A Randomized Double-Blind Trial of Enalapril in Older Patients With Heart Failure and Preserved Ejection Fraction

Effects on Exercise Tolerance and Arterial Distensibility

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Background—Exercise intolerance is the primary symptom in older patients with heart failure and preserved ejection fraction (HFPEF); however, little is known regarding its mechanisms and therapy.

Methods and Results—Seventy-one stable elderly (70±1 years) patients (80% women) with compensated HFPEF and controlled blood pressure were randomized into a 12-month follow-up double-blind trial of enalapril 20 mg/d versus placebo. Assessments were peak exercise oxygen consumption; 6-minute walk test; Minnesota Living with HF Questionnaire; MRI; Doppler echocardiography; and vascular ultrasound. Compliance by pill count was excellent (94%). Twenty-five patients in the enalapril group versus 34 in the placebo group completed the 12-month follow-up. During follow-up, there was no difference in the primary outcome of peak exercise oxygen consumption (enalapril, 14.5±3.2 mL/kg/min; placebo, 14.3±3.4 mL/kg/min; $P=0.99$), or in 6-minute walk distance, aortic distensibility (the primary mechanistic outcome), left ventricle mass, or neurohormonal profile. The effect size of enalapril on peak exercise oxygen consumption was small (0.7%; 95% CI, 4.2% to 5.6%). There was a trend toward improved Minnesota Living with HF Questionnaire total score ($P=0.07$), a modest reduction in systolic blood pressure at peak exercise ($P=0.02$), and a marginal improvement in carotid arterial distensibility ($P=0.04$).

Conclusions—In stable, older patients with compensated HFPEF and controlled blood pressure, 12 months of enalapril did not improve exercise capacity or aortic distensibility. These data, combined with those from large clinical event trials, suggest that angiotensin inhibition does not substantially improve key long-term clinical outcomes in this group of patients. This finding contrasts sharply with observations in HF with reduced EF and highlights our incomplete understanding of this important and common disorder. **(*Circ Heart Fail*. 2010;3:477-485.)**

Key Words: aging ■ exercise ■ heart failure ■ diastole ■ vasculature

Heart failure (HF) afflicts >3 million Americans annually[1] and is the only major cardiovascular disorder that is increasing in incidence and prevalence.[2] HF is primarily a disorder of elderly persons, with >75% of patients with this condition being ≥65 years old. The majority of patients with HF have a preserved left ventricular (LV) ejection fraction (HFPEF).[3–7]

Clinical Perspective on p 485

Exercise intolerance, manifested by dyspnea and fatigue during exertion, is the primary chronic symptom experienced by patients with HF[6,8] and can be quantified objectively by measurement of peak exercise oxygen consumption (Vo_2). We have previously shown that this measurement is valid and reproducible in older patients with HF.[9] We have also shown that peak exercise Vo_2 is severely reduced in older patients with HFPEF compared to age-matched healthy volunteers to a similar degree as patients with HF with severely reduced ejection fraction (HFREF) and is accompanied by diminished quality of life.[8] However, the pathophysiology and therapy of exercise intolerance in this important disorder are not well understood.

Several lines of evidence have suggested that decreased arterial distensibility, with subsequent increases in LV afterload, concentric ventricular remodeling, and abnormal diastolic relaxation, may contribute to exercise intolerance in older patients with HFPEF.[10–14] In healthy persons, arterial distensibility decreases with age and correlates with age-related decline in exercise capacity.[15] This age-related decline in arterial distensibility is accelerated by hypertension, a

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common precursor to HFPEF. We have previously shown that aortic and carotid distensibility are severely reduced in older patients with HFPEF compared to healthy age-matched controls, with the former strongly correlated with peak Vo_2.[16,17]

Multiple lines of evidence have suggested a potential role for angiotensin II in the pathophysiology and therapy of exercise intolerance in HFPEF.[18–22] Decreased arterial distensibility appears to be mediated at least in part by angiotensin II and has been shown to be modifiable by inhibition of angiotensin II in animal models of aging and hypertension as well as in humans with hypertension.[21–23] We and others have shown that patients with HFPEF have abnormal activation of the renin-angiotensin system.[18] We also have shown that angiotensin receptor antagonists (angiotensin II receptor blockers [ARBs]) improve exercise tolerance and quality of life in patients with a hypertensive response to exercise and evidence of diastolic LV dysfunction.[24,25] Aronow et al[26] reported that angiotensin converting enzyme inhibition (ACEI) improved exercise tolerance in older patients with HFPEF following an acute myocardial infarction. It also has been reported that angiotensin antagonism can improve quality of life and exercise capacity in patients with HFREF.[27]

The purpose of this study was to test the hypothesis that the severe exercise intolerance experienced by older patients with HFPEF can be improved by targeting angiotensin II and that this improvement would be mediated at least partly by improvements in arterial distensibility. To test this hypothesis, we performed a 12-month prospective, randomized, double-blind, placebo-controlled trial of the standard ACEI enalapril with detailed measurements of exercise performance, health-related quality of life, and cardiac and vascular structure and function.

Methods

Study Design

The study protocol was approved by the Wake Forest University (Winston-Salem, NC) Institutional Review Board, and written informed consent was obtained. All tests were performed in a postabsorptive state, with medications held for 12 hours prior to testing, except for the study medication. Testing was then repeated after 4 months and 12 months. Placebo and active drug were prepared and distributed by the research pharmacy, using secure methodology. All investigators, staff, and patients were fully blinded to treatment group assignment throughout the entire study period; during data abstraction, clean-up, and image analyses; and until the database had been locked. The study drug was initiated at 2.5 mg BID and titrated up to 10 mg BID as tolerated by the patient within the first 4 weeks of the study. Compliance was assessed by actual pill count. To assure patient safety, adherence, and retention in the study, patients were seen by clinic visit or contacted by telephone regularly.

Patients

As previously described, isolated HFPEF was defined as history, symptoms, and signs of HF; a preserved LVEF) (≥50%); and no evidence of significant coronary, valvular, or pulmonary disease or other medical condition that could mimic HF symptoms, such as anemia or thyroid dysfunction.[8,9,16,28] Coronary disease was excluded by history, medical records, ECG, and rest and exercise echocardiogram. The diagnosis of HF was based on clinical criteria as previously described that included an HF clinical score from the National Health and Nutrition Examination Survey-I of ≥3 and those used by Rich et al[29] and verified by a board-certified cardiologist.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Enalapril (n=35)	Placebo (n=36)	*P*
Age, y	69±8	70±7	0.67
Female sex	28 (80%)	32 (89%)	0.30
Black race	3 (9%)	2 (6%)	0.42
Body weight, kg	82±16	79±17	0.47
BSA, m^2	1.88±0.21	1.83±0.22	0.41
BMI, kg/m^2	30±5	30±5	0.61
Body fat, %	38±9	39±7	0.69
LVEF, %	65±8	65±7	0.99
Sinus rhythm	32 (91%)	34 (91%)	0.56
NYHA class			
II	29 (83%)	27 (75%)	0.42
III	6 (17%)	9 (25%)	0.35
History of pulmonary edema	6 (18%)	4 (12%)	0.49
Diabetes mellitus	3 (9%)	6 (17%)	0.31
History of hypertension	25 (71%)	27 (75%)	0.73
Blood pressure, mm Hg			
Systolic	143±17	144±18	0.80
Diastolic	82±10	83±7	0.58
Diastolic function			
Normal	4 (12%)	1 (3%)	0.18
Delayed	26 (79%)	31 (86%)	0.26
Pseudonormal	3 (9%)	4 (11%)	0.35
Hemoglobin, g/dL	13.5±1.5	12.7±1.4	0.45
Creatinine, mg/dL	1.1±0.2	1.1±0.2	0.67
Peak Vo_2, mL/kg/min	14.9±2.9	14.3±3.3	0.42
Respiratory exchange ratio	1.11±0.08	1.12±0.07	0.46
Workload	76±26	69±26	0.23
Exercise time, min	10.1±2.8	9.0±3.1	0.16
Current medication			
β-blockers	10 (29%)	14 (39%)	0.36
Ca channel blockers	11 (31%)	8 (22%)	0.38
Digoxin	0 (0%)	0 (0%)	1.00
Diuretics	17 (49%)	21 (58%)	0.41
Nitrates	0 (0%)	2 (6%)	0.16

Data are presented as mean±SD or count (%). BMI indicates body mass index; BSA, body surface area; NYHA, New York Heart Association.

*$P<0.05$.

†$P\leq0.01$.

‡$P\leq0.001$ enalapril versus placebo.

Patients were excluded if they had ever been prescribed an ACEI or ARB.

Exercise Capacity

Exercise testing was performed as previously described, with participants in the upright position on an electronically braked bicycle.[8,9,16,28,30–32] Expired gas analysis was carried out using a metabolic cart calibrated with a standard gas of known concentration and volume. Metabolic gas exchange was measured continuously during exercise and averaged over 15-second intervals. Peak values were averaged from the final 30 seconds of the exercise test. A 6-minute walk test was performed as described by us[8] and Guyatt et al.[33]

Table 2. Exercise Performance

	Enalapril			Placebo			
	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
Peak exercise (bike)							
Vo_2, mL/min	1210±289	1210±306	1165±319	1114±379	1094±349	1079±355	0.72
Indexed Vo_2, mL/kg/min	15.0±3.2	14.8±2.9	14.5±3.2	14.2±3.4	14.1±2.9	14.3±3.4	0.99
Time, min	10.1±2.4	10.0±2.4	9.7±2.5	9.0±3.1	8.9±3.1	8.9±3.2	1.00
Workload, W	77±22	73±19	73±23	69±26	66±26	67±26	1.00
Heart rate, bpm	129±20	128±17	125±20	133±16	131±19	133±19	0.95
Respiratory rate, breaths/min	34±9	35±9	34±10	33±10	34±9	34±9	1.00
Oxygen pulse, mL/beat	9.5±2.1	9.4±2.0	9.4±2.3	8.4±2.7	8.3±2.6	8.2±2.5	1.00
Vco_2, mL/min	1334±340	1333±341	1298±383	1242±444	1215±412	1234±433	1.00
VE, l/min	48±11	48±12	47±12	45±14	46±16	46±16	1.00
RER	1.11±0.07	1.11±0.08	1.12±0.07	1.12±0.07	1.12±0.08	1.13±0.09	1.00
VE/Vco_2 slope	33±5	34±5	34±5	34±5	34±6	34±6	0.99
VAT, mL/min	710±153	725±168	717±169	708±193	701±151	690±169	0.99
6-min walk, ft	1481±259	1493±209	1461±258	1481±315	1423±321	1490±314	1.00

Data are presented as mean±SD. *P* represents comparison of least square means at combined follow-up visits following adjustment for baseline values, age, and sex. *P* values shown are following Bonferroni adjustment, except for Vo_2 in mL/min, the primary outcome. RER indicates respiratory exchange ratio; VAT, ventilatory anaerobic threshold; Vco_2, carbon dioxide production; VE, minute ventilation.

Aortic Distensibility and LV Structure and Function

MRI scans were performed on a 1.5T CVi scanner with a phased-array surface coil applied to optimize signal to noise. Multislice coronal, gradient-echo sequences were used to obtain scout images of the chest and thus locate the heart and aorta. After locating the aorta, a series of sagittal and axial images in both standard and oblique planes was obtained. Assessment of aortic distensibility was then defined and calculated according to previously published techniques.[28,31,34]

As previously described, LV volumes (end-diastolic volume and end-systolic volume) and LV mass were assessed from a series of multislice, multiphase, gradient-echo sequences positioned perpendicular to the long axis of the LV (short axis), spanning apex to base.[16,31,34] For LV volume and mass determinations, the epi- and endocardial borders of each slice were traced manually at end diastole and end systole, and volumes were calculated by summation (Simpson rule).[16,34] LV stroke volume and EF were calculated from standard formulas.

Carotid Artery Stiffness

Standardized longitudinal B-mode images of the left common carotid artery were recorded with the subject in the supine position.[35] A 10-second sequence of images was recorded from an optimal interrogation angle. The 4 boundaries defining the media-adventitia and blood-intima interfaces on the near and far wall were traced and recorded. The following data were then computed from each image: mean, maximum, and minimum values of the arterial diameter, the lumen diameter, and wall thickness. Carotid artery stiffness indexes were then calculated using standard equations.[35]

LV Diastolic Filling

Mitral annulus tissue and blood-flow Doppler were performed using an ultrasound imaging system with a multiple frequency transducer. Doppler tracings were then analyzed using a digital echocardiography workstation as previously described.[8,34,36–38]

Quality of Life

The Minnesota Living with Heart Failure Questionnaire (MLHF) is an HF-specific measure. It was administered to assess the impact of the intervention on quality of life.[8,39]

Statistical Analysis

The study was designed to test for an effect of enalapril on two primary outcome measures: peak exercise Vo_2 and total score of the MLHF. The sample size was derived from a formal power analysis using data from our previously published studies and our pilot study conducted specifically to inform the design of the present trial.[8,16,30,32,40] These data indicated that a final sample size of 56 evaluable patients at the end of the study (70 patients randomized at the beginning of the study and assuming up to a 20% dropout rate during 12-month follow-up) would provide 80% power to detect a 10% change in peak exercise Vo_2 and a 20% change in the total MLFH score.

Group comparisons of outcome measures between intervention groups were made by repeated-measures analysis of covariance procedures. By prospective study design in order to reduce bias and increase precision, the analyses were adjusted for prerandomization values of the outcome measure being considered as well as for other factors (age, sex) significantly associated with the outcome variable after adjusting for the other terms in the model.[41] The values of the outcome measures taken at 4 months and 12 months were considered the repeated measures. A test of the group by time interaction was used to check the consistency of any intervention effect at each of the 2 end point evaluations. If the interaction was nonsignificant at the 0.10 level, then the overall effect of the intervention over the experimental period was estimated. Data are presented as raw, unadjusted mean±SD at each visit for each group along with the *P* value corresponding to the adjusted least squares outcomes means from the analysis of covariance procedures accounting for all data at all follow-up visits. Significance was set at $P<0.05$. Unadjusted *P* values are presented for testing the effect of enalapril on the 2 primary end points (ie, peak exercise Vo_2 and MLHF total score). Analyses for a number of secondary mechanistic variables are presented. Bonferroni-adjusted *P* values are presented for the number of variables being tested within each family of variables: 11 for exercise performance, 4 for blood pressure, 4 for aortic function, 2 for carotid function, 6 for LV volume and mass, 6 for LV diastolic function, 2 for quality-of-life subscales, and 5 for neurohormones. Non-Bonferroni-adjusted *P* values are presented for testing the effect of enalipril on the 2 primary end points. All available data were analyzed from all outcome assessments in all patients, using the intent-to-treat approach.

Table 3. Blood Pressures

	Enalapril			Placebo			
	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
Resting							
Systolic BP	137±19	128±19	131±17	140±16	139±16	137±16	0.12
Diastolic BP	75±12	69±12	70±10	75±11	74±12	74±11	0.04
Peak exercise							
Systolic BP	195±23	181±23	182±27	192±24	194±23	183±27	0.02
Diastolic BP	86±9	85±7	82±9	87±11	87±8	83±10	0.46

Data are presented as mean±SD. *P* represents comparison of least square means at combined follow-up visits following adjustment for baseline values, age, and sex. *P* values shown are following Bonferroni adjustment. BP indicates blood pressure.

Results

Patient Characteristics

Participants were recruited using a staged screening process: 4538 patient charts were selected by electronic search criteria and reviewed, 506 of those patients were contacted and screened by telephone, and 164 of those were scheduled for a screening clinic visit. A total of 71 patients were enrolled in the trial, 35 randomized to receive enalapril and 36 randomized to receive placebo. There were no significant differences between the treatment groups with regard to age, sex, race, weight, EF, or New York Heart Association class (Table 1).

Compliance, Adverse Events, and Retention

Compliance by pill count was excellent in both groups (enalapril, 94%; placebo, 96%). Ten (14%) patients received less than a full dose or were downtitrated (n=9 for the enalapril group, and n=1 for the placebo group). In the 9 downtitrated patients in the enalapril group, the total daily final dose was 10 mg in all but 1 for whom the dose was 5 mg. The most common reasons for not achieving full dose were dizziness and cough.

Twenty adverse events occurred during the study period (n=12 for the enalapril group, and n=8 for the placebo group). According to the blinded investigators, 3 events (cough, alopecia, asymptomatic hypotension) that occurred in 3 separate patients within the enalapril group were possibly related to study medication. There were no deaths during the trial period, but there 13 patients were hospitalized during the study (chest pain [myocardial infarction ruled out], 3 versus 2 for enalapril versus placebo, respectively; elective orthopedic surgery [knee surgery, screw replacement, hip replacement], 1 versus 4 for enalapril versus placebo, respectively; dehydration, 1 for enalapril; vertigo, 1 for enalapril; removal of adnexal mass [found to be benign], 1 for placebo).

Thirty patients in the enalapril group and 34 in the placebo group completed 4 months of follow-up, and 25 in the enalapril group and 34 in the placebo group completed 12 months of follow-up. With slight variation between variables, these numbers of patients for each testing visit in the data are

Table 4. LV Function

	Enalapril			Placebo			
	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
LV volumes and mass (MRI)							
Mass, g	129±20	125±21	121±18	118±28	117±27	113±26	0.82
Mass/end-diastolic volume ratio	1.9±0.5	1.8±0.4	1.9±0.4	1.8±0.4	1.8±0.6	1.7±0.4	1.00
End-diastolic volume, mL	70±16	72±17	67±14	68±16	67±18	70±16	1.00
End-systolic volume, mL	24±6	24±7	23±6	23±7	23±8	24±8	0.88
Stroke volume, mL	46±11	48±12	44±10	45±13	44±13	46±11	1.00
EF, %	65±6	66±6	66±6	66±7	65±7	66±8	0.99
Doppler LV diastolic function (ultrasound)							
Early mitral annulus velocity, cm/s	9.4±2.1	9.1±2.0	8.4±1.4	8.0±1.7	7.5±1.7	7.1±1.5	0.10
Early deceleration time, ms	220±45	220±58	208±58	237±48	240±60	242±62	0.65
Isovolumetric relaxation time, ms	70±19	70±16	71±13	77±15	81±18	76±17	0.37
Early mitral flow velocity, cm/s	76±17	78±17	81±16	71±16	70±15	73±17	0.30
Early/atrial mitral flow velocity ratio	1.01±0.5	1.02±0.5	1.10±0.7	0.84±0.3	0.84±0.2	0.84±0.3	0.94
E/Ea	8.5±2.2	8.9±2.6	9.9±2.4	9.4±3.2	9.7±2.7	10.8±3.6	1.00

Data are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values, age, and sex. *P* values shown are following Bonferroni adjustment. E indicates early mitral flow velocity; Ea, mitral annulus velocity.

Table 5. Arterial Function

	Enalapril			Placebo			
	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
Aortic function (MRI)*							
Pulse pressure/stroke volume	1.36±0.4	1.34±0.4	1.42±0.5	1.56±0.7	1.56±0.6	1.40±0.5	0.98
Phasic area change, mm^2	46±20	54±35	51±23	42±25	47±27	55±29	1.00
Distensibility, 10^{-3}/mm Hg	0.98±0.48	1.31±1.20	1.21±0.86	0.93±0.73	0.97±0.53	1.29±0.89	0.93
Aortic compliance, mm^2	0.80±0.44	1.04±0.88	0.94±0.60	0.73±0.55	0.76±0.41	1.04±0.82	0.99
Carotid function (ultrasound)*							
Phasic area change, mm^2	0.38±0.18	0.36±0.18	0.43±0.52	0.34±0.19	0.35±0.17	0.36±0.21	0.09
Distensibility, 10^{-3}/mm Hg	1.09±0.59	1.38±0.94	1.19±1.73	0.82±0.45	0.82±0.31	0.88±0.49	0.04

Data are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values, age, and sex. *P* values shown are following Bonferroni adjustment.

shown in Tables 2 through 6. There were significantly more patients who did not complete the study in the enalapril group relative to the placebo group (10 versus 2; $P=0.01$ by Fisher exact test). The 12 patients not represented in the 12-month follow-up data were accounted for by 8 dropouts and 4 patients who were unable to complete testing. The dropouts were due to patient request (n=3), pancreatitis (n=1), elective rotator cuff surgery (n=1), alopecia (n=1), worsening cough (n=1), and hypotension (n=1). According to the blinded investigators, only the latter 3 were possibly related to study medication, and all were in the enalapril group. The 4 patients who completed the 12-month medication but were unable to perform the 12-month follow-up testing were due to elective knee replacement surgery (placebo); ankle fracture (enalapril); exacerbation of knee arthritis (enalapril); and leg and hip pain and fatigue associated with nonvolitional 30-lb weight loss (enalapril).

Exercise Performance

At baseline, peak exercise Vo_2 was severely reduced in both groups compared to that expected for age (Table 1). Patients gave an exhaustive effort at baseline and follow-up testing as evidenced by a mean respiratory exchange ratio >1.10, and there was equal effort between the groups as shown by no significant difference in respiratory exchange ratio values (Table 2). There was no significant difference in peak exercise Vo_2—the primary outcome—during 12-month follow-up by analyses of adjusted means (14.4±0.2 versus 14.4±0.2; $P=0.99$) or of unadjusted data (Figure; Table 2). There were no significant differences between the groups in any other measure of peak exercise capacity, including exercise time and exercise workload, or in any measure of submaximal exercise performance, including the ventilatory anaerobic threshold and 6-minute walk distance. The estimated treatment effect size on peak exercise Vo_2 was only 0.1±0.4 mL/kg/min (0.7%; 95% CI, −0.6 to 0.8 mL/kg/min [−4.2% to 5.6%]).

Blood Pressures

During 12 months of follow-up, there were modest reductions in diastolic blood pressure at rest ($P=0.04$). Systolic blood pressure at peak exercise also was modestly reduced ($P=0.02$) (Table 3).

LV Structure and Function

By Doppler echocardiography during the 12-month follow-up, early mitral annulus tissue Doppler velocity was found to be higher in the enalapril group than in the placebo group (adjusted mean, 8.5±0.2 versus 7.7±0.2; $P=0.01$). However, after Bonferroni adjustment, there were no significant differences in any Doppler LV diastolic function variable (Table 4). Two patients in the enalapril group had atrial fibrillation and, thus, did not have evaluable Doppler data. By cardiac MRI, there were no differences during follow-up in LV mass; LV volume; EF; or the ratio of LV mass to end-diastolic volume, a measure of concentric LV remodeling.

Arterial Function

Carotid distensibility during 12-month follow-up was significantly greater in the enalapril group than in the placebo group ($P=0.04$) (Table 4). However, aortic distensibility by MRI, the primary mechanistic outcome, was not significantly

Table 6. Quality of Life

	Enalapril			Placebo			
MLHFQ Scale	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
Emotional	5±6	4±6	4±6	5±6	4±5	6±6	0.28
Physical	14±10	12±11	12±10	15±9	13±11	16±10	0.10
Total	26±24	22±26	23±25	28±19	22±20	29±20	0.07

Data are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values, age, and sex. *P* values shown are following Bonferroni adjustment, except for total score, a prespecified coprimary outcome.

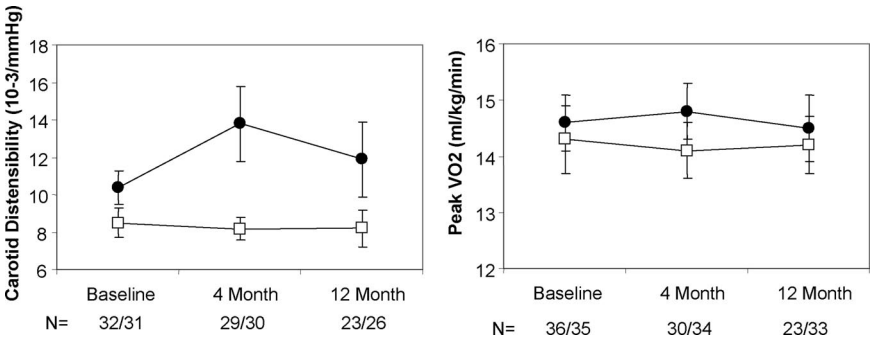

Figure. Raw, unadjusted means ±1 SE at baseline and 4-month and 12-month follow-up visits for enalapril (circles) and placebo (squares) for carotid arterial distensibility and peak exercise Vo_2 by expired gas analysis. The number of evaluable patients is shown for the specific outcome at each visit (enalapril versus placebo). During 12 months of follow-up, the primary outcome of peak exercise Vo_2 (P=0.99) and the primary mechanistic outcome of aortic distensibility (not shown) were unchanged. Carotid arterial distensibility at rest was marginally improved in the enalapril group (P=0.04).

different between groups during follow-up, nor was the ratio of pulse pressure to stroke volume.

Quality of Life

The total score on the MLHF showed a trend toward being lower (improved) in the enalapril group than in the placebo group (P=0.07) (Table 6).

Neurohormones

No differences were observed in measured neurohormones during 12-month follow-up except for plasma renin, which was increased in the enalapril group (Table 7). The physical score appeared to be affected more than the emotional score.

Discussion

This randomized, double-blind, placebo-controlled study examined the potential for 12-month treatment with the ACEI enalapril to improve exercise tolerance and quality of life in patients with HFPEF and alterations in LV and arterial function that are thought to contribute to the pathophysiology of this important and incompletely understood disorder. Patients at baseline were stable and compensated and had controlled blood pressure. Contrary to our primary hypothesis, there was no difference in peak exercise capacity or in submaximal exercise performance, aortic distensibility, or LV mass and volume. There was a trend to improved disease-specific quality of life as measured by the MLHF, modest reductions in resting diastolic and peak exercise systolic blood pressure, and mild improvement in carotid arterial distensibility. Doppler LV diastolic function was not significantly changed.

Although many trials have examined the key outcome of exercise performance in patients with HFREF, similar studies in HFPEF are lacking. The only previously reported trial was an unblinded study of enalapril and included only 21 patients, all of whom were men with a prior myocardial infarction.[26] None of the large randomized clinical event trials of ACEI and ARB treatment in patients with HFPEF assessed exercise performance. Furthermore, none of these studies, including the PEP-CHF (Perindorpil in Elderly People with Chronic Heart Failure) trial,[42] the PEF arm of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial,[43] and the recently reported I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Study) trial,[44] had clear positive effects on their primary outcomes. Therefore, the results of the present study are conceptually consistent with these large clinical event trials and, taken together, suggest that angiotensin II may not play as strong a role in HFPEF as previously thought.

We previously found that ARBs improved exercise treadmill time in patients who at baseline had a mitral inflow early-to-late left ventricular filling velocity ratio <1.0 and an exaggerated systolic blood pressure response to exercise >200 mm Hg.[24,25,37] The present study differed both in the agent used and in patient selection criteria. Although the present study used an ACEI rather than an ARB, most exercise outcomes studies that have directly compared an ACEI to an ARB in patients with HFREF have not found significant differences.[45–47] Patients in the present study had relatively controlled blood pressure at rest, a key characteristic shared with the 3 large clinical event trials previously

Table 7. Neurohormones

	Enalapril			Placebo			
	Baseline	4 mo	Final	Baseline	4 mo	Final	*P*
Aldosterone	9.9±4.9	NP	9.1±5.7	11.3±8.6	NP	12.7±10.8	0.52
Angiotensin II	44.7±24.7	37.3±21.7	35.3±17.9	43.5±21.9	40.9±21.2	35.7±16.9	0.77
CRP	0.36±0.35	0.47±0.42	0.36±0.36	0.51±0.43	0.52±0.43	0.59±0.46	1.00
Renin	0.76±0.68	4.80±9.77	2.81±5.00	1.12±1.58	1.21±1.83	1.38±3.62	<0.001
BNP	78±71	100±137	84±76	64±66	77±73	67±43	1.00

Data are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values, age, and sex. Logarithmic transformation was used for these nonnormally distributed variables that were highly skewed. *P* values shown are following Bonferroni adjustment. BNP indicates B-type natriuretic peptide; CRP, C-reactive protein; NP, not performed.

noted, and were not selected to have an exaggerated systolic blood pressure response during exercise, suggesting, along with our prior studies,[24,25,37] that when present, an exaggerated exercise blood pressure response may be a key therapeutic target in patients with diastolic dysfunction.

Reports from our group and others have indicated that increased aortic and arterial stiffness could be a contributor to the pathophysiology HFPEF.[16,17,34,48,49] In the present study, carotid arterial distensibility was marginally improved with enalapril, but aortic distensibility was not. Aortic distensibility was chosen as the primary mechanistic outcome because of its influence on ventricular-vascular coupling, its observed relationship with peak exercise Vo_2 in a prior cross-sectional study of HFPEF, and the suggestion from other studies that it was mediated partly by angiotensin II and was modifiable.[22] The severely decreased aortic distensibility in older patients with HFPEF probably developed over many years; was likely caused by multiple mechanisms, including calcification and fibrosis; and may thus have limited potential for reversibility. Notably, in a prior study, the glucose cross-link breaker alagebrium did not improve aortic distensibility or exercise capacity in HFPEF.[34]

Importantly, mechanistic studies of exercise intolerance in patients with HFREF indicate that exercise intolerance in HF is multifactorial and a complex interaction of cardiac, vascular, pulmonary, hematologic, and skeletal muscle factors,[14,32,50–53] which may help to explain why pharmacological treatments that have produced significant short-term improvements in hemodynamics in patients with HFREF have not reliably produced long-term improvements in exercise intolerance.[14,54] Furthermore, trials of ACEI for the outcome of exercise capacity in HFREF have not been uniformly positive, particularly during long-term follow-up.[46,55] For instance, a randomized, double-blind, placebo-controlled trial of 48 weeks of enalapril in 41 men with HFREF found no difference in peak exercise Vo_2 or exercise time.[46]

Other possible explanations for the neutral results include measurement reliability, patient selection, drug and dose compliance, and sample size. Our laboratory has substantial experience in performing accurate and reproducible measurements of the outcomes assessed in this trial.[8,9,16] Patient demographic characteristics in the present study were similar to those reported in large, population-based, observational studies,[3–6] and mean baseline measurements for the key variables were similar to those reported in our previously published studies.[8,16,28,31,32,40] Compliance with the medication was excellent.

Enalapril was chosen as the ACEI in the present trial because it had been shown to improve mortality in HFREF, was the ACEI used in published trials of exercise tolerance in HFREF,[46,56] had been reported to improve exercise treadmill time in a published open-label trial of 21 older patients with HFPEF following myocardial infarction,[26] and had improved the primary and mechanistic outcomes in our pilot study. The sample size was derived from a formal power analysis using data from our previously published studies and our pilot study[8,16,30,32,40]; however, the effect size on peak exercise Vo_2 we observed in the present study of only 0.1 ± 0.4 mL/kg/min (0.7%; 95% CI, −0.6 to 0.8 mL/kg/min [−4.2% to 5.6%]) excludes improvements in peak exercise Vo_2 of 1.0 mL/kg/min (10%), which generally are accepted as the minimal clinically relevant improvement.

Limitations

We cannot exclude that a larger sample size or lower dropout rate could have affected our ability to detect a treatment effect. There were more dropouts in the enalapril arm than in the placebo arm. Some of these dropouts were due to known side effects of enalapril, such as cough, alopecia, and hypotension. We also observed that over the 12-month trial period, patients in both groups had a number of unexpected events that were unrelated to the study, the medication, or even their underlying disorder of HFPEF; however, the dropout rate was within the projected range in the power analysis.

Our observation highlights the importance of the multiple comorbidities that are nearly uniformly present in older patients with HF.[57] This observation was present not only in the current study, but also in the PEP-CHF and the I-PRESERVE trials. In the I-PRESERVE trial, 52% of the hospitalizations during follow-up were for noncardiovascular causes.[44]

Although we used the standard dose of enalapril used in the large trials with HFREF, we cannot exclude that a larger dose of ACEI alone or in combination with an ARB may have produced different results. In addition, the patients with HFPEF had severely reduced exercise capacity and evidence of diastolic dysfunction (Table 1). However, by design, enrolled patients were stable and well-compensated and had no recent exacerbations or evidence of significant coronary, valvular, pulmonary, or renal disease or anemia. Thus, the results of the present study may not apply to patients with more severe or poorly compensated disease.

Conclusions

Twelve months of treatment with enalapril did not improve exercise capacity, aortic distensibility, or LV mass and volume. Along with results of large clinical event trials, these findings suggest that inhibiting angiotensin II in patients with stable, compensated HFPEF and controlled blood pressure does not substantially improve key long-term clinical outcomes, contrasting with observations in patients with HFREF, highlighting our incomplete understanding of HFPEF, and suggesting the need for new paradigms for this important and common disorder.

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CLINICAL PERSPECTIVE

Exercise intolerance is the primary symptom in patients with heart failure and preserved ejection fraction (HFPEF); however, little is known regarding its therapy. This randomized, double-blind, placebo-controlled study examined the effect of 12 months of treatment with the angiotensin-converting enzyme inhibitor enalapril on exercise tolerance and quality of life as well the alterations in left ventricular and arterial function that may contribute to HFPEF pathophysiology. Patients at baseline were stable and compensated and had controlled blood pressure. Contrary to our primary hypothesis, the angiotensin-converting enzyme inhibitor produced no differences in exercise performance, aortic distensibility, or left ventricle mass and volume. There was a trend toward improved quality of life, modest reductions in resting diastolic and peak exercise systolic blood pressures, and mild improvement in carotid arterial distensibility. Doppler measurements of left ventricular diastolic function were not significantly changed. Along with results of large clinical event trials, these findings suggest that using angiotensin II as a therapeutic target in patients with stable, compensated HFPEF and controlled blood pressure does not substantially improve key clinical outcomes; suggest that our understanding of HFPEF may be incomplete; and highlight the need for new treatment paradigms for this important and common disorder.

A Randomized Double-Blind Trial of Enalapril in Older Patients With Heart Failure and Preserved Ejection Fraction: Effects on Exercise Tolerance and Arterial Distensibility

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