Angiotensin-Converting Enzyme Inhibitor Therapy Improves Respiratory Muscle Strength in Patients With Heart Failure*

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Study objectives: Respiratory muscle strength has been shown to be reduced in patients with chronic heart failure. The purpose of this prospective study was to determine whether long-term therapy with the angiotensin-converting enzyme (ACE) inhibitor perindopril improves respiratory muscle strength in patients with chronic heart failure.

Patients and methods: Eighteen patients with stable chronic heart failure were administered perindopril, 4 mg/d, in addition to their standard therapy for a period of 6 months. Fourteen patients completed the study. Maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax) expressed in percentage of predicted values, left ventricular ejection fraction (LVEF) determined by means of two-dimensional echocardiography, and pulmonary volumes were obtained before and after therapy.

Measurements and results: As compared to baseline, there was a significant increase in both PImax and PEmax after therapy (57 ± 27% predicted vs 78 ± 36% predicted and 62 ± 20% predicted vs 73 ± 15% predicted, respectively; each p < 0.05). LVEF increased (34 ± 5% vs 41 ± 10%; p < 0.05); functional class improved by ≥ 1 New York Heart Association (NYHA) class in five patients. There were no changes in pulmonary volumes. No correlation was found between changes in PImax and PEmax and changes in either LVEF or NYHA functional class.

Conclusions: In patients with chronic heart failure, long-term therapy with the ACE inhibitor perindopril improved respiratory muscle strength, as indicated by significant increases in PImax and PEmax.

(CHEST 2001; 119:1755–1760)

Key words: angiotensin; heart failure; respiratory muscles

Abbreviations: ACE = angiotensin-converting enzyme; EDV = end-diastolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PEmax = maximum expiratory pressure; PImax = maximum inspiratory pressure; RV = residual volume; TLC = total lung capacity; Vd/Vt = ratio of physiologic dead space to tidal volume; VO2 = oxygen consumption; VT = tidal volume

Respiratory muscle weakness and pulmonary abnormalities are likely to be responsible for some of the limiting symptoms in patients with chronic heart failure. Numerous studies1–7 have reported decreased maximum respiratory mouth pressures in chronic heart failure patients. The reduction in muscle strength may contribute to dyspnea by increasing the ratio of the pressure developed at the mouth during tidal ventilation to the maximum inspiratory pressure (PImax).4 Efforts to prevent or to reverse the development of respiratory muscle weakness in patients with symptomatic left ventricular dysfunction are therefore warranted. Selective respiratory muscle training8 and nasal continuous positive airway pressure9 have been shown to improve respiratory muscle function in chronic heart failure patients. In addition, aerobic training10 and cardiac transplantation11 help reduce the excessive ventilatory response to exercise in these patients.
Angiotensin-converting enzyme (ACE) inhibitors prolong life and may significantly improve both symptoms and exercise tolerance in patients with heart failure. Improvements in exercise capacity are associated with a gradual reversal of chronic structural alterations in peripheral skeletal muscle. In animal models of chronic cardiac disease, the ACE inhibitor perindopril tends to prevent the reduction in intrinsic diaphragm performance. The possibility that ACE inhibitor therapy improves respiratory muscle function has not been studied in patients with chronic heart failure.

The aim of this prospective study was to investigate the effects of long-term ACE inhibitor therapy on respiratory muscle strength in patients with chronic heart failure. Accordingly, maximum respiratory mouth pressures, lung volumes, left ventricular ejection fraction (LVEF), and symptoms of heart failure were determined before and after long-term therapy with perindopril. The relations between the respiratory findings and the degree of cardiac improvement after therapy were also analyzed.

**Materials and Methods**

**Patient Population**

Patients < 75 years of age meeting the following criteria were included in our 6-month prospective study: a history of chronic heart failure as defined by symptoms of left ventricular dysfunction, left ventricular dilation, and resting LVEF ≤ 40%. Patients were excluded if they had had the following: (1) a myocardial infarction within 3 months, (2) recent congestive heart decompensation (within 10 days), (3) prior treatment with ACE inhibitors, or (4) an episode of respiratory tract infection within 1 month. Other exclusion criteria included primary pulmonary or neuromuscular diseases, aortic stenosis, chronic renal failure, women of child-bearing age, and contraindications to ACE inhibitor therapy. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de l'Hôpital de Bicêtre. Written informed consent was obtained from all subjects prior to enrollment.

**Study Design**

Clinical assessment, LVEF, and respiratory data were registered at baseline (premedication measurements) and at the end of the study period. Perindopril was administered at an initial dose of 2 mg po once daily. After 15 days, the dose was increased to 4 mg/d unless symptoms of hypotension or other side effects developed. Medication was kept constant throughout the study period in all patients who completed the study. During the study period, patients did not receive any forms of cardiac or pulmonary rehabilitation. Follow-up visits occurred at 15 days, 3 months, and 6 months after the beginning of ACE therapy.

**Respiratory Muscle Strength and Pulmonary Function**

Respiratory muscle strength was assessed by measuring maximum static respiratory pressures. P_{max} at residual volume (RV) and maximum expiratory pressure (P_{max}) at total lung capacity (TLC) were used as indexes of inspiratory and expiratory muscle strength, respectively. All measurements were performed by the same experienced technician. Patients breathed through a mouth piece attached to a three-way valve connected to a spirometer. Mouth pressures were measured with a pressure transducer (Respiratory Pressures Module type; Medical Graphics; St. Paul, MN [pressure range of ± 300 cm H_{2}O]). Measurements were made with patients in the seated position, and efforts were sustained for 2 to 3 s. Cheek compression was maintained to minimize facial muscle contribution to pressure measurements during the P_{max} maneuver. A small leak via a 22-gauge needle was incorporated during the P_{max} and P_{max} maneuvers to help keep the glottis open, thereby preventing the subject from generating additional negative pressure with facial or pharyngeal muscles. Each effort was displayed on a digital monitor, and the patients were vigorously coaxed by the examiner to better their efforts using visual feedback. After instruction in the techniques for performing each maneuver, P_{max} and P_{max} were recorded in triplicate or until a stable value was achieved. Results were expressed in absolute values and as percentage of predicted values based on normal values for age, sex, and body surface area.

FVC, FEV_{1}, TLC, RV, and tidal volume (VT) were determined by plethysmography (D Body Plethysmograph; MedGraphics system 1085; Medical Graphics). FEV_{1}, FVC, and TLC were expressed both in absolute values and as percentage of normal predicted values. The ratio of physiologic dead space to VT (V_{D}/VT) was calculated from the Bohr equation: V_{D}/VT = (P_{aco_{2}} - P_{aco_{2}})/P_{aco_{2}} × VT, where P_{aco_{2}} is the mixed expired carbon dioxide partial pressure. All the respiratory function measurements were performed on the same day, allowing sufficient rest between each maneuver.

**Cardiac Function and Symptom Assessment**

Symptoms of chronic heart failure were assessed according to the New York Heart Association (NYHA) functional class. In class I, chronic heart failure does not limit physical activity; in class II and III, chronic heart failure results in slight (class II) or marked (class III) limitation of physical activity; in class IV, chronic heart failure results in inability to carry any physical activity without discomfort. Two-dimensional echocardiographic studies were performed according to the recommendations of the American Society of Echocardiography. We used a Sonos 2500 device equipped with a 2.5 to 3.5-MHz probe (Hewlett Packard; Andover, MA). Left ventricular end-diastolic volume (EDV) and end-systolic volume were obtained from the apical four-chamber and two-chamber views by a modified Simpson’s rule, from which LVEF was automatically calculated as the difference between EDV and end-systolic volume normalized to EDV.

**Statistical Analysis**

Data were analyzed on an intention-to-treat basis. The analysis set was defined as all patients having at least one evaluation of the main criteria (ie, P_{max} and P_{max} during treatment). Comparisons of values at the end of the study with baseline values were made using two-tailed paired t tests. Relationships among variables were examined by least-squares linear regression analysis. Correlations between changes (from baseline) in P_{max} and P_{max} on the one hand and changes in NYHA functional class, LVEF, and spirometry on the other hand were also studied. Data are expressed as mean values ± SD unless otherwise indicated. A value of p < 0.05 was considered significant.
Results

Patient Population

Eighteen patients with stable chronic heart failure were included in the study (17 men and 1 woman). Baseline clinical characteristics of the study population are given in Table 1. The cause of heart failure was coronary artery disease (n = 7) or dilated cardiomyopathy (n = 11), while three patients presented with concomitant significant mitral insufficiency. At entry to the study, four patients were in NYHA functional class I, six patients were in class II, and eight patients were in class III. Patients were treated with diuretics (n = 7), digitalis (n = 4), vasodilators (n = 7), β-blockers (n = 4), and antiarrhythmic drugs (n = 5). Nine patients had a history of smoking, and six patients were current smokers (41 ± 25 pack-years). Four patients were withdrawn from the study for the following reasons: death (n = 1), drug-related adverse events (cough, n = 1; arterial hypotension, n = 1), and unavailable for follow-up (n = 1). The analysis was performed on the 14 patients who completed the study.

Pulmonary Function Data

Pulmonary function data are summarized in Table 2. At baseline, chronic heart failure patients showed a slight reduction in predicted FVC and FEV1 values, with no change in the FEV1/FVC ratio. Vd/Vt was slightly increased. There were no significant changes in lung volumes over the course of the study (Table 2).

Maximum Inspiratory and Expiratory Pressures

The influence of ACE inhibitor therapy on Pimax and PEmax is depicted in Fig 1. At baseline, Pimax and PEmax were approximately 57% to 62% of predicted normal values, respectively (Fig 1). Over the study period, there was a significant increase in both Pimax (62 ± 33 cm H2O at baseline vs 83 ± 42 cm H2O at the end of the study period [representing, respectively, 57 ± 27% and 78 ± 34% of predicted values; p < 0.05]) and PEmax (84 ± 28 cm H2O at baseline vs 98 ± 20 cm H2O [representing, respectively, 62 ± 20% and 73 ± 15% of predicted values; p < 0.05]). No significant correlation was found between changes in maximum mouth pressures and spirometric data.

Symptom Assessment and Left Ventricular Function

Functional class improved by one or more NYHA class in 5 of 14 patients. There was no significant correlation between changes in NYHA functional class and changes in respiratory parameters. Individual echocardiographic LVEF before and after perindopril therapy are shown in Figure 2. LVEF increased significantly (34 ± 5% vs 41 ± 10%; p < 0.05). There was no correlation between changes in LVEF and changes in respiratory muscle pressures.

Discussion

We examined the effects of long-term therapy with the ACE inhibitor perindopril on respiratory muscle function in chronic heart failure patients. Our results suggest that perindopril improved maximum inspiratory and expiratory muscle strength in patients with stable chronic heart failure. Changes in respiratory pressures did not correlate with changes in LVEF, pulmonary volumes, or NYHA functional class.

The present study provides the first evidence that respiratory muscle weakness in chronic heart failure patients is at least partially reversible with ACE

Table 1—Clinical Characteristics of the Included Population*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>17/1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.5 ± 8.3</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.59 ± 0.14</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Duration of heart failure, mo</td>
<td>42 ± 57</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>80 ± 17</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>131 ± 19</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated (n = 18).

Table 2—Respiratory Data at Baseline and After 6 Months of Therapy With Perindopril in Patients With Chronic Heart Failure*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>3.1 ± 0.7</td>
<td>3.1 ± 0.8</td>
</tr>
<tr>
<td>% predicted</td>
<td>90 ± 13</td>
<td>78 ± 15</td>
</tr>
<tr>
<td>FEV1, L/s</td>
<td>2.5 ± 0.6</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>% predicted</td>
<td>83 ± 17</td>
<td>80 ± 18</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>81 ± 6</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>% predicted</td>
<td>103 ± 10</td>
<td>101 ± 11</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.1 ± 0.7</td>
<td>6.2 ± 0.8</td>
</tr>
<tr>
<td>% predicted</td>
<td>93 ± 11</td>
<td>94 ± 12</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.8 ± 0.6</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>% predicted</td>
<td>117 ± 23</td>
<td>118 ± 25</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>0.45 ± 0.09</td>
<td>0.42 ± 0.09</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SD (n = 14). There were no significant changes in lung volumes over the course of the study.
inhibitor therapy. As compared to baseline, chronic heart failure patients demonstrated a 21% absolute improvement in P\textsubscript{max} after long-term therapy with perindopril while P\textsubscript{e\textsubscript{max}} improved by about 10% (Fig 1). Numerous studies\textsuperscript{1–6} have reported a reduction in maximum respiratory mouth pressure in patients with chronic heart failure comparable to those seen in our patients. In these studies, as in ours, maximum respiratory mouth pressures were used as an estimate of respiratory muscle strength. Although dependent on maximal patient effort, maximum static mouth pressures have been shown to be highly reproducible over time.\textsuperscript{21} In a study\textsuperscript{7} involving patients with chronic heart failure, when esophageal pressure was recorded during maximal sniff, the reduction obtained in diaphragm strength was more moderate than that obtained from static mouth pressure maneuvers. This suggests that maximum static mouth pressure may overestimate the reduction in diaphragm strength in chronic heart failure patients. However, it is generally considered that one can gain reliable information by monitoring changes in maximum respiratory mouth pressure over time in the individual patients.\textsuperscript{21} Lung volume is a major determinant of the length and curvature of the respiratory muscles, and may therefore influence maximum mouth pressure. An increase in P\textsubscript{max} may result from a change in RV, but no such change was observed in our patients over the study period (Table 2). Furthermore, there was no correlation between the changes in respiratory pressures and those in lung volumes. Therefore, changes in lung volumes cannot account for improvement in respiratory pressures in perindopril-treated chronic heart failure patients. Taken together, these findings strongly suggest that increases in P\textsubscript{max} and P\textsubscript{e\textsubscript{max}} after long-term perindopril therapy reflected an improvement in respiratory muscle strength in chronic heart failure patients. This result is consistent with the improved intrinsic diaphragm performance reported after perindopril therapy, both in a genetically polymyopathic model\textsuperscript{17,18} and in a rabbit model of chronic cardiac overload.\textsuperscript{19}

The increase in P\textsubscript{e\textsubscript{max}} was lower than the increase in P\textsubscript{max}. Importantly, abdominal muscles are known to contribute substantially to P\textsubscript{e\textsubscript{max}} while P\textsubscript{max} is essentially dependent on diaphragm muscle.\textsuperscript{21} Structural and functional differences between diaphragm and other skeletal muscles during chronic heart failure\textsuperscript{2,3,19} may help explain the different effects of ACE therapy on inspiratory and expiratory pressures.

In chronic heart failure patients, previous studies\textsuperscript{13,15} have demonstrated beneficial effects of ACE inhibitors on exercise capacity. Long-term therapy
with ACE inhibitors improves peripheral skeletal muscle flow, femoral oxygen consumption, and peak oxygen consumption (VO2) during exercise in chronic heart failure patients.13,15 A highly significant correlation has been reported between peak exercise femoral blood flow and peak VO2.13,15 In addition, inspiratory muscle strength is a determinant of peak VO2 in chronic heart failure.21 Improved Pmax after selective respiratory muscle training in chronic heart failure patients is associated with a significant increase in peak VO2.8 It is thus possible that the increased Pmax observed in our study may help explain the increased peak VO2 after ACE inhibitor therapy. However, since peak VO2 was not determined in our study, further studies are needed to clarify this point.

In the present study, changes in respiratory mouth pressure did not correlate with changes in LVEF. These findings are consistent with previous studies showing that exercise intolerance correlates poorly with LVEF.14,24 although respiratory muscle weakness has been found to be more pronounced in more severe chronic heart failure patients according to the NYHA classes.5,25 Increases in muscle mass and in fiber area,16 and partial reversal of mitochondrial and metabolic abnormalities16 have been reported after ACE inhibitor therapy. In experimental animal models of cardiac failure, improved diaphragm muscle performance after ACE therapy has been attributed mainly to a beneficial effect on crossbridge number.18,19,28 Enhanced muscle performance after long-term ACE inhibitor therapy likely reflected intrinsic changes in the biochemical and structural characteristics of skeletal muscle. Such mechanisms may help improve respiratory muscle strength, thereby improving Pmax and Pmax.

Our study has several limitations. It was an uncontrolled study. ACE inhibitor therapy is so far the only treatment that prolongs life in chronic heart failure. Therefore, for ethical reasons, a comparison group of chronic heart failure patients treated with placebo was not included. The population studied was composed predominantly of men, with only one woman in the group. It would be interesting to perform additional analyses on different subsets of patients with chronic heart failure with regard to the heart function, lung volume, or NYHA-class variables. However, the sample size of chronic heart failure patients was too small for such valuable multivariate analysis to be performed. Improvement in respiratory muscle performance after ACE inhibitor therapy requires confirmation in larger trials. It was not within the scope of our study to test the cardiopulmonary exercise responses after long-term administration of ACE inhibitor. Further studies are needed to determine whether improved respiratory muscle strength after ACE inhibitor therapy correlates with the improvement in exercise endurance in stable congestive heart failure. In our study, four patients were receiving digoxin at inclusion. Diaphragmatic strength improves significantly after acute digoxin administration in patients with COPD.20 However, there are a number of arguments against the potential confounding effects of digoxin on our data. Our patients did not suffer from COPD. Two of these patients withdrew from the study, so that only two patients treated with digoxin were taken into account in the full analysis set. In addition, one of the two remaining treated patients had been receiving digoxin for at least 3 years, the other being treated for 1 month. Thus, baseline measurements were performed in patients already treated with digoxin for at least several weeks. The effects of long-term digoxin administration on respiratory pressures in patients with chronic heart failure have yet to be established. Taking these limitations into account, the present study indicates that long-term therapy with the ACE inhibitor perindopril partially reverses respiratory muscle weakness, as assessed by a significant improvement in maximum respiratory pressures.

**References**

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