Contrasting Peripheral Short-term and Long-term Effects of Converting Enzyme Inhibition in Patients With Congestive Heart Failure
A Double-Blind, Placebo-Controlled Trial

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To discover the underlying mechanisms involved in the beneficial long-term effects of angiotensin converting enzyme (ACE) inhibitors, we investigated the systemic and peripheral effects of short- and long-term ACE inhibition in patients with chronic heart failure. After assessing the short-term effects and dose titration with cilazapril, a new long-acting ACE inhibitor, 21 patients were randomized to receive either placebo or the ACE inhibitor. Seventeen patients completed the 3-month treatment. Central hemodynamic output, femoral blood flow (measured by thermodilution), oxygen saturation, and lactate and norepinephrine levels were determined simultaneously in the femoral vein and radial artery during treatment and after a 3-month rest and during symptom-limited bicycle exercise. Short-term ACE inhibition improved rest and exercise hemodynamic output, but it did not alter peak femoral blood flow, calculated leg oxygen consumption, or systemic oxygen uptake during exercise, despite significant reduction in femoral norepinephrine extraction and arterial angiotensin levels during exercise. In contrast, long-term ACE inhibition further improved exercise cardiac output and increased leg blood flow (from 2.3 to 2.9 l/min, \( p < 0.05 \)), leg oxygen consumption (from 277 to 403 ml/min, \( p < 0.05 \)), and systemic oxygen uptake (from 1,133 to 1,453 ml/min, \( p < 0.05 \)), whereas these variables remained unchanged with placebo treatment (\( p < 0.02 \) between groups). Moreover, a moderate but significant increase in femoral oxygen extraction occurred after long-term therapy (ACE inhibitor: from 76% to 83%, \( p < 0.05 \); placebo: from 75% to 74%, NS; \( p < 0.01 \) between groups).

We conclude that long-term ACE inhibition is clinically beneficial in that it improves blood flow to skeletal muscle during exercise over time. The long-term effects of ACE inhibition are, in part, probably related to peripheral (vascular) mechanisms, for example, by reversing the inability of peripheral vessels to dilate and by improving oxygen utilization. (*Circulation* 1989;79:491–502)

In recent studies concerning the short-term effects of angiotensin converting enzyme (ACE) inhibition, captopril improved cardiac performance at rest and during exercise in patients with chronic heart failure.1,2 However, neither exercise performance, as determined by maximal oxygen consumption, nor blood flow to exercising skeletal muscle increased.3,4 After long-term therapy, ACE inhibitors improve cardiac hemodynamic output and exercise performance in patients with chronic heart failure. Several studies have shown that this improvement during long-term ACE inhibition emerges gradually over time.5,6 Experimental and clinical data suggest that exercise tolerance and \( V_{O2max} \) in patients with heart failure are correlated to the limited maximal blood flow to skeletal muscle,7 although intrinsic abnormalities of skeletal muscle may be present as well.8 This reduced muscular blood flow during exercise seems, in part, due to an impairment of the
Peripheral vessels to dilate in response to vasodilator stimuli.9–11

Peripheral flow and metabolism during exercise by long-term ACE inhibition12 may be improved over time by interference of ACE inhibition with the renin-angiotensin system (reducing circulating and vascular angiotensin II levels), plasma prostaglandins E and I, the sympathetic nervous system, or by reduction of vascular sodium content. This would, in turn, improve oxygen availability of working muscle and finally would improve systemic oxygen consumption.

Moreover, these and other mechanisms of long-term ACE inhibition (i.e., less dyspnea by reduction of left ventricular filling pressure) may increase exercise training capability and, thereby, improve oxygen extraction and reverse intrinsic abnormalities of working muscle. In a double-blind, placebo-controlled manner, this study investigates the systemic and peripheral effects of short-term and long-term ACE inhibition in patients with chronic heart failure. To gain insight into the mechanisms underlying the beneficial long-term effects of ACE inhibitors, systemic and peripheral hemodynamic output and short-term and long-term metabolic responses to ACE inhibition were measured and the symptoms were assessed objectively.

A new, very potent, and long-acting ACE inhibitor, cilazapril, was used13,14 that allows a once-daily administration. Cilazapril, a monoethyl ester prodrug,15 had a rapid onset (within 1 hour), a prolonged duration (up to 8 hours), and a peak effect between 2 and 6 hours in normal individuals and patients with hypertension and heart failure.14–16

Methods

Patients

Twenty-one patients with chronic heart failure (New York Heart Association [NYHA] functional Class II and III) and a left ventricular ejection fraction less than 45% (see also baseline echocardiography data) were studied after giving written, informed consent to a protocol approved by the Ethical Committee of the University of Freiburg, Freiburg, FRG. After baseline studies (predrug measurements and after short-term drug administration), the patients were randomized into two groups to receive either cilazapril or placebo. This study provides the results of those seventeen patients that underwent short- and long-term (systemic and peripheral) hemodynamic studies. Four patients did not complete the 3-month trial. One patient suffered from myocardial infarction and died from cardiogenic shock. One patient was taken off the trial medication because of an increase in body weight (both placebo groups). The condition of one patient on active treatment deteriorated, and he was recommended for heart transplantation, and another experienced unexplained dyspnea and, therefore, was withdrawn from the study.

All patients had clinical, radiologic, or echocardiographic signs of cardiomegaly and congestive heart failure despite treatment with digitalis or diuretics or both and, in nine patients, other vasodilators. Patients with chronic lung disease, primary valvular heart disease, angina, claudication, and myocardial infarction within 3 months or systemic arterial hypotension or both (systolic blood pressure <100 mm Hg) were excluded. Preliminary assessment was made 2–4 weeks before the study. Previous treatment with isosorbide dinitrate or nifedipine or both of seven patients (four patients randomized to receive placebo and three to receive cilazapril) was discontinued 5–7 days before study. In two patients (one each in the placebo and cilazapril group), captopril therapy was stopped 4 weeks before study. One patient with borderline systolic pressure (100–105 mm Hg) received a 12.5-mg captopril test dose 1 week before the study. There were no differences in drug effects between patients pretreated with these vasodilators and those without pretreatment. Patients were hospitalized at least 3 days before the study, and their conditions were stabilized while receiving constant doses of digitalis and diuretics. However, diuretics were withheld for at least 12 hours before hemodynamic measurements were made until short-term hemodynamic evaluation was completed.

To qualify for inclusion, each patient underwent a prestudy assessment with supine bicycle exercise. The workload began at 25 W and advanced by 25 W every 3 minutes until the patient was exhausted. According to this protocol, patients had to be able to exercise for at least 3 minutes at a workload of 25 W or at a maximal workload of 75 W and to achieve an endpoint consistent with heart failure, dyspnea, or fatigue (symptom-limited maximal exercise response). This qualifying assessment of maximal workload and exercise time, in addition, determined the timing of measurements during subsequent exercise hemodynamic studies.

Study Design

After baseline hemodynamic measurements were obtained, patients 1–10 received a single dose of 2.5 mg cilazapril, and hemodynamic output was determined as described below. This dose was increased to 5 mg the next day (the day after obtaining hemodynamic measurements) if systolic blood pressure decreased less than 15%, provided that mean arterial pressure was greater than 70 mm Hg after the first drug administration (2.5 mg cilazapril given the day before) or no symptomatic hypotension occurred or both. In patients 11–21, 5 mg cilazapril was given as a first dose. Because the hemodynamic effects from 2.5 and 5 mg cilazapril did not differ, the short-term hemodynamic measurements are summarized irrespective of the initial dosage given. Six of the nine patients of the cilazapril group were discharged on 5 mg cilazapril daily, whereas five of eight patients of the placebo group were discharged.
with the 5-mg titration dose. All other patients received 2.5 mg/day during long-term therapy. The titrated dose of cilazapril or a similar amount of placebo (identical tablets) was administered in a double-blind manner once daily during a 3-month period. Patients were evaluated at the end of weeks 4 and 8 on an outpatient basis. Test dose, digoxin, and diuretics were kept constant throughout the 3-month period in all patients who completed the study.

At the end of the 3-month period, patients were admitted to the hospital again and underwent hemodynamic studies while receiving their medication in a blinded manner. The procedures for the second evaluation were identical to those of the first evaluation. Hemodynamic, metabolic, and neurohumoral variables were measured during uninterrupted therapy 1, 2, 4, and 6 hours after administration of placebo or cilazapril at rest. After the evaluation during the 6-hour resting period, measurements were obtained during exercise (at the workload identical to that during control exercise). All patients were then given the option of receiving long-term cilazapril therapy. NYHA functional class and exercise capacity were recorded before and after 3 months of therapy.

**Hemodynamic Assessment**

The day before hemodynamic measurements were taken, right heart catheterization with a 7F thermodilution catheter was performed. A 5F thermodilution catheter (with the thermistor at 2 cm and injection port at 12 cm) was inserted into the femoral vein (approximately 4 cm distal to the groin) under fluoroscopic guidance as described by Wilson et al. To position the tip of the catheter at a distance from a run-in of internal veins, contrast injections were used. The patients were monitored overnight, and low-dose heparin was perfused into the distal port of the femoral catheter. The next day, a short polyethylene catheter was inserted under local anesthesia in a radial or brachial artery, and the position in the femoral vein was checked (position corrected in two patients). Patients then rested for at least 1 hour before hemodynamic levels were measured. After baseline measurements were obtained, supine bicycle exercise was performed with the chest at a 45° upright angle. Similar to the protocol of the prestudy exercise test, exercise was performed until limiting symptoms of dyspnea or fatigue occurred (symptom-limited maximal exercise response). During exercise, the electrocardiogram and arterial and pulmonary artery pressures were monitored continuously, and pulmonary wedge pressure and cardiac output (by thermodilution) were measured twice during the last 60 seconds of each workload. In two patients, the pulmonary artery diastolic pressure was substituted for a technically unsatisfactory or unobtainable wedge pressure tracing. In these two patients, concordance between pulmonary diastolic and mean wedge pressure had been established. Femoral flow was determined at each workload as described below. Arterial and femoral vein blood samples were obtained simultaneously (at highest workload common to the control and cilazapril groups) for determination of oxygen saturation, lactate concentrations, and norepinephrine levels. In addition, blood samples drawn from the pulmonary artery were used for determining oxygen saturation and pH.

After this baseline exercise test, 2.5 or 5 mg cilazapril was administered orally, and resting hemodynamic levels were measured after 1, 2, 4, 6 hours. After the 6-hour resting measurements were obtained, a second exercise test was done with the identical protocol; thus, the control and postdrug exercise tests were separated by at least 6 hours. Measurements were obtained at the same workload as that during the baseline study and again at peak exercise in patients who exercised further. Results are reported for workloads similar to those during the baseline measurements (Table 2-4, Figures 1-4), except for the data in Figure 5 in which maximal values after long-term therapy were used.

**Leg Blood Flow**

Blood flow of the exercising leg was determined by the bolus thermodilution technique in the femoral vein (3 ml saline solution, 0°C) as described by Jorfeldt et al and more recently by Wilson et al. Output curves were displayed on the screen of a cardiac output computer (Gould SP 1435 or Edwards Laboratories). Jorfeldt et al demonstrated that femoral vein flow measured by this technique agrees closely with leg flow determined by continuous infusion thermodilution or by indocyanin green technique. The method we used is somewhat different, however, with a single thermistor catheter. Flow measurements at rest, in our experience, are unreliable because of insufficient mixing and, therefore, are not reported. The technique was tested in an open loop system with known flow rates (0.25–2.3 l/min) and a polyethylene tubing (6–9 mm in diameter) with a high-precision pump and by volume sampling of the perfused saline in a vial (correlation for thermodilution vs. pump flow: r=0.962, p<0.001).

The coefficient of variation of duplicate flow measurements taken sequentially during the same exercise test was 14±10%. This variation is, in part, due to normal phasic alterations in flow. Therefore, flow measurements were performed in triplicate during each workload and averaged. Studies for reproducibility (during two exercise tests) of femoral flow measurements with this bolus technique were recently reported and demonstrated similar values when the measurements were repeated on the same day.

**Derived Peripheral Values**

Systemic oxygen consumption was calculated from the product of cardiac output and arteriovenous oxygen difference (arterial oxygen content...
minus central venous oxygen content). Femoral (leg) oxygen consumption was determined from the product of femoral flow and the difference of arterial and femoral venous oxygen content. Blood oxygen content was calculated by the product of hemoglobin 1.34 ml O₂/g of hemoglobin and the percentage of oxygen saturation (Co-oximeter). Changes in hemoglobin concentration and pH during exercise may affect the calculation of oxygen content. Because the analysis of oxygen extraction is confined to the comparison of exercise data only, our interpretation should be valid, particularly because neither hemoglobin concentration (at rest) nor pH during exercise (as measured in the pulmonary artery) changed significantly with long-term therapy. Femoral oxygen extraction was calculated as the ratio of the arteriovenous oxygen difference and arterial oxygen content. Femoral lactate and norepinephrine extraction were calculated as (arterial lactate concentration minus femoral venous lactate concentration) divided by arterial lactate concentration multiplied by 100 and (arterial norepinephrine level minus femoral venous norepinephrine level) divided by arterial norepinephrine level multiplied by 100. Leg lactate release was calculated as leg flow multiplied by (femoral vein minus arterial lactate concentration).

Plasma norepinephrine levels were measured by a radioisotope enzymatic method. Blood for lactate determinations was deproteinized immediately with perchloric acid and assayed with a spectrophotometric technique. Arterial blood samples for determination of angiotensin II levels were obtained at rest (before and 6 hours after cilazapril administration) and during peak exercise (baseline and short- and long-term cilazapril). Measurements were performed in extracts with a hydrophobic adsorbent resin. Cross reactivities of the angiotensin II antibodies were angiotensin III 100%, angiotensin I 0.04%, human tetradecapeptide renin substrate 0.2%. The sensitivity of the assay was about 1–2 pg/ml plasma. Duplicate measurements were performed. Recovery of exogenously added angiotensin II to human and dog plasma was 93% and 83%, respectively. More than 95% of the endogenous angiotensin II–like immunoreactivity of dog plasma eluted from reverse-phase high-performance liquid chromatography, capable of separating angiotensin I, angiotensin II, and angiotensin III in the position of the angiotensin II octapeptide. All neurohumoral determinations were performed with the samples coded and with the individual investigators unaware of the identities.

Statistical Analysis

Intraindividual comparison of baseline short- and long-term cilazapril effects of each group (placebo or cilazapril) were evaluated by analysis of variance for repeated measures. When the F test was significant, individual comparisons were made by the Student-Newman-Keuls test. The two long-term peripheral treatment effects (placebo vs. ACE inhibition) were compared by Fisher’s exact test. Baseline values of both groups were compared by a two-tailed, unpaired t test. Control values and effects of short-term cilazapril (pooled data of all 17 patients) were compared by two-tailed paired t test. Data are reported as mean±SD. A p value less than 0.05 was considered significant.

Results

The characteristics of the treatment groups were not significantly different (Table 1). The predrug and postdrug (short-term and 3-month) measurements for the two groups are shown in Tables 2–4. There were no significant differences in the predrug values between groups.

Short-term Effects of ACE Inhibition

Cilazapril significantly affected resting central hemodynamic values, including increased cardiac index and stroke volume and decreased systemic vascular resistance and right and left ventricular filling pressures (as estimated by right atrial and pulmonary wedge pressures) (Table 2). Plasma angiotensin II levels 6 hours after cilazapril administration were reduced, indicating maintained ACE inhibition. During exercise, pulmonary wedge pressure, mean arterial pressure, and systemic vascular resistance decreased significantly with cilazapril administration (Table 2); likewise, cardiac output increased. Femoral norepinephrine extraction was increased; that is, femoral norepinephrine production during exercise decreased after a single dose of cilazapril. Similarly, arterial angiotensin II levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACE inhibitor group (n=9)</th>
<th>Placebo group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>59±8</td>
<td>50±11</td>
</tr>
<tr>
<td>Range</td>
<td>41–76</td>
<td>35–67</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>2/7</td>
<td>1/7</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Valvular heart disease (after valve replacement)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Durations of symptoms (yr)</td>
<td>4.3±1.4</td>
<td>4.0±2.3</td>
</tr>
<tr>
<td>NYHA functional Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.54±0.04</td>
<td>0.57±0.05</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>6.8±1.7</td>
<td>5.9±1.8</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>70±6</td>
<td>74±6</td>
</tr>
<tr>
<td>LV systolic diameter (mm)</td>
<td>58±5</td>
<td>64±8</td>
</tr>
<tr>
<td>Fraction fiber shortening (%)</td>
<td>0.16±0.04</td>
<td>0.14±0.03</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; NYHA, New York Heart Association; LV, left ventricular.

No significant differences occurred between the placebo and cilazapril groups for any of the baseline variables.

TABLE 1. Clinical Characteristics of Patient Groups at Baseline

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Table 2. Short-term Effects of Cilazapril on Systemic Hemodynamic Measurements and Metabolic Variables at Rest and During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ACE short-term</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 13.3</td>
<td>79.8 ± 11.4</td>
<td>128 ± 23</td>
<td>128 ± 25</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>92 ± 12</td>
<td>81 ± 14†</td>
<td>118 ± 16</td>
<td>112 ± 14†</td>
</tr>
<tr>
<td>Right arterial pressure (mm Hg)</td>
<td>6.4 ± 4.7</td>
<td>3.6 ± 4.4†</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.7 ± 0.8</td>
<td>3.1 ± 0.7†</td>
<td>4.3 ± 1.3</td>
<td>4.8 ± 0.6†</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>34 ± 9</td>
<td>39 ± 9†</td>
<td>34 ± 10</td>
<td>38 ± 11†</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne · sec/cm²)</td>
<td>1,665 ± 684</td>
<td>1,247 ± 424†</td>
<td>1,384 ± 578</td>
<td>1,159 ± 468†</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>16 ± 8</td>
<td>10 ± 6†</td>
<td>31 ± 7</td>
<td>28 ± 7‡</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>16.9 ± 5</td>
<td>11.2 ± 5†</td>
<td>25 ± 16</td>
<td>9.9 ± 5†</td>
</tr>
<tr>
<td>V̇O₂max (ml/min)</td>
<td>—</td>
<td>—</td>
<td>1,080 ± 351</td>
<td>1,162 ± 341</td>
</tr>
<tr>
<td>Leg flow (l/min)</td>
<td>—</td>
<td>—</td>
<td>2.2 ± 1.0</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td>Leg V̇O₂ (ml/min)</td>
<td>—</td>
<td>—</td>
<td>271 ± 109</td>
<td>303 ± 111</td>
</tr>
<tr>
<td>Femoral oxygen extraction (%)</td>
<td>—</td>
<td>—</td>
<td>74 ± 6</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>Leg lactate release (mmol/min)</td>
<td>—</td>
<td>—</td>
<td>2.5 ± 1.0</td>
<td>2.6 ± 1.2</td>
</tr>
<tr>
<td>Femoral norepinephrine extraction (%)</td>
<td>—</td>
<td>—</td>
<td>-46 ± 26</td>
<td>11 ± 15†</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
Data after cilazapril administration represent peak effect of the drug (defined by maximal improvement in cardiac output and pulmonary wedge pressure), usually occurring 2 hours after administration.
ACE, angiotensin converting enzyme.
†p<0.01 vs. corresponding control value; ‡p<0.02 vs. corresponding control.

During exercise were lower after short-term administration of cilazapril. Plasma angiotensin II levels did not rise significantly with exercise after ACE inhibition compared with the resting values. Systemic oxygen consumption, leg (femoral) blood flow, femoral oxygen extraction, and leg lactate release did not change with short-term administration of cilazapril (Table 2).

Long-term Response to Cilazapril

Tables 3 and 4 depict the measurements after long-term (3-month) administration of cilazapril. The cilazapril dosage was increased after short-term hemodynamic evaluation (dose titration). Furthermore, pharmacokinetics and dynamics of cilazapril (or in general, of long-term ACE inhibition) are likely to be altered over time. Therefore, the short-term and the 3-month measurements are not truly comparable. To determine the hemodynamic long-term effect of cilazapril, we compared the resting peak effects after short-term administration with those obtained after long-term therapy (after ingestion of the randomized active treatment or placebo). In the cilazapril group, the drug-mediated effects on blood pressure, pulmonary wedge pressure, and right atrial pressure were maintained after 3 months of therapy. Cardiac output during exercise was further increased after long-term therapy compared with the short-term drug-mediated response (short-term: 5.0 ± 1.8; long-term: 5.6 ± 1.3, p<0.05). Consequently, calculated systemic vascular resistance during exercise had decreased further (although not significantly) with long-term treatment. This con-

Table 3. Long-term Effects of Cilazapril on Systemic Hemodynamic and Plasma Angiotensin II Levels at Rest

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n=8)</th>
<th>ACE group (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 3 mo</td>
<td>Control 3 mo</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 14 80 ± 14</td>
<td>74 ± 9 73 ± 8</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>93 ± 11 86 ± 13</td>
<td>91 ± 14 79 ± 10*</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>18 ± 10 16 ± 9</td>
<td>15 ± 7 9 ± 6*</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>6 ± 3 5 ± 3</td>
<td>7 ± 6 3 ± 3*</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.8 ± 0.9 3.0 ± 0.6</td>
<td>2.6 ± 0.7 3.3 ± 0.5*</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>34 ± 10 38 ± 10</td>
<td>35 ± 9 45 ± 10*</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne · sec/cm²)</td>
<td>1,688 ± 827 1,360 ± 462</td>
<td>1,644 ± 581 1,088 ± 254*</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>14.5 ± 6 20.2 ± 18</td>
<td>19.4 ± 8 14.8 ± 10*</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
Angiotensin II (n=5 for each group).
ACE, angiotensin converting enzyme.
*p<0.05 vs. control.
TABLE 4. Long-term Effects of Cilazapril on Systemic Hemodynamic Levels, and Peripheral, Neurohumoral, and Metabolic Factors During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n=8)</th>
<th>ACE group (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>3 mo</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>129±22</td>
<td>129±20</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>117±14</td>
<td>113±14</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>32±8</td>
<td>37±6</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>4.0±1.2</td>
<td>4.3±1.1</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>31±8</td>
<td>34±7</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes⋅sec/cm²)</td>
<td>1,470±654</td>
<td>1,225±442</td>
</tr>
<tr>
<td>Femoral norepinephrine extraction (%)</td>
<td>−58±29</td>
<td>−19±41</td>
</tr>
<tr>
<td>Femoral lactation release (%)</td>
<td>−34±20</td>
<td>−40±29</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>21±14</td>
<td>22±14</td>
</tr>
<tr>
<td>Leg lactation release (mmol/min)</td>
<td>2.44±0.8</td>
<td>2.93±1.3</td>
</tr>
</tbody>
</table>

Data are mean±SD.
Angiotensin II (n=5 for each group).
ACE, angiotensin converting enzyme.
*p<0.05 vs. control.

Contrasts with the long-term hemodynamic effects in the placebo group.

The effects of long-term cilazapril on femoral norepinephrine extraction and arterial angiotensin II levels during exercise were maintained in the cilazapril group. However, the long-term angiotensin II levels and norepinephrine extraction data were not significantly different from baseline (at rest and during exercise) in the placebo group (Table 3). Most important, peak systemic oxygen consumption increased and femoral blood flow improved during exercise in the cilazapril group (from 15.6 to 20.0 ml/min/kg, p<0.05) but not in the placebo group (peak VO₂: from 14.1 to 14.9 ml/min/kg, NS) (Figures 1, 2, and 5).

Moreover, femoral oxygen extraction improved slightly, but significantly, after long-term therapy in the cilazapril group only (Figure 4). Mean values of femoral venous lactate (at identical levels during exercise) did not decrease significantly after long-term treatment in both groups, although values were lower in the cilazapril group (baseline vs. short-term vs. long-term: 4.9±1.1 vs. 4.2±1.3 vs. 3.9±1.2 mmol/l). However, femoral venous lactate concentration decreased substantially in four of those five patients who showed substantial increases in femoral blood flow during exercise after long-term cilazapril therapy (baseline vs. long-term: 5.6±0.3 vs. 3.4±0.4 mmol/l). Moreover, those patients having substantial increases in femoral blood flow during exercise had clinically relevant improvement in peak systemic oxygen consumption, as indicated by the close correlation between change in femoral flow and change in peak systemic oxygen consumption (Figure 5). Similarly, a relation occurred between the increase in cardiac out-

**FIGURE 1:** Bar graph of effect of long-term angiotensin converting enzyme (ACE) inhibition (placebo and cilazapril) on systemic peak oxygen consumption during exercise. Data are mean±SD. *p<0.05 vs. corresponding control values; †p<0.02 for long-term treatment with placebo vs. ACE inhibitor.
put and the increase in femoral blood flow during exercise after long-term therapy, although it was not significant ($r=0.694, p=0.056$).

Leg lactate release during exercise at similar workloads did not change significantly after long-term ACE inhibition compared with control measurements. Similarly, mean values of femoral lactate production determined by femoral arteriovenous extraction (at identical levels of exercise) did not change with long-term cilazapril therapy.

Before cilazapril therapy, peak systemic $\dot{V}O_2$ averaged 1,133 ml/min for the entire body, 554 ml/min for the lower limb and 579 ml/min for the rest of the body. During long-term therapy with cilazapril, systemic peak oxygen consumption increased to 1,453 ml/min, 804 ml/min for the lower limb and 647 ml/min for the rest of the body. This implies that increasing oxygen delivery to the exercising skeletal muscle is of primary importance, whereas oxygen delivery to the rest of the body did not significantly change with ACE inhibition.

The exercise time of the placebo group was the same throughout the study (baseline vs. short-term vs. long-term cilazapril: 5.91±1.77 vs. 5.91±1.8 vs. 5.84±2.2 minutes); however, exercise time increased significantly after long-term cilazapril therapy (6.83±1.7 vs. 7.04±1.3 vs. 8.5±2.2, $p<0.01$ for long-term cilazapril therapy vs. baseline). NYHA functional class did not change in patients receiving placebo, but it did improve by one class in seven of nine patients on long-term cilazapril therapy.

No severe adverse effects could be attributed to cilazapril in the 17 patients who completed the 3-month treatment period. One patient experienced dizziness 3–4 hours after ingestion of the drug but was asymptomatic when the dosage was reduced.
from 5 to 2.5 mg. Another patient suffered from left ventricular thrombus and cerebral embolism with temporary hemiplegia (8 weeks after cilazapril therapy) but had a complete recovery.

Discussion

Short-term ACE Inhibition

Short-term ACE inhibition does not immediately improve the peripheral metabolic state of working muscle or peak systemic oxygen consumption. Femoral vein oxygen extraction, femoral flow, and femoral vein lactate extraction during exercise were not affected by short-term administration of the ACE inhibitor, which is in keeping with recent observations.3,4 Similarly, skeletal muscle blood flow, which was determined more directly by the microsphere technique, was unchanged by captopril during exercise in a rat model of myocardial infarction and failure.22 This indicates that blood flow redistribution favoring working muscle did not occur. Speculatively, therefore, the renin-angiotensin system does not interfere with blood flow to working muscle during exercise.4 Regarding unchanged cardiac output and skeletal muscle flow during exercise (reported by Wilson and Ferraro4), one would not be surprised that metabolic indexes and peak oxygen consumption did not rise with short-term ACE inhibition. However, maximal oxygen consumption did not increase even in a group of patients having significantly increased exercise cardiac output after short-term administration of captopril.2

FIGURE 4. **Bar graph of effect of long-term angiotensin converting enzyme (ACE) inhibition (placebo and cilazapril) on femoral oxygen extraction during exercise (similar workloads).** Data are mean ± SD. *p<0.05 vs. corresponding control values; †p<0.01 for long-term treatment effects placebo vs. ACE inhibitor.

FIGURE 5. **Plot of correlation between the maximal increase in leg blood flow with long-term angiotensin converting enzyme inhibition during exercise and the increase in peak oxygen consumption at maximal exercise.**
Long-term ACE Inhibition

Although numerous studies have evaluated the long-term response to ACE inhibition in patients with chronic heart failure, double-blind trials reporting short- and long-term hemodynamic effects during exercise are scarce. Webster et al.\(^1\) have reported only minor changes in hemodynamic output during exercise and in exercise time after enalapril therapy for 12 weeks. More important, plasma angiotensin levels were not significantly reduced by enalapril in this study, which may indicate that ACE inhibition was incomplete. We found a significant increase in systemic cardiac output during exercise, in exercise tolerance, and in peak systemic oxygen consumption with improved NYHA class. These findings are consistent with the observations reported earlier.\(^1,2\)

Of note, exercise cardiac output increased only slightly with short-term ACE inhibition, but further improvement was observed after treatment for 3 months. Similarly, systemic vascular resistance decreased further after long-term therapy. Peak leg and systemic oxygen consumption during exercise increased, primarily due to improved femoral blood flow and to increased oxygen extraction.

Massie et al.\(^2\) reported a lack of relation between short-term hemodynamic effects of captopril and subsequent clinical responses. However, consistent with the present findings, five of their seven patients who underwent recatheterization (and study of hemodynamic levels) during long-term therapy responded clinically and showed greater beneficial changes in resting and exercise hemodynamic levels. Thus, if long-term ACE inhibitor therapy improves systemic cardiac output during exercise, it may improve femoral (muscle) blood flow and peak oxygen consumption. In fact, a close relation between blood flow to skeletal muscle per gram of tissue and maximal oxygen consumption was recently demonstrated in normal humans.\(^26\) Similarly, the inability of the muscular vasculature to dilate adequately during exercise and to subsequent pharmacologic intervention seems an important factor limiting maximal exercise capacity in patients with chronic heart failure.\(^10,11\)

Because of improved skeletal muscle blood flow, one would expect a decrease in femoral lactate production because a shift to anaerobic metabolism would be delayed in the face of an improved oxygen delivery per gram of tissue. However, femoral lactate levels did not change for the cilazapril group as a whole. Marked reductions in femoral vein lactate levels were observed in four of five patients who had a substantial improvement in femoral blood flow and peak femoral and systemic oxygen uptake. Nevertheless, leg lactate release during exercise did not change with long-term ACE inhibition. These findings may indicate that long-term ACE inhibition improves lactate clearance but may not affect lactate production in working muscle, in analogy to the hypothesis of Donovan and Brooks\(^27\) that endurance training does not affect production of lactate but does affect its clearance rate.

The short-term effects of ACE inhibition on femoral norepinephrine extraction and arterial angiotensin II levels (during exercise) were maintained during long-term therapy, suggesting sustained and effective ACE inhibition. Because ACE inhibition was similarly effective after short- and long-term therapy, the contrasting short- and long-term effects of ACE inhibition cannot be solely related to these neurohumoral alterations. However, there is now increasing evidence that a vascular renin-angiotensin system is operative.\(^28\) The importance of the tissue renin-angiotensin system, rather than its plasma counterpart, in determining the long-term blood pressure response to ACE inhibition has been demonstrated by several investigators.\(^29,30\) One may speculate, therefore, that excess vascular renin-angiotensin activity increases vascular tone in chronic heart failure. Long-term, but not short-term, therapy may effectively interfere with the local tissue renin-angiotensin system. This may account, in part, for the delayed effect of cilazapril on skeletal muscle blood flow. Alternatively, or in addition, the improved femoral blood flow after long-term therapy could be due to beneficial effects of ACE inhibition on renal function and sodium balance of the vascular wall. An intrinsic defect in the skeletal muscle vasculature of patients with heart failure, such as increases in vascular sodium content, that interferes with the delivery of nutritional flow has been proposed.\(^9\) After long-term ACE inhibition with captopril, a decrease in abnormal cellular permeability to sodium has been shown to occur in hypertensive rats.\(^31\) Thus, by analogy, the delayed effect of captopril in chronic heart failure may be attributed to the latter effects of the drug. Similarly, a delayed reversal of impaired vasodilation was recently reported in congestive heart failure after heart transplantation. This impaired vasodilation may be secondary to deconditioning of blood vessels.\(^32\)

Interestingly, improved cardiac output, for example, with short-term administration of dobutamine or dopamine, does not increase blood flow to exercising muscle but rather may increase shunt flow to nonmetabolically active tissues.\(^33,34\) Because femoral flow increased only after long-term ACE inhibition and because cardiac output was improved further with long-term ACE inhibition compared with short-term, it is hypothesized that the beneficial effect of long-term ACE inhibition is brought about primarily by a peripheral vascular effect. Nevertheless, other effects of ACE inhibition, that is, on the myocardium,\(^35,36\) pulmonary vasculature and mechanics, plasma prostaglandins,\(^37,38\) and kidneys,\(^39\) may contribute as well.

Intrinsic Abnormalities of Skeletal Muscle

Of note, femoral oxygen consumption with long-term therapy increased by 44%, but femoral blood
flow increased by only 29%. In contrast to a recent report, 12 a slight, but significant, increase in femoral oxygen extraction during exercise occurred after long-term therapy (no changes were present in the placebo group). Thus, this increased peripheral oxygen extraction of working muscle contributed, in part, to the improved femoral and systemic oxygen uptake. Different exercise protocols in the two studies may account, in part, for the dissimilar observations. Our measurements at peak exercise (that is, maximal symptom-limited exercise) may not represent data that were obtained during true maximal oxygen consumption suggested by the peak hemodynamic and metabolic effects obtained during exercise. However, these measurements may be clinically more important and representative for the symptomatic status of the patient with chronic heart failure. Furthermore, our patient population differs from the patients studied by Mancini et al. 12 Heart failure was less severe in the present study as judged from ejection fraction, peak oxygen consumption, and maximal work load achieved. In more severe heart failure, oxygen extraction by the exercising muscles is near maximal, 40 which clearly indicates a limitation to the benefits of physical training and drug therapy. In contrast, in a preliminary report on exercise conditioning for 6 months, a significant increase in arteriovenous oxygen difference was observed in patients with moderate heart failure. 41 Recent studies with nuclear magnetic resonance spectroscopy indicated abnormal metabolism of skeletal muscle that is not primarily due to either muscle atrophy or impaired flow. 8, 42 Although these metabolic studies with spectroscopy do not identify the underlying mechanism, they strongly suggest an intrinsic muscle abnormality or a shift to glycolysis, for example, a different pattern of muscle fiber type recruitment (and consequently altered perfusion pattern). We recently reported such a redistribution of blood flow within working muscle in a rat model of chronic heart failure. 43 Ultrastructural analysis of skeletal muscle obtained by needle biopsy suggested that oxidative capacity of skeletal muscle is significantly reduced in patients with severe heart failure. 44 It is tempting to speculate that long-term ACE inhibition improved oxidative capacity of skeletal muscle, which was indicated by improved oxygen extraction of working muscle in the present study. Combined improvement in femoral blood flow and in physical activity (thereby exerting a training effect) could account for this increased peripheral oxygen extraction and oxidative capacity of working muscle. Several effects of long-term ACE inhibition may increase physical training capacity, such as the pulmonary vascular response, reduction of increased cost of respiration during heart failure, 45 decreased filling pressures as observed in some studies, 1, 2, 24, 46 and increased cardiac output.

Indeed, the systemic and peripheral effects of long-term ACE inhibition strongly resemble those recently observed in patients with heart failure after 6 months of endurance training. 41 An increased mitochondrial content, known to be a fundamental adaptation to endurance training, 47 is likely to increase oxygen exchange (or oxygen extraction) between the capillaries of skeletal muscle, for example, by decreasing the distance for oxygen diffusion. 48 Furthermore, such an adaptation would improve aerobic metabolism during exercise. Clinical studies have shown that oxygen consumption during each level of exercise is significantly reduced when compared with normal subjects. 5, 10 In the present study, long-term ACE inhibition increased oxygen consumption at similar workloads during exercise (compared with baseline exercise), suggesting again that ACE inhibition indeed caused beneficial effects in working muscle, which may be, in part, due to increased exercise training.

In Summary

The present study suggests that the beneficial clinical long-term effects of ACE inhibitors are related to peripheral mechanisms. Long-term ACE therapy appears to reverse, in part, some of the abnormalities of the peripheral circulation in patients with heart failure, that is, the inability of vessels to dilate adequately during exercise. Moreover, long-term ACE inhibition may improve oxygen utilization of working muscle, possibly due to increased exercise training.

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References

6. Cowley AJ, Rowley JM, Stainer K, Hampton JR: Effects of captopril on abnormalities of the peripheral circulation and
respiratory function in patients with severe heart failure. Lancet 1984;1120


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