ORIGINAL ARTICLE

Angiotensin-Converting Enzyme Inhibition as an Adjunct to Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Epidemiological studies in older individuals have found an association between the use of angiotensin-converting enzyme (ACE) inhibition (ACE-I) therapy and preserved locomotor muscle mass, strength, and walking speed. ACE-I therapy might therefore have a role in the context of pulmonary rehabilitation (PR).

Objectives: To investigate the hypothesis that enalapril, an ACE inhibitor, would augment the improvement in exercise capacity seen during PR.

Methods: We performed a double-blind, placebo-controlled, parallel-group randomized controlled trial. Patients with chronic obstructive pulmonary disease, who had at least moderate airflow obstruction and were taking part in PR, were randomized to either 10 weeks of therapy with an ACE inhibitor (10 mg enalapril) or placebo.

Measurements and Main Results: The primary outcome measurement was the change in peak power (assessed using cycle ergometry) from baseline. Eighty patients were enrolled, 78 were randomized (age 67 ± 8 years; FEV_1 48 ± 21% predicted), and 65 completed the trial (34 on placebo, 31 on the ACE inhibitor). The ACE inhibitor–treated group demonstrated a significant reduction in systolic blood pressure (Δ, −16 mm Hg; 95% confidence interval [CI], −22 to −11) and serum ACE activity (Δ, −18 IU/L; 95% CI, −23 to −12) versus placebo (between-group differences, $P < 0.0001$). Peak power increased significantly more in the placebo group (placebo Δ, +9 W; 95% CI, 5 to 13 vs. ACE-I Δ, +1 W; 95% CI, −2 to 4; between-group difference, 8 W; 95% CI, 3 to 13; $P = 0.001$). There was no significant between-group difference in quadriceps strength or health-related quality of life.

Conclusions: Use of the ACE inhibitor enalapril, together with a program of PR, in patients without an established indication for ACE-I, reduced the peak work rate response to exercise training in patients with chronic obstructive pulmonary disease.

Keywords: COPD; renin–angiotensin system; exercise; rehabilitation

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At a Glance Commentary

Scientific Knowledge on the Subject: Evidence associates the renin–angiotensin system with the control of skeletal muscle bulk and function, and implicates angiotensin II in the skeletal muscle dysfunction seen in individuals with chronic obstructive pulmonary disease (COPD). Thus, manipulation of this pathway may allow greater response to exercise interventions such as pulmonary rehabilitation.

What This Study Adds to the Field: We report on the first placebo-controlled, double-blind, randomized trial to investigate if angiotensin-converting enzyme inhibition, without a conventional existing clinical indication, could enhance the impact of pulmonary rehabilitation on exercise capacity in patients with COPD. Contrary to expectation, angiotensin-converting enzyme inhibition mediated by enalapril administration actually attenuated the increase in maximal exercise capacity resulting from pulmonary rehabilitation in COPD.

Skeletal muscle dysfunction is a common and important extrapulmonary complication of chronic obstructive pulmonary disease (COPD) that is associated with reduced endurance exercise capacity and physical activity levels (1, 2), impaired healthcare status (3), and greater mortality (4). Although pulmonary rehabilitation (PR) is a high-value treatment modality (5–7), its effects begin to decline toward baseline at 12 to 18 months (8, 9), and some patients with skeletal muscle dysfunction may respond suboptimally to this intervention (10). Thus, there is a need for adjunctive agents to ensure that patients gain the greatest response from rehabilitation programs and maintain this for as long as possible.

As components of circulating and tissue renin–angiotensin systems (RASs), angiotensin-converting enzyme (ACE) plays a key role in the synthesis of angiotensin II and degradation of vasoactive kinins, most notably, bradykinin. Evidence suggests a role for chronic activation of the intramuscular RAS in regulating skeletal muscle phenotype and contributing to the skeletal muscle dysfunction seen in COPD (11). There are several potential levels of action of ACE inhibition (ACE-I) in promoting effective skeletal muscle function, including attenuation of the activity of angiotensin II, which contributes to proinflammatory pathways, impairs glucose handling, and promotes skeletal muscle atrophy (11). Bradykinin activity is also known to influence insulin sensitivity (12), to protect against oxidative damage (13), and to promote angiogenesis (11), which are all essential components of skeletal muscle function.

Epidemiological studies in older populations have shown ACE inhibitor therapy to be associated with preserved locomotor muscle mass (14), leg strength (15), and walking speed (15); thus, it could be predicted to affect exercise capacity, although these are observational findings, and the exact mechanisms behind these associations have not been fully investigated. In line with this, individuals with genetically low serum and tissue ACE levels, which is associated with a polymorphism of the human ACE gene, have improved exercise characteristics in both healthy and athletic populations (16, 17) and improved mechanical efficiency in response to training (18). Notably, patients with COPD who possess the same genotype were shown to have greater peak workload during incremental cardiopulmonary exercise testing than those with higher intrinsic levels of ACE activity (19). Observational work has also shown that the bradykinin receptor polymorphism leading to reduced activity at the bradykinin receptor (+9/+9 BK_2R) is associated with both reduced fat-free mass and quadriceps strength in COPD (20, 21).

In an older adult population with restricted mobility, ACE-I was associated with an improvement in 6-min walking distance (22). Furthermore, in patients with COPD pharmacological reduction in angiotensin II has been associated with improvements in both quadriceps strength (23) and exercise capacity as assessed by incremental cardiopulmonary exercise testing, with a 7% increase in peak workload achieved after 4 weeks of therapy with enalapril in those with moderate-to-severe airflow obstruction (24). However, in another study in patients with COPD who were stratified on the basis of quadriceps weakness (quadriceps maximal volitional contraction strength <120% body mass index [BMI]), the use of the ACE inhibitor fosinopril did not improve either quadriceps strength or endurance (25). However, animal studies have suggested a potential synergistic role for ACE-I and exercise in ensuring a more favorable skeletal muscle phenotype to promote greater exercise capacity (26). This raises the possibility that a training stimulus may be required to ensure maximal benefit from reduced angiotensin II activity.

Thus, the aim of this study was to investigate the effects of therapy with an ACE inhibitor as an adjunctive therapy to a standardized program of PR in a population with COPD, with a focus on the effects on exercise capacity, strength, health-related quality of life, and daily physical activity.

Methods

Patient Selection

All subjects provided written informed consent before enrollment in the study, which was approved by the London Bloomsbury Research Ethics Committee (REC reference 12/LO/0331) and registered prospectively on a publicly accessible database (www.controlled-trials.com/ISRCTN79038750).

Patients with stable COPD in Global Initiative for Chronic Obstructive Lung Disease stages II to IV (27), who were referred for PR and who had a Medical Research Council dyspnea score of at least 3 or 2 with functional limitation (28), were considered for inclusion. Individuals already using ACE inhibitors or angiotensin-receptor blockers or who had other reasons to benefit from these medicines (including ischemic heart disease, impairment of ventricular function, and diabetes mellitus) were excluded from the study. Other principle exclusion criteria were renovascular disease or significant renal impairment (defined as an estimated glomerular filtration rate <50 ml/min/1.73 m^2), pulmonary exacerbation within 1 month, recent (<3 months) previous PR course, or other comorbid factors that either significantly impaired exercise capacity or the ability to participate in rehabilitation, including significant musculoskeletal, neurological, and aortic valve disease. Individuals with hypotension (defined as a systolic blood pressure

<100 mm Hg) were excluded from participation.

Study Design

The study was a double-blind, placebo-controlled, parallel-group randomized trial. The primary outcome measure was the between-group difference in the absolute change in peak power achieved on incremental cycle ergometry. This measure is a validated endpoint in COPD and provides an effective evaluation of whole body exercise capacity, taking into consideration both cardiorespiratory and skeletal muscle function, having been used in large trials such as the National Emphysema Treatment Trial study (29). Leg fatigue has been shown to be more likely to limit cycle-based tasks than walking exercise (30). Hence, cycle ergometry may be more discriminatory in the assessment of interventions that influence skeletal muscle function. Both genotype-based studies (19) and clinical research (24) have shown reduced angiotensin II activity to be associated with improved peak power achieved during incremental cardiopulmonary exercise testing in COPD. Secondary outcome measures included the between-group differences in the change in quadriceps maximal volitional contraction force, health-related quality of life, and daily physical activity level.

Intervention and Randomization

Patients were randomly allocated to receive either an ACE inhibitor (10 mg enalapril once daily) or placebo (microcrystalline cellulose) for 10 weeks in a 1:1 manner using block randomization and a block size of four. Randomization was performed by Imperial College Trials Unit using a stratified approach, based on the baseline peak power achieved on incremental cycle ergometry (using 50 W as a cutoff) and ACE genotype [II, ID, or DD; I represents the insertion allele and D the deletion allele; the I allele is associated with lower ACE activity (20, 21, 31)]. ACE genotype was assessed by polymerase chain reaction on DNA isolated from a saliva sample, the method for which is included in the online supplement. Both subjects and the assessor were blind to treatment allocation.

Study Conduct

Subjects were assessed at baseline and started enalapril or placebo treatment 1 week before the initiation of PR. The multidisciplinary outpatient PR program was 8 weeks in duration, with a combination of educational and exercise sessions, incorporating both aerobic and strength training individualized to the patient as per national and international guidelines (5, 28). The program delivered 3 exercise sessions per week, 2 under direct supervision, and 1 for the patient to undertake independently at home. Supervised sessions included 1 hour of exercise and 1 hour of education. The exercise sessions were delivered in a circuit style program with a goal-setting and progressive approach, with continuous reassessment to allow an increase throughout the program as tolerated. Aerobic training included treadmill and cycle exercise, with subjects prescribed exercise at an intensity of 60% to 80% of their predicted V_{O_2} peak. Strengthening exercises incorporated both upper and lower limb resistive exercise with weights, including sit-to-stand, knee lifts/extension, bicep curls, and push ups; workload was increased as tolerated. Education classes covered a variety of self-management topics, including exercise, medication use, diet, coping strategies, increasing physical activity, and recognizing and managing infections.

Blood pressure and renal function were checked 1 week after starting treatment, and if symptomatically hypotensive (systolic blood pressure <100 mm Hg or fall from baseline of >10 mm Hg, with accompanying symptoms) or with evidence of significant decline in renal function (serum creatinine increase >30% beyond baseline), subjects were withdrawn from the study.

Subjects were re-assessed within 1 week of completion of the PR program and continued therapy until completion of the study. Subjects' assessments performed at baseline and after completion of rehabilitation included blood pressure, full pulmonary function, maximal symptom-limited incremental cycle ergometry, fat-free mass assessed by bioelectrical impedance analysis, health-related quality of life assessment, quadriceps maximal volitional contraction, mid-thigh computed tomography scan, and physical activity monitoring using a triaxial accelerometer. Further details of these assessments are available in the online supplement.

Data Analysis and Statistics

The primary endpoint selected in this study was peak workload achieved on incremental cycle ergometry. Sample size was determined based on previous data that showed an increase in peak power after rehabilitation, from 55 ± 19 to 63 ± 9 W (32). To show an additional 10% improvement with ACE-I, at an 80% statistical power with a significance level of 0.05, 54 subjects would need to complete the study. Allowing for a 10% withdrawal rate and subjects with genetically low ACE levels (II genotype, expected prevalence 25%) potentially responding to a lesser degree led to a sample size of 80. Data are presented as mean ± SD or 95% confidence interval (CI), and compared using two-sided paired (for comparison of pre- and post-rehabilitation) or unpaired (comparing treatment groups) *t* tests. Categorical data are presented as percentages and comparisons performed using the χ^2 test. Analysis was performed on a per protocol basis using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, CA). A P value <0.05 was considered to be statistically significant.

Results

Subjects

Eighty subjects were enrolled into the study, of whom 65 completed the full study protocol. There were five withdrawals in the placebo group and eight in the treatment group, further explanation of which is provided in the Consolidated Standards of Reporting Trials diagram (Figure 1).

Baseline Characteristics

The baseline characteristics of the group are presented in Table 1. The participants were representative of patients with COPD referred for PR, with a mean age of 67 ± 8 years, FEV_1 of 48 ± 21% predicted, systolic blood pressure of 137 ± 18 mm Hg, Medical Research Council dyspnea score of 3 ± 1, quadriceps strength of 73 ± 22% predicted, and daily average step count of 5,428 ± 3,633. Seventy-nine percent of the subjects displayed evidence of ventilatory limitation at baseline [as assessed by the ratio of peak ventilation to the estimated maximal ventilation of ⩾0.9 (33)]. The groups were well-matched for age, sex, lung function, and exercise capacity at baseline. Although the difference in

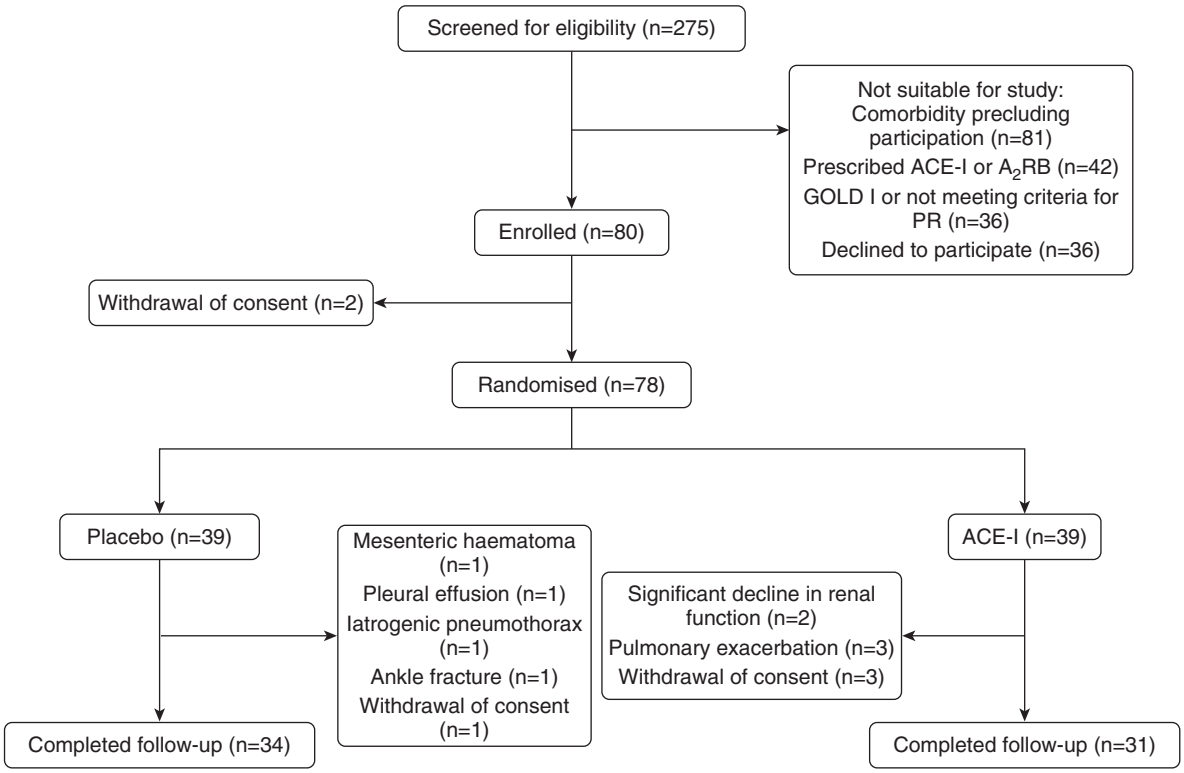

Figure 1. Consolidated Standards of Reporting Trials recruitment diagram for enrollment and study completion. ACE-I = angiotensin-converting enzyme inhibitor; A_2RB = angiotensin II receptor blocker; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PR = pulmonary rehabilitation.

BMI reached statistical significance, it was not considered to be a clinically important difference. The ACE genotypes were consistent with Hardy-Weinberg equilibrium in both groups, and the distribution did not differ between the treatment arms.

Effect of ACE-I on Blood Pressure Parameters

In the placebo arm, systolic blood pressure was unchanged from baseline (Δ, −1 mm Hg; 95% CI, −5 to 4; $P = 0.78$), whereas it was significantly reduced in the ACE-I arm (Δ, −16 mm Hg; 95% CI, −22 to −11; $P < 0.0001$), with a significant between-group difference (−15 mm Hg; 95% CI, −21 to −9; $P < 0.0001$) (Figure 2). Similar changes were also noted with diastolic blood pressure (placebo Δ, +1 mm Hg; 95% CI, −3 to 4; $P = 0.71$ vs. ACE-I Δ, −9 mm Hg; 95% CI, −11 to −6; $P < 0.0001$; between-group difference, −10 mm Hg; 95% CI, −14 to −5; $P = 0.0001$) (Figure 2).

Effect of ACE-I on Serum ACE Levels

There was a significant reduction in serum ACE levels in the ACE-I arm that was not seen in the placebo arm (placebo Δ, +4 IU/L; 95% CI, 0 to 8; $P = 0.05$ vs. ACE-I Δ, −18 IU/L; 95% CI, −23 to −12; $P < 0.0001$; between-group difference, −22 IU/L; 95% CI, −29 to −15; $P < 0.0001$) (Figure 3).

Effect of ACE-I on Exercise Capacity

The peak power achieved on incremental cycle ergometry increased in both groups after PR, but the change was only significantly greater in the placebo group (placebo Δ, +9 W; 95% CI, 5 to 13; $P < 0.001$ vs. ACE-I Δ, +1 W; 95% CI, −2 to 4; $P = 0.62$; between-group difference, 8 W; 95% CI, 3 to 13; $P = 0.001$) (Figure 4). A similar pattern was seen in the change in peak pulmonary oxygen uptake (placebo Δ, +1.37 ml/min/kg; 95% CI, 0.79 to 2.02; $P = 0.0001$ vs. ACE-I Δ, +0.33 ml/min/kg; 95% CI, −0.41 to 1.08, $P = 0.45$; between-group difference, 1.04 ml/min/kg; 95% CI, 0.08 to 2.01; $P = 0.035$).

There were no significant between-group differences in the change in the V_E/V_{CO_2} slope from baseline to after PR (placebo Δ, −1.25; 95% CI, −3.21 to 0.72; $P = 0.45$ vs. ACE-I Δ, −0.87; 95% CI, −2.17 to 0.43; $P = 0.18$; between-group difference, 0.38; 95% CI, −2.02 to 2.78; $P = 0.57$). The oxygen uptake efficiency slope altered from baseline to after PR more in the placebo group, although the between-group difference failed to reach statistical significance (placebo Δ, 151; 95% CI, 40 to 261; $P = 0.009$ vs. ACE-I Δ, 29; 95% CI, −109 to 167; $P = 0.67$; between-group difference, 122; 95% CI, −49 to 292; $P = 0.08$).

Effect of ACE-I on Quality of Life, Lung Function Variables, and Strength

Health-related quality of life scores, as assessed by the St. George's Respiratory Questionnaire for COPD, improved in both treatment arms after PR, but there were no significant between-group differences (Table 2). Lung function variables, measures of quadriceps strength, and muscle bulk showed no significant between-group differences (Table 2). Daily physical activity as assessed by the physical activity level (PAL) increased in the placebo arm, but was actually reduced in the treatment arm, producing a significant between-group difference (Table 2).

Table 1. Demographic and Baseline Clinical Characteristics of the Subjects

	Placebo Group (*n* = 34)	ACE-I Group (*n* = 31)	*P* Value
Sex, % female	41	55	0.27
Age, yr	68 (7)	66 (10)	0.28
ACE genotype (II, ID, DD), %	21, 47, 32	23, 42, 35	0.92
BMI, kg/m^2	26.9 (5.9)	24.0 (4.6)	0.033*
Systolic BP, mm Hg	139 (17)	133 (15)	0.10
Diastolic BP, mm Hg	79 (11)	78 (9)	0.73
LAMA, %	71	84	0.20
LABA-ICS, %	79	71	0.43
MRC dyspnea score	3 (1)	3 (1)	0.52
CAT score	18 (7)	17 (7)	0.65
SGRQ-C total	46.25 (18.59)	46.78 (17.68)	0.91
Average daily step count†	4883 (2,668)	6685 (4,234)	0.15
Average PAL†	1.39 (0.20)	1.49 (0.19)	0.10
FEV_1, L	1.31 (0.53)	1.10 (0.54)	0.12
FEV_1% predicted	51.6 (20.2)	48.2 (22.5)	0.37
FVC, L	3.25 (0.67)	2.96 (0.88)	0.15
D_{LCOc} % predicted	54.2 (22.7)	51.1 (23.1)	0.59
RV/TLC ratio, %	52.8 (8.5)	56.5 (9.0)	0.09
Pa_{O_2}, kPa	10.4 (1.6)	10.4 (1.6)	0.87
Pa_{CO_2}, kPa	4.7 (0.6)	4.9 (0.6)	0.22
Peak power on cycle, W	51 (22)	54 (29)	0.62
Peak $\dot{V}o_2$, ml/min/kg	14.1 (3.1)	16.1 (5.4)	0.19
$\dot{V}_E/\dot{V}co_2$ slope	31.26 (7.84)	30.16 (7.59)	0.38
OUES, (ml/min O_2)/(L/min $\dot{V}_E$)	1,686 (485)	1,658 (520)	0.73
FFMI, kg/m^2	17.1 (2.3)	15.7 (1.8)	0.0089*
QMVC, kg	30.4 (11.0)	28.9 (10.1)	0.58
MTMCSA, mm^2	9,969 (2,012)	9,120 (2,417)	0.12
Quadriceps CSA, mm^2	4,348 (950)	4,027 (1,277)	0.27

Definition of abbreviations: ACE = angiotensin-converting enzyme; ACE-I = angiotensin-converting enzyme inhibition; BMI = body mass index; BP = blood pressure; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CSA = cross-sectional area; D = deletion allele; D_{LCOc} = diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FFMI = fat-free mass index; I = insertion allele; LABA-ICS = long-acting β-agonist and inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; MRC = Medical Research Council; MTMCSA = mid-thigh muscle cross-sectional area; OUES = oxygen uptake efficiency slope; PAL = physical activity level; QMVC = quadriceps maximal volitional contraction; RV = residual volume; SGRQ-C = St. George's Respiratory Questionnaire for COPD.

Data shown are mean (SD) unless otherwise noted.

*$P < 0.05$.

†Data are analyzed from 53 subjects (29 placebo, 24 treatment arm) who recorded an adequate period for physical activity assessment.

Effect of ACE-I on Rate of Adverse Events, Rehabilitation, and Drug Compliance

There was no difference in the rate of either pulmonary exacerbations or other adverse events comparing the study arms. Although there was a statistically significant difference in the number of supervised rehabilitation sessions attended (placebo group, 13; 95% CI, 12–14 vs. ACE-I group, 11; 95% CI, 10–12; $P = 0.002$), the actual difference was small and unlikely to have provided a more favorable training stimulus in the placebo group. Drug compliance was excellent in both arms (placebo group, 96% compliance; 95% CI, 93–98 vs. ACE-I, 96% compliance; 95% CI, 94–99; $P = 0.45$).

Two patients in the ACE inhibitor arm showed significant decline in renal function (>30% increase in serum creatinine) and were withdrawn from the study. Only one patient in the ACE-I arm described a persistent cough, outside the context of a pulmonary exacerbation, but this did not lead to cessation of therapy.

Discussion

The main finding of this study was that enalapril, rather than enhancing the improvement in maximal exercise capacity seen with PR in COPD, in fact, reduced it. Enalapril did lower both blood pressure and serum ACE activity, confirming that a biologically relevant dose had been administered. Therefore, the present data do not support the use of ACE inhibitors to help ameliorate the skeletal muscle dysfunction in COPD when assessed through incremental cardiopulmonary exercise testing, and suggested that caution should be applied in this context. It is important to note that this conclusion applies only to individuals who do not have a clinically established reason for being on an ACE inhibitor.

Significance of the Findings

Studies of molecular pathways have suggested that the RAS is an important component of the skeletal muscle dysfunction seen in COPD (11), and previous experimental work has suggested a potential beneficial effect from ACE-I on skeletal muscle phenotype; therefore, the results of the present study were unexpected. However, this was the first randomized controlled trial of ACE-I as an adjunct to PR. Our findings emphasized the important role of prospective blinded randomized trials particularly as much previous work on both epidemiological cohorts (14, 15) and ACE genotype polymorphisms (16, 19), which suggest ACE-I might have beneficial effects was observational in nature.

Previous randomized controlled trials have suggested that manipulation of the RAS could produce favorable effects on exercise capacity in subjects with COPD. Andreas and colleagues showed that use of the angiotensin receptor blocker irbesartan for 4 months in severe COPD led to numerical improvements in quadriceps strength (23), and a small pilot study that used enalapril for 4 weeks in 21 subjects with moderate-to-severe COPD showed improved peak power achieved on incremental cycle ergometry (24). However, our own group studied the administration of the ACE-inhibitor fosinopril to a group of patients with moderate-to-severe COPD selected for quadriceps weakness and showed no improvement in either quadriceps strength, endurance, or functional outcomes as measured by the incremental shuttle walk test (25). Despite exercise training not being administered in that study, an increase in quadriceps maximal volitional force of contraction was seen in both groups, but to a lesser extent in the ACE inhibitor–treated group

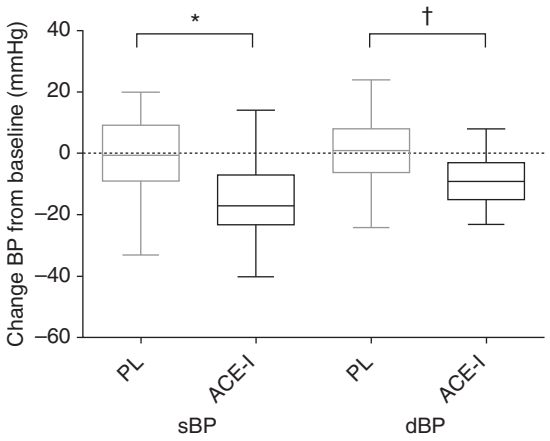

Figure 2. Alterations in blood pressure (BP) parameters (systolic BP [sBP] and diastolic BP [dBP]) from baseline to after pulmonary rehabilitation in the placebo (PL) and angiotensin-converting enzyme inhibitor (ACE-I) treatment arms. The *box* represents 25–75th percentiles, the *solid line* represents the median, and the *whiskers* represent minimum to maximum values. Comparisons were made using unpaired *t* tests, $^{*}P < 0.0001$; $^{\dagger}P = 0.0001$.

than the placebo group, which was consistent with the present findings. Recognized limitations of that study included the failure to stratify by ACE genotype and lack of a training stimulus, both issues that were addressed in the present study.

We specifically excluded individuals with ischemic heart disease, ventricular failure, and diabetes, and thus, although we cannot support use of ACE inhibitors for targeting skeletal muscle dysfunction in COPD, many such individuals will have other indications for ACE inhibitor therapy. It is well recognized that cardiovascular comorbidities are of a higher prevalence in COPD (34), and we would not support avoidance or cessation of ACE inhibitors when comorbidities known to benefit from such therapy are present.

Possible Mechanism of Action of ACE Inhibitors

Despite epidemiological evidence suggesting ACE-I should improve skeletal muscle function, the molecular basis for this remains unclear. Several mechanisms have been proposed, including improved glucose sensitivity, promotion of hypertrophic pathways, reduction in local inflammation, and enhancement of the effects of bradykinin (11). There are several possible mechanisms by which ACE-I may have attenuated the acute response to PR, although the exact basis for the attenuation of gain in maximal exercise capacity in the present study remains unclear. It could be hypothesized that reductions in total peripheral vascular resistance may divert blood flow away from actively exercising muscle and reduce perfusion pressure to the muscle vascular bed, impeding effective matching of blood flow to metabolic demand, although evidence suggests that, at least in the resting state, ACE-I improves skeletal muscle blood flow by reducing vascular resistance (35, 36).

Interestingly, there is increasing evidence that tissue capillarity is reduced in COPD and is associated with muscle contractile fatigue (37), and that increased capillarity is one mechanism through which rehabilitation is beneficial (10). The RAS is implicated in angiogenesis and reactivity of the microvasculature of the skeletal muscle, with the administration of captopril in a rat model associated with reduced arteriolar density, diameter (38), and response to vasodilator stimuli (39) associated with reduced exercise tolerance (40). The RAS is a complicated pathway, and angiotensin (1–7), itself a breakdown product of angiotensin II, is known to have muscle anti-atrophic effects (41); thus, it is possible that ACE-I has several counter-regulatory effects.

Although angiotensin II is recognized to have adverse effects on skeletal muscle, as with cardiac muscle, angiotensin II is important for tetanic strength and hypertrophy in response to mechanical loading (42). It is recognized that individuals with COPD with high intrinsic levels of angiotensin II (ACE DD genotype) have maintained strength (31). In addition, peripheral muscle strength is known to be an important contributor to endurance capacity in patients with COPD who attend PR (1), and it might be that by reducing angiotensin II activity, we attenuated strength capacity, which in turn affected exercise performance. In line with this, histological work in young healthy subjects has shown the ACE DD genotype to be associated with a higher proportion of fast twitch type IIb and a lower proportion of oxidative slow twitch type I skeletal muscle fibers, thus favoring anaerobic capacity (43). This may in part underlie the link between high angiotensin II levels and strength. Thus, it may be that the impact of high angiotensin II levels on strength and hypertrophic response to loading outweighs the

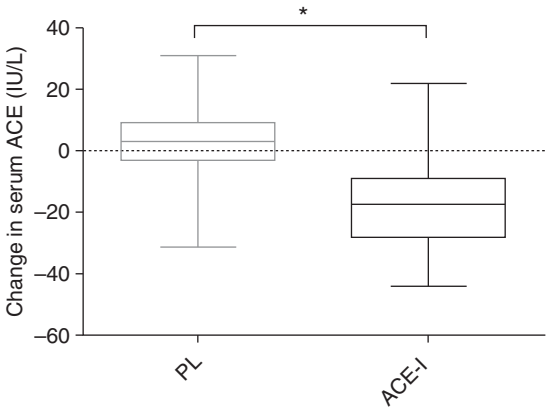

Figure 3. Change in serum angiotensin-converting enzyme (ACE) levels from baseline to after pulmonary rehabilitation in the placebo (PL) and ACE inhibitor (ACE-I) treatment arms. The *box* represents 25–75th percentiles, the *solid line* represents the median, and the *whiskers* represent minimum to maximum values. Comparison was made using an unpaired *t* test, $^{*}P < 0.0001$.

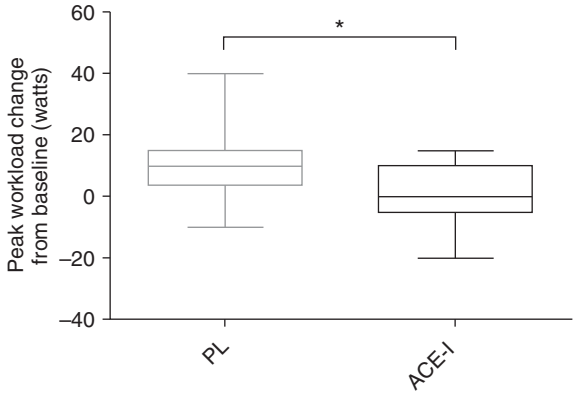

Figure 4. Change in peak workload achieved during incremental cycle ergometry from baseline to after pulmonary rehabilitation in the placebo (PL) and angiotensin-converting enzyme inhibitor (ACE-I) treatment arms. The *box* represents 25–75th percentiles, the *solid line* represents the median, and the *whiskers* represent minimum to maximum values. Comparison was made using an unpaired *t* test, $^*P = 0.001$.

impact of lower levels on exercise capacity in this context.

It was interesting to note the reduced physical activity of those treated with ACE-I in comparison to the rise seen in response to training in the placebo group. Although this could have been a consequence of hypotension, only two subjects in the ACE inhibitor group reported symptomatic dizziness; this was transient, settled spontaneously, and did not require cessation of therapy. In addition, the change in symptom scores was comparable between treatment arms, suggesting that the ACE inhibitor–treated group did not subjectively feel worse. Although the quality-of-life questionnaires we used understandably focused on respiratory disability and may have not detected other relevant symptoms, patients in the treatment group did not report adverse effects that would explain the differences noted.

Table 2. Change in Outcome Measures from Baseline to after Pulmonary Rehabilitation

	Placebo Group (*n* = 34)	ACE-I Group (*n* = 31)	*P* Value
ΔCAT score	−1 (3)	1 (4)	0.05
ΔSGRQ-C symptoms	−0.55 (12.48)	−3.00 (11.43)	0.56
ΔSGRQ-C activity	−6.51 (13.30)	−9.03 (15.65)	0.49
ΔSGRQ-C impacts	−1.83 (7.82)	−2.62 (10.63)	0.52
ΔSGRQ-C total	−3.14 (6.10)	−4.66 (8.71)	0.42
ΔFEV_1, L	−0.02 (0.10)	−0.01 (0.13)	0.91
ΔFEV_1 % predicted	0.02 (3.77)	−0.10 (6.68)	0.93
ΔD_{LCOc} % predicted	−1.45 (4.82)	−1.96 (5.61)	0.70
ΔRV/TLC ratio, %	0.39 (2.67)	0.09 (3.65)	0.70
ΔPa_{O_2}, kPa	−0.02 (1.16)	0.00 (1.12)	0.95
ΔPa_{CO_2}, kPa	0.08 (0.38)	0.02 (0.41)	0.60
ΔFFMI, kg/m^2	−0.31 (0.87)	−0.18 (0.54)	0.58
ΔQMVC, kg	2.09 (4.70)	0.37 (5.29)	0.17
ΔMTMCSA, mm^2	53 (498)	−52 (601)	0.45
ΔQuadriceps CSA, mm^2	81 (284)	69 (223)	0.86
ΔDaily step count*	561 (2,528)	−382 (2,082)	0.30
ΔPAL*	0.04 (0.15)	−0.06 (0.16)	0.030†

Definition of abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CSA = cross-sectional area; D_{LCOc} = diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FFMI = fat-free mass index; MTMCSA = mid-thigh muscle cross-sectional area; PAL = physical activity level; QMVC = quadriceps maximal volitional contraction; RV = residual volume; SGRQ-C = St. George's Respiratory Questionnaire for COPD.

Data shown are mean (SD).

*Data are analyzed from 40 subjects (22 placebo, 18 treatment arm) who recorded an adequate period for physical activity assessment both at baseline and after rehabilitation.

†$P < 0.05$.

Methodological Issues

This study was prospectively stratified by ACE genotype, which is important because previous work has shown a greater response to exercise training in the II ACE genotype group (44). In the present study, the response to PR was not influenced by ACE genotype, whether the subjects received ACE-I or placebo therapy, although the study was not powered to support subgroup analysis. A strong primary endpoint was selected, and the groups were well-matched at baseline, lending confidence to the findings.

We chose to use an ACE inhibitor to ensure effects on both angiotensin II and bradykinin activity. Bradykinin receptor polymorphisms have been shown to affect skeletal muscle phenotype in COPD (20, 21), and previous experimental work has shown bradykinin to have positive effects on skeletal muscle metabolism, including through the generation of nitric oxide, reduced oxidative stress, and improved skeletal muscle insulin sensitivity (12, 13). Thus, we chose an agent that would not only reduce angiotensin II activity but also enhance bradykinin activity. Previous beneficial effects in COPD have been shown in trials with perindopril (22) and enalapril (24), although not with fosinopril (25). Because enalapril has previously been noted to improve peak work rate in subjects with COPD (24), which was our selected primary outcome measure, this seemed to be an appropriate agent to select. There was physiological evidence of adequate dosing, which was manifested by reduced blood pressure and serum ACE activity, although it was impossible to determine the effects on the skeletal muscle RAS without direct sampling. The study cannot prove that the same effect would have been seen with all ACE inhibitors, but it is in line with our previous work (25), suggesting that this was likely a class effect. It also remains unclear as to the time period over which ACE inhibitors should be administered to influence the skeletal muscle phenotype, although shorter periods of treatment than we provided in this study have been associated with changes in exercise capacity (24).

Potential Study Limitations

There are several possible limitations of the present study that deserve further mention. The enalapril-treated group attended a slightly lower number of physiotherapist-led training sessions than the placebo-treated group. Although we believe this is unlikely to have been sufficient to account for the differences seen in outcomes, it is possible this assumption is incorrect. It is also possible that beneficial effects might have been noted had different exercise tests, such as endurance capacity during constant rate submaximal exercise, been used; this cannot be resolved without further study.

It is conceivable that certain subgroups of patients with COPD may experience benefit from ACE-I whereas others may experience detrimental effects, although the present study was not sufficiently powered to allow effective subgroup analysis beyond the chosen stratification variables to confirm or refute this. We used quality-of-life questionnaires that focused on respiratory disability, and it was possible that different questionnaires might have been more effective at detecting symptomatic changes induced by ACE-I that influenced physical activity levels and exercise capacity.

Conclusions

Our results suggest that ACE-I actually reduced the response to exercise training compared with placebo in patients with COPD, and thus ACE inhibitors cannot be recommended for this indication. The biological mechanisms underlying this unexpected finding might warrant further scrutiny. We caution that our study specifically excluded patients with an established indication for ACE-I, and therefore, our data do not support withdrawing ACE inhibitors from such patients during PR. ■

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