone.⁴

Losartan is well tolerated by patients with severe CHF who are maximally treated with ACE inhibitors in addition to standard therapy,⁵ but the effects of combined therapy on functional capacity in patients with severe CHF are unknown. Accordingly, the present study was undertaken to determine the effects of losartan versus placebo on exercise capacity and functional class in patients with CHF who were severely symptomatic despite treatment with optimal doses of ACE inhibitors, digoxin, and diuretics.

Methods

The study was a prospective, double-blind, randomized, placebo-controlled trial conducted at 4 centers (Appendix). The study was approved by the ethical review board at each site; all patients gave written informed consent before participation.

Patient Population

Thirty-three patients whose symptoms of CHF were compatible with functional class III to IV of the New York Heart Association (NYHA) were studied. In addition to digoxin and diuretics, all patients had been treated with ACE inhibitors at maximally recommended or tolerated doses for ≥ 3 months. Clinical characteristics and medications are detailed in Tables 1 and 2. None of the patients...
TABLE 1. Patient Clinical Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Losartan (n=16)</th>
<th>Placebo (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.7±13</td>
<td>60±10</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.2±0.4</td>
<td>3.1±0.1</td>
</tr>
<tr>
<td>Left ventricular ejection</td>
<td>26.5±2</td>
<td>25.9±2</td>
</tr>
<tr>
<td>fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</td>
<td>13.5±2.3</td>
<td>14.1±2.5</td>
</tr>
<tr>
<td>Patient characteristics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>5 (31)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Former smoking history</td>
<td>4 (25)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (56)</td>
<td>13 (76)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (31)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Ischemic CHF</td>
<td>5 (31)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Nonischemic CHF</td>
<td>11 (69)</td>
<td>13 (71)</td>
</tr>
<tr>
<td>Background medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>15 (94)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>16 (100)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>16 (100)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (44)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>3 (19)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Antiplatelites</td>
<td>6 (38)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Potassium supplements</td>
<td>5 (32)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

had participated in a physical conditioning program. Patients randomized to losartan and placebo were similar except for a preponderance of men and a higher dose of captopril in the losartan group.

Study Design
Randomization to losartan or placebo was preceded by a 2-week single-blind tolerability phase, which has been reported previously. All patients tolerated losartan 50 mg/d. Patients were then randomized to therapy with losartan 50 mg or placebo for 6 months. Clinical assessments and laboratory evaluations were performed weekly for 1 month and monthly thereafter. Peak oxygen uptake (VO₂, mL·kg⁻¹·min⁻¹) during symptom-limited maximal treadmill exercise was measured at baseline in duplicate and subsequently after 3 and 6 months of double-blind therapy.

Study End Points and Data Analysis
The primary end points of the study were peak VO₂ and NYHA functional class. Secondary end points were laboratory safety parameters and doses of concomitant background medications. Prerandomization peak VO₂ was determined as the highest value of 2 exercise tests with <10% variation. Peak VO₂ at months 3 and 6 was derived from a single maximal exercise test.

Case reports were centrally collected, and data were analyzed by Lynn Sleeper, ScD (New England Research Institute, Watertown, Mass). Repeated-measures ANOVA (SAS Institute Inc, PROC MIXED) was used to analyze peak VO₂, laboratory safety parameters, and doses of background medications. An SAS macro for repeated-measures cumulative logistic regression was used to analyze NYHA functional class. The daily dose of furosemide was square root–transformed to meet the normality assumption because of the wide dosing range for this agent. Probability values reported are from models that incorporate time as a continuous covariate. Values are expressed as mean±SEM.

Results

Primary End Points
Peak VO₂ at baseline and after 3 and 6 months was 13.5±0.6, 15.1±1.0, and 15.7±1.1 mL·kg⁻¹·min⁻¹, respectively, in patients receiving losartan and 14.1±0.6, 14.3±0.9, and 13.6±1.1 mL·kg⁻¹·min⁻¹, respectively, in patients receiving placebo (P<0.02 for treatment group–by-time interaction, Figure 1). Functional class improved by ≥1 NYHA class in 9 of 16 patients receiving losartan and 1 of 17 patients receiving placebo. Functional class at baseline and after 3 and 6 months was 3.2±0.4, 2.9±0.6, and 2.5±0.8, respectively, in patients receiving losartan and 3.0±0.4, 3.0±0.5, and 3.0±0.5, respectively, in patients receiving placebo (P<0.001 for treatment group–by-time interaction, Figure 2).

Secondary End Points
Serum electrolytes, creatinine, and blood urea nitrogen were unchanged in both treatment groups. The furosemide dose (square root–transformed) at baseline and after 3 and 6 months was 11.5±1.1, 10.9±1.1, and 10.5±1.2, respectively, in patients receiving losartan and 9.9±1.0, 10.0±1.1, and 10.8±1.1, respectively, in patients receiving placebo (P<0.05 for treatment group–by-time interaction). Doses of other background medications were unchanged in both treatment groups. The combination of study drug and ACE inhibitors in both treatment groups was well tolerated, without adverse side effects.

Four patients in the placebo group and 3 patients in the losartan group did not complete the study. In the placebo

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*Maximum recommended dose was 150 mg/d for captopril and 40 mg/d for the long-acting ACE inhibitors.
Discussion

The present data indicate that losartan improves peak aerobic capacity and relieves symptoms in patients with CHF who are severely symptomatic despite treatment with optimal doses of ACE inhibitors, digoxin, and loop diuretics.

The therapeutic efficacy of losartan has been demonstrated in patients with CHF in the absence of ACE inhibitors. Acute administration of losartan results in arterial and venous dilatation comparable to that with ACE inhibition. The acute hemodynamic effects of losartan are greatest at a dose of 50 mg and persist without attenuation for 12 weeks. In patients in whom previous ACE inhibition therapy was withdrawn, losartan and enalapril have comparable effects on exercise performance. The present study assessed the long-term effects of AT₁ receptor blockade in patients with severe CHF receiving optimal doses of ACE inhibitors. Data collected from previous clinical trials have suggested that an escape phenomenon may occur during prolonged ACE inhibition. Whether partial deactivation is attributable to an escape from ACE inhibition during long-term therapy or to other metabolic pathways for biosynthesis of angiotensin II cannot be ascertained from the present study. Our findings are consistent with the additive effects of combined angiotensin-converting enzyme inhibition and angiotensin II antagonism on blood pressure and renin release in sodium-depleted normotensives. The acute hemodynamic effects of losartan are greatest at a dose of 50 mg and persist without attenuation for 12 weeks. In patients in whom previous ACE inhibition therapy was withdrawn, losartan and enalapril have comparable effects on exercise performance.

In summary, the present data demonstrate that addition of AT₁ receptor blockade to optimal ACE inhibition therapy improves peak exercise performance and function capacity in patients with severe heart failure. These striking findings in 33 patients require confirmation in larger trials.

Appendix

Trial Centers and Investigators

Albert Einstein College of Medicine: Glenn Hamroff, MD; Ira Blaufarb, MD; Rachel Bijou, MD; Rajoo Patel, MD; Sylvia Thomas, MS, RPh; and Thierry H. Le Jemtel, MD. Columbia Presbyterian Hospital Center: Stuart D. Katz, MD; and Donna Mancini, MD. University of Nebraska Medical Center: Maria-Teresa Olivari, MD. Hôpital Ambroise Paré: Guillaume Jondeau, MD.

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