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Enhanced External Counterpulsation Improves Exercise Tolerance in Patients With Chronic Heart Failure

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OBJECTIVES The PEECH (Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure) study assessed the benefits of enhanced external counterpulsation (EECP) in the treatment of patients with mild-to-moderate heart failure (HF).

BACKGROUND Enhanced external counterpulsation reduced angina symptoms and extended time to exercise-induced ischemia in patients with coronary artery disease, angina, and normal left ventricular function. A small pilot study and registry analysis suggested benefits in patients with HF.

METHODS We randomized 187 subjects with mild-to-moderate symptoms of HF to either EECP and protocol-defined pharmacologic therapy (PT) or PT alone. Two co-primary end points were pre-defined: the percentage of subjects with a 60 s or more increase in exercise duration and the percentage of subjects with at least 1.25 ml/min/kg increase in peak volume of oxygen uptake (V_{O_2}) at 6 months.

RESULTS By the primary intent-to-treat analysis, 35% of subjects in the EECP group and 25% of control subjects increased exercise time by at least 60 s ($p = 0.016$) at 6 months. However, there was no between-group difference in peak V_{O_2} changes. New York Heart Association (NYHA) functional class improved in the active treatment group at 1 week ($p < 0.01$), 3 months ($p < 0.02$), and 6 months ($p < 0.01$). The Minnesota Living with Heart Failure score improved significantly 1 week ($p < 0.02$) and 3 months after treatment ($p = 0.01$).

CONCLUSIONS In this randomized, single-blinded study, EECP improved exercise tolerance, quality of life, and NYHA functional classification without an accompanying increase in peak V_{O_2}. (J Am Coll Cardiol 2006;48:1198–205) © 2006 by the American College of Cardiology Foundation

Enhanced external counterpulsation (EECP) is a noninvasive, pneumatic technique that utilizes electrocardiogram-gated diastolic inflation of a series of lower-extremity cuffs

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to effectively increase diastolic and mean intracoronary pressures as well as coronary flow while reducing systolic pressure in the central aorta and the coronary artery (1). In addition, EECP improves diastolic filling, decreases left ventricular (LV) end-diastolic pressure, and improves LV peak filling rate, end-diastolic volume, and time to peak filling rate (2). This combination of systolic unloading and increased coronary perfusion pressure with external counterpulsation mimics the hemodynamic consequences of intra-aortic balloon counterpulsation. Indeed, EECP was initially evaluated in the treatment of patients with cardiogenic shock (3). Repeated administration of EECP has been shown to have salutary benefits in patients with symptoms of coronary artery disease and normal LV function despite optimal medical therapy (4); patients receiving 35 h of active counterpulsation over a 4- to 7-week period demonstrated reduced angina symptoms and extended time to exercise-induced ischemia, when compared with a group of patients randomized to receive sham counterpulsation (4). In addition, EECP effected a significant improvement in health-related quality of life up to 12 months after completion of treatment (5). Although the specific mechanisms responsible for the beneficial clinical effects of EECP therapy in patients with symptomatic coronary artery disease remain unclear, recent studies have demonstrated that a positive

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Abbreviations and Acronyms

EECP = enhanced external counterpulsation
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
MLWHF = Minnesota Living with Heart Failure
NYHA = New York Heart Association
PEECH = Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure trial
PT = protocol-defined pharmacologic therapy
V_{O_2} = oxygen uptake

response to EECP is associated with enhanced peripheral endothelial function (6). In addition, EECP improved stress myocardial perfusion both at baseline and at maximal exercise levels (7), reduced plasma levels of brain natriuretic peptides (2), and improved regional myocardial oxygen metabolism (8).

In the initial clinical evaluations of EECP, patients were required to have normal LV function. However, several studies suggested that EECP might also benefit patients with LV dysfunction. Approximately 22.3% of patients enrolled in a voluntary registry of patients undergoing EECP therapy for treatment of angina pectoris had LV dysfunction as evidenced by a left ventricular ejection fraction (LVEF) of ≤35% (9). These patients had increased severity of angina symptoms and higher rates of the composite outcome of death/myocardial infarction/or revascularization as compared with patients with preserved ventricular function. However, patients who did not have an outcome event had improved anginal status and nitroglycerin use that was comparable to that seen in patients with normal LV function. Furthermore, EECP improved exercise capacity and quality of life without adverse consequences in a small group of patients with stable heart failure (HF) who underwent 35 sessions of EECP (10). To address the efficacy of EECP in patients with symptomatic HF secondary to systolic dysfunction, we conducted a multicenter, controlled clinical trial comparing protocol-defined pharmacologic therapy (PT) (per published guidelines) with 35 1-h sessions of EECP with PT alone.

METHODS

The PEECH (Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure) trial was conducted at 29 centers in the U.S. and the U.K. The complete protocol has been described elsewhere (11). Enrollment criteria included New York Heart Association (NYHA) functional class II to III symptoms secondary to either ischemic or nonischemic cardiomyopathy, LVEF ≤35%, and PT consisting of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker (for at least 1 month) and a beta-blocker (for at least 3 months) unless they were not tolerated. Digoxin, diuretics, and other medications used to treat HF could be given at the investigator's discretion. After providing written informed consent, eligible patients were randomized in a 1:1 ratio to treatment with EECP or to continued PT. The study personnel responsible for evaluating study subjects as well as the steering committee, the end points committee, the exercise core laboratory, and the sponsor were unaware of the treatment assignments. Other personnel at the study centers were not blinded to the randomization and were charged with providing clinical care and assessing adverse experiences. Study files were organized to preserve blinding of the investigators responsible for evaluating the subjects.

Patients randomly assigned to EECP received 35 1-h sessions over a period of 7 to 8 weeks. Three pneumatic cuffs were placed around the lower limbs and buttocks and were inflated sequentially upward at the onset of diastole, and released rapidly and simultaneously before the onset of systole. The protocol-specified applied pressure was 300 mm Hg and was reached within 5 min of the initiation of treatment. Pulse oximetry was monitored continuously during the treatment session, and the subject's clinical status was re-evaluated if the oxygen saturation dropped by ≥4%. Patients in both treatment groups were seen in follow-up at 1 week, 3 months, and 6 months after treatment.

The 2 co-primary end points were the percentage of subjects with at least a 60-s increase in exercise duration from baseline and the percentage of subjects with at least a 1.25-ml/min/kg increase in peak volume of oxygen uptake (V_{O_2}) from baseline to 6 months. The exercise test was standardized across all centers using a modified Naughton protocol and a calibrated treadmill. Peak V_{O_2} was defined as the oxygen consumption observed at the maximum level of exercise, as shown by a respiratory exchange ratio (RER) >1, a rating of >14 using the Borg scale of perceived exertion (15-point, 6 to 20 scale), and identifying the anaerobic threshold, when reached. Raw exercise data were analyzed by a core exercise laboratory, blinded to treatment assignment and sequence, which provided the results used in the analysis. Secondary end points included change in exercise duration, peak V_{O_2}, NYHA functional class status, quality of life, and the occurrence of cardiovascular clinical outcomes during the treatment phase and the 6-month follow-up. The NYHA functional classification was assessed and graded by the blinded investigator at each participating site. Quality of life was assessed using the Minnesota Living with Heart Failure (MLWHF) instrument (12).

Primary analysis was by intent-to-treat, and data from patients who did not complete the study were analyzed by carrying forward the last observation. In a secondary analysis, data from patients who withdrew before reaching the 6-month end point were censored at the time of the last evaluation. The primary analysis was a logistic regression which factors site and baseline. Other variables were analyzed using the Cochran-Mantel-Haenszel test, adjusted for investigator. Continuous variables were analyzed using an

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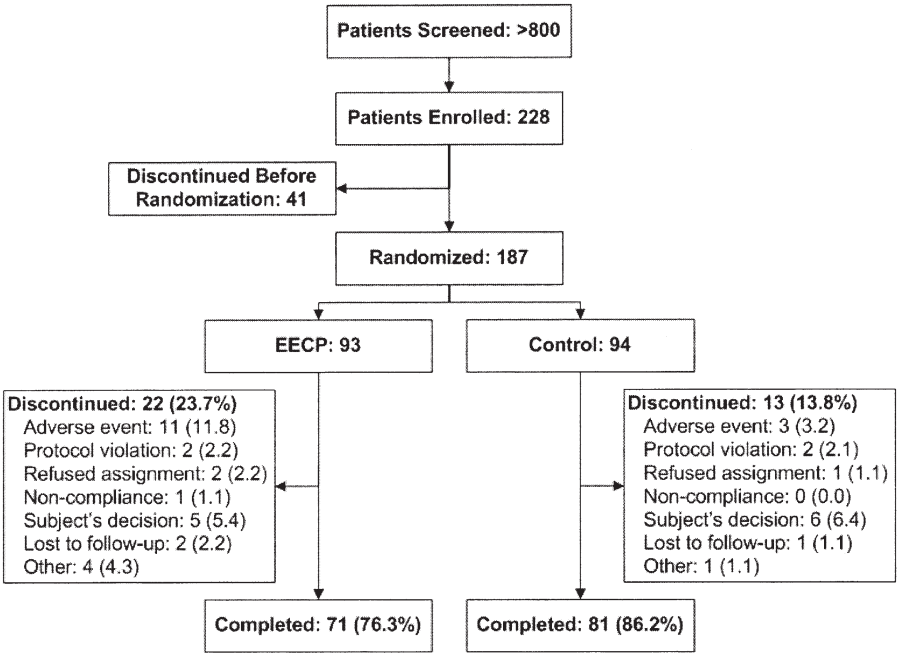

Figure 1. Enrollment and follow-up of patients in the PEECH study. EECP = enhanced external counterpulsation.

analysis of variance, with treatment as a main effect and investigator as a blocking factor. Treatment by investigator interaction was tested at the 0.1 level of significance. The treatment comparison of the 2 co-primary parameters (exercise duration and peak Vo_2) was made according to Hochberg's closed testing procedure (13), with control of the overall type 1 error at 0.05.

Assumptions with respect to the sample size have been described previously (11). The trial was designed to detect at least a 60-s increase from baseline in 50% of EECP patients compared with 20% of control patients and a 1.25 ml/min/kg increase in peak Vo_2 in 50% of EECP patients compared with 30% of control patients. Under these design assumptions, the study had a 90% power to detect a statistically significant difference at the 0.025 level of significance and was designed to be positive if there was a statistically significant difference in either primary end point at the 0.025 level or in both end points at the 0.05 level.

The study was managed by an independent coordinating center (Anabase International Corporation, Stockton, New Jersey) who performed the statistical data analysis. The sponsor had no role in the data collection or analysis. A steering committee oversaw the scientific and clinical aspects of the study. Exercise data were conveyed to an independent core laboratory where study quality and data results were analyzed. Medical staff at the coordinating center were trained to assess the quality of data and tracings from the cardiopulmonary exercise tests and, together with the core laboratory, monitored performance of the testing and instructed sites to repeat when necessary to obtain a fully evaluable test. A data and safety monitoring board oversaw all safety aspects of the study, and an independent clinical end-points committee classified adverse events. The study was approved by the institutional review board of each participating center and was conducted according to the Declaration of Helsinki.

RESULTS

Between March 2001 and February 2004, 187 patients were randomized (93 to EECP and 94 to PT alone) (Fig. 1). There were no significant differences in baseline variables or background therapy between the 2 treatment groups

Table 1. Baseline Patient Characteristics*

Characteristics	EECP	PT Control
Number of patients	93	94
Men, n (%)	72 (77.4)	71 (75.5)
Race, Caucasian, n (%)	76 (81.7)	75 (79.8)
Age (mean yrs, SD)	62.4 (11.7)	63.0 (10.4)
Etiology, ischemic, n (%)	64 (68.8)	66 (70.2)
NYHA, n (%)		
Functional class II	60 (64.5)	62 (66.0)
Functional class III	33 (35.5)	32 (34.0)
Heart rate, beats/min (SD)	70.7 (11.2)	70.6 (12.0)
Blood pressure, mm Hg (SD)		
Systolic	116.7 (17.7)	114.8 (18.4)
Diastolic	70.9 (10.2)	70.8 (10.8)
LVEF, mean % (SD)	25.9 (6.1)	26.7 (6.5)
Number of patients completing protocol	80	84
Exercise duration, s (SE)	610.6 (27.8)	570.9 (26.1)
Peak Vo_2, ml/kg/min (SE)	14.7 (0.4)	14.1 (0.4)
RER (mean, SE)	1.04 (0.01)	1.04 (0.01)
VE, l/min	47.9 (1.8)	46.9 (1.6)
Borg scale score, mean (SE)	16.7 (0.2)	16.6 (0.2)

*There was no significant difference between groups.

EECP = enhanced external counterpulsation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PT = protocol-defined pharmacologic therapy; RER = respiratory exchange ratio; VE = minute ventilation; Vo_2 = volume of oxygen uptake; + = sitting blood pressure.

Table 2. Protocol-Defined Pharmacologic Therapy Utilization Rate and Dose Equivalents at Baseline*

HF Treatment	EECP	PT Control
ACE inhibitors, n (%)	70 (75.3)	73 (77.7)
Enalapril daily dose equivalent (mg)		
Mean (SD)	11.8 (10.1)	13.5 (9.9)
Median	10	10
ARBs, n (%)	18 (19.4)	18 (19.1)
Losartan daily dose equivalent (mg)		
Mean (SD)	63.2 (42.0)	60.5 (38.5)
Median	50	50
Beta-blockers, n (%)	79 (84.9)	81 (86.2)
Carvedilol daily dose equivalent (mg)		
Mean (SD)	39.4 (29.7)	39.7 (30.1)
Median	25	25

*There were no significant differences between groups.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure. Other abbreviations as in Table 1.

(Tables 1 and 2). Patients were predominantly Caucasian men with NYHA functional class II HF symptoms who had a mean ejection fraction of 26 ± 6%. Utilization rates of background pharmacologic therapy and average equivalent doses at baseline demonstrated compliance with guideline-recommended therapy (Table 2). Although medication changes occurred in individual patients during the trial, there were no significant differences between treatment groups, and average equivalent doses remained the same at each time point. In particular, there were no differences in diuretic dosing during the study (data not shown).

Exercise duration increased by 60 s or more in 35.4% of patients in the group assigned to EECP as compared with 25.3% of patients in the pharmacologic treatment group at the 6-month follow-up visit ($p = 0.016$) (Fig. 2). By contrast, the percentage of subjects who demonstrated an increase in peak V_{O_2} of ≥1.25 ml/kg/min did not differ between the 2 treatment groups (22.8% vs. 24.1%) at the same visit. EECP treatment was also associated with a significant increase in exercise time at 1 week, 3 months, and 6 months when compared with those patients receiving pharmacologic therapy alone (Table 3). While there was a trend at 1 week and 3 months, EECP did not effect a significant increase from baseline in peak V_{O_2} at any time point. Similarly, there was no change in ventilatory equivalent for carbon dioxide (Ve/VCO_2) at any time point (data not presented). There were no between-group differences in RER or Borg score (overall median = 17) at baseline or any follow-up time points. However, there were differences in ventilatory response at 1 week and 3 months after treatment (Table 3). The benefit of EECP on exercise duration was also evident when data from patients who withdrew from the study were censored at the time of the last visit (data on file). Analysis of site interaction on the primary end points yielded no statistically significant differences. In addition, evaluation of the primary end point at those sites with larger enrollments demonstrated results that were consistent with the overall study results. Consistent with an improvement in exercise time, EECP also effected a significant improvement in NYHA functional class and quality of life. The percentage of patients who demonstrated an improvement in NYHA symptoms was significantly larger in the group receiving EECP than in patients receiving pharmacologic therapy alone at 1 week, 3 months, and 6 months after therapy (Fig. 3). Similarly, EECP effected a statistically significant improvement in quality of life as measured by the MLWHF questionnaire at 1 week and 3 months after completion of EECP therapy, but not at

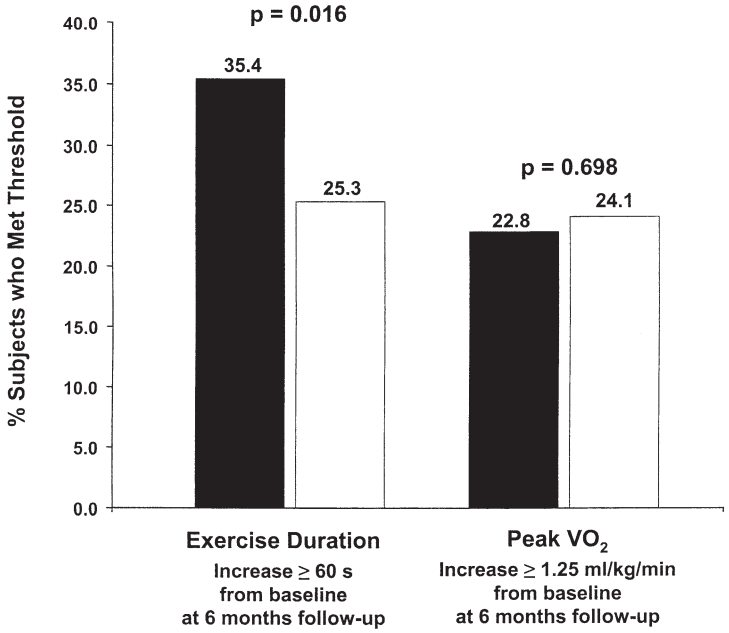

Figure 2. The percentage of patients who had at least a 60-s increase from baseline in exercise duration and the percentage of patients with at least a 1.25 ml/kg/min from baseline at 6 months after treatment (co-primary end points; intent-to-treat analysis, last observation carried forward). V_{O_2} = oxygen uptake. **Solid bar** = enhanced external counterpulsation; **open bar** = control subjects.

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Table 3. Mean Change From Baseline in Exercise Duration and Peak Vo_2

	EECP		PT Control		
	No.	Mean Change ± SE	No.	Mean Change ± SE	p Value*
1-Week Follow-Up					
Change exercise duration (s)	77	26.4 ± 12.2	78	−5.5 ± 11.7	0.010
Ischemic	53	24.6 ± 15.7	54	−16.7 ± 14.2	0.007
Nonischemic	24	30.2 ± 18.3	24	19.9 ± 20.3	0.836
Change in peak Vo_2 (ml/kg/min)	77	0.1 ± 0.3	78	−0.4 ± 0.3	0.071
Ischemic	53	0.2 ± 0.4	54	−0.7 ± 0.4	0.008
Nonischemic	24	−0.2 ± 0.5	24	−0.4 ± 0.5	0.987
Change in RER	77	0.01 ± 0.01	78	0.00 ± 0.01	0.363
Change in VE (l/min)	77	0.4 ± 1.0	78	−2.1 ± 1.0	0.011
3-Month Follow-Up					
Change exercise duration (s)	78	34.5 ± 13.9	82	−7.0 ± 12.7	0.014
Ischemic	54	34.2 ± 17.2	57	−17.3 ± 13.1	0.017
Nonischemic	24	35.4 ± 23.8	25	16.7 ± 28.9	0.741
Change in peak Vo_2 (ml/kg/min)	78	0.2 ± 0.3	82	−0.4 ± 0.3	0.119
Ischemic	54	−0.0 ± 0.4	57	−0.4 ± 0.3	0.122
Nonischemic	24	0.6 ± 0.5	25	−0.2 ± 0.8	0.437
Change in RER	78	0.00 ± 0.01	82	−0.01 ± 0.01	0.252
Change in VE (l/min)	78	0.5 ± 0.9	82	−2.3 ± 1.2	0.010
6-Month Follow-Up					
Change exercise duration (s)	79	24.7 ± 15.2	83	−9.9 ± 13.2	0.013
Ischemic	54	20.6 ± 18.5	57	−25.8 ± 13.9	0.010
Nonischemic	25	33.5 ± 26.8	26	24.7 ± 28.3	0.724
Change in peak Vo_2 (ml/kg/min)	79	−0.3 ± 0.3	83	−0.6 ± 0.3	0.315
Ischemic	54	−0.4 ± 0.3	57	−0.9 ± 0.3	0.115
Nonischemic	25	−0.3 ± 0.5	26	0.2 ± 0.6	0.935
Change in RER	79	0.00 ± 0.01	83	0.00 ± 0.01	0.161
Change in VE (l/min)	79	−0.8 ± 1.0	83	−2.4 ± 1.1	0.094

Intent-to-treat analysis, last observation carried forward. *p value was obtained from analysis of covariance with main effects etiology, investigator, and etiology by investigator, if significant, and covariate baseline value.

Abbreviations as in Table 1.

6 months after treatment (Fig. 3). Analysis of changes in improvement in NYHA functional classification and quality of life did not change when data from patients who withdrew from the study were censored at the time of withdrawal (data on file).

We assessed whether differences existed in response to EECP therapy in patients with HF secondary to either ischemic or nonischemic dilated cardiomyopathy. Albeit, in a relatively small sample size, subgroup analysis based on etiology of disease demonstrated benefit in patients with ischemic cardiomyopathy, while this difference was not seen in the small number of patients with nonischemic disease (Table 3). Similarly, when assessing the effects of EECP on NYHA functional classification, there was a greater proportion of patients showing improvement in the EECP group when compared with those receiving pharmacologic therapy alone at all time points in the group with ischemic disease (1 week: 37.0% EECP vs. 12.7%, $p = 0.004$: 3 months: 34.5% vs. 12.3%, $p = 0.025$; 6 months: 36.4% vs. 15.5%, $p = 0.026$). In addition, quality of life was significantly improved in the ischemic group at 3 months of follow-up (-6.5 ± 3.2 EECP vs. -1.5 ± 2.1 PT, $p = 0.046$) but not at any time point in patients receiving EECP who had a nonischemic etiology. However, no significant differences in the parameters of exercise duration, peak Vo_2, functional classification, or quality of life were detected within treatment assignment subgroups.

We also performed a post-hoc analysis to assess whether any predictors of response to EECP were identifiable. Analysis of co-primary end point responder rates based upon age, gender, race, etiology, NYHA functional classification, LVEF, height, weight, and body mass index above versus below median values were performed. No statistically significant differences were found between responders and nonresponders in the EECP group, while younger age ($p = 0.004$), female gender ($p = 0.006$), higher LVEF ($p = 0.027$), and less weight ($p = 0.027$) predicted response in the control group.

Fewer patients completed the study in the active treatment group (76%) than in the control group (86%), largely due to more patients in the EECP group discontinuing due to an adverse experience (11.8% EECP vs. 3.2% PT). Adverse events that occurred in relation to the application of EECP therapy resulting in discontinuation included sciatica (1 patient), leg pain (1 patient), and arrhythmia, which interfered with application of the therapy (2 patients). One other EECP subject suffered a non–Q-wave myocardial infarction during the treatment period not attributable to

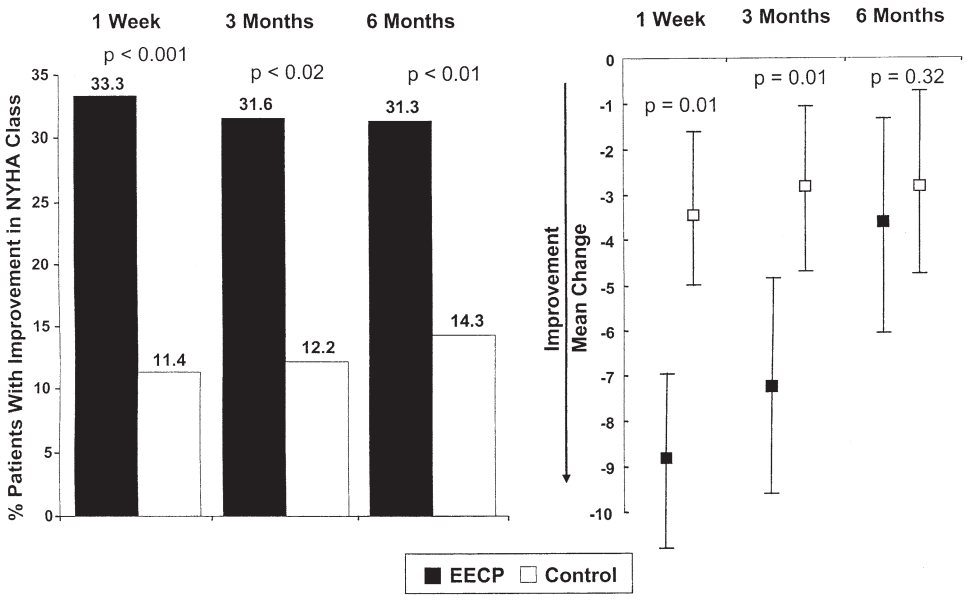

Figure 3. Percentage of patients who improved in their New York Heart Association (NYHA) functional class **(left)** and mean change in quality-of-life score **(right)** at 1 week, 3 months, and 6 months compared with baseline. EECP = enhanced external counterpulsation.

the therapy. During the follow-up period, 6 additional subjects from the EECP group discontinued due to worsening HF (4 patients), biventricular pacemaker implantation (1 patient), and worsening lung cancer (1 patient). Adverse events in the control group leading to discontinuation included 2 deaths during the treatment period and 1 instance of atrioventricular block during the follow-up period.

However, the number of pre-defined clinical events that occurred during the trial was not different between the group of patients who received EECP and those in the control group (Table 4). In addition, the number of adverse events and the number of serious adverse events were equal in the 2 treatment groups. The number of subjects randomized to EECP therapy that experienced any adverse event or a serious adverse event was nearly identical to that in the pharmacologic therapy group. Two patients had serious adverse events that the site investigator attributed to EECP during the treatment period: 1 patient experienced worsening HF while a second patient developed a pulmonary embolism. During the post-treatment period, an additional patient developed a deep venous thrombosis that was attributed by the investigator to EECP. A temporary decrease in oxygen saturation observed by pulse oximetry occurred in 11 (12.4%) subjects in 30 (1%) of 2,859 EECP therapy sessions administered during the trial. Except for 1 case of oxygen desaturation followed by a worsening of HF after the treatment session, all other episodes were reversed by a protocol-mandated brief interruption of the treatment session and improved breathing.

DISCUSSION

The results of the PEECH trial demonstrate that 35 1-h sessions of EECP over a period of 7 weeks benefited patients with mild-to-moderate HF and systolic LV dysfunction who were receiving PT. Enhanced external counterpulsation effected a statistically significant increase ($p = 0.016$) in the percentage of patients exceeding a 60-s improvement in exercise time, making this a positive trial based on the predefined statistical criteria for the primary end-point analysis. However, it must be noted that EECP did not alter the percentage of patients demonstrating an increase of ≥1.25 ml/kg/min in peak Vo_2. Consistent with the improvement in the percentage of patients exceeding a 60-s improvement in exercise time, patients receiving active therapy also demonstrated a modest increase in exercise time when assessed as increase from baseline and an improvement in NYHA HF symptoms. These benefits of EECP were demonstrable after completion of EECP therapy as well as for up to 6 months. The active treatment group also reported an improvement in quality of life that was sustained for 3 but not 6 months. Peak Vo_2, when measured as change from baseline, showed a trend towards benefit in the active treatment group at 1 week and 3 months, but there was not a statistically significant difference between the 2 study groups.

Overall, the use of EECP was well tolerated. Two patients had serious adverse events during the treatment period. One patient had a pulmonary embolism. Because EECP "milks" the vasculature of the lower extremities, this is a recognized side effect and points out that patients at risk for deep venous thrombosis should be carefully evaluated before undergoing EECP therapy and monitored closely during the course of treatment. A second patient experienced worsening HF. This may have been secondary to increased venous load during EECP therapy. A larger number of patients withdrew from the study in the EECP group due to adverse events, most of which were associated

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Table 4. SAEs*

	EECP	PT Control
Subjects with SAEs, n (%)	27 (30.3)	26 (29.5)
Occurring during treatment period		
Subjects with SAEs, n (%)	7 (7.9)	8 (9.1)
SAEs related to treatment		
WHF	1	
Pulmonary embolism	1	
Occurring during follow-up		
Subjects with SAEs, n (%)	21 (23.6)	23 (26.1)
SAEs related to treatment		
WHF		1
Deep venous thrombosis	1	
Pre-defined clinical events	89	88
WHF with IV, n (%)	8 (9.0)	12 (13.6)
WHF with no IV, n (%)	8 (1.1)	4 (2.3)
ACS, n (%)	1 (1.1)	0 (0.0)
MI, n (%)	4 (4.5)	0 (0.0)
Cardiovascular death, n (%)	0 (0.0)	2 (2.3)

*There were no significant differences between groups.

ACS = acute coronary syndrome, non-MI; EECP = enhanced external counterpulsation; MI = myocardial infarction; PT = protocol-defined pharmacologic therapy; SAEs = serious adverse events; WHF = worsening heart failure; WHF with IV = worsening heart failure, hospitalized, requiring IV therapy; WHF with no IV = worsening heart failure not requiring IV therapy.

with the application of EECP. Some patients experienced discomfort that obviated their continued participation. However, it is noteworthy that the number of adverse events or serious adverse events did not differ between the 2 study groups over the course of the trial.

The design of the PEECH trial was influenced by concerns that "sham" EECP altered vascular hemodynamics. Indeed, even low-pressure EECP is associated with a marked increase in right ventricular filling, while not associated with a decrease in peripheral vascular resistance (A.D. Michael, unpublished data, November 2003). Thus, investigators were concerned that "sham" EECP might actually increase the incidence of HF because increased right ventricular loading would not be offset by decreased peripheral vascular resistance. Furthermore, it was observed in the MUST EECP (Multicenter Study of Enhanced External Counterpulsation) trial that changes in exercise time were seen in patients treated with "sham" EECP (4). Thus, we believed that EECP could only be evaluated using an unblinded control group. To obviate bias on the part of investigators, each study site had 2 separate teams, an investigative team and a patient care team, and both patients and coordinators were educated regarding the need for confidentiality between the members of these 2 groups. Furthermore, study coordinators who came into contact with the patient on a daily basis during active treatment were instructed not to address clinical issues with their patients. Thus, assiduous efforts were undertaken to separate the study team from the clinical care team, consistent with the single-blind trial design. That there was consistency across all study centers with respect to protocol mandates was evidenced by the fact that there were no intercenter differences in study results. However, this design may not mitigate against the possibility that daily visits for a period of 7 weeks might have benefited patients in the active treatment group.

The finding that EECP increased exercise time but did not effect a statistically significant change in peak Vo_2 raises an interesting conundrum. One possible explanation for this disparity is that the beneficial effects of EECP in the PEECH study were attributable to a "placebo" effect in the active treatment group in view of the fact that these patients were not blinded to their treatment assignment. The finding that significant improvements in quality-of-life scores decreased over time in the EECP group is also suggestive of a placebo effect. Alternatively, we may have underpowered the trial for a change in peak Vo_2 as there was a trend towards an increase in peak Vo_2 at both 1 week and 3 months, though these trends did not reach statistical significance. Metra et al. (14) recently found that treatment with carvedilol effected a significant improvement in exercise duration without an accompanying change in peak Vo_2 in a small group of optimally medicated patients with predominantly NYHA functional class II to III HF symptoms. It is unlikely that our failure to see a change in peak Vo_2 was due to our selection of thresholds as the thresholds of $\geq$60 s improvement in exercise duration and $\geq$1.25 ml/kg/min improvement in peak Vo_2 were significantly greater than what had been observed in control groups of major HF treatment trials reported before the planning phase of this trial.

In summary, EECP improved exercise tolerance and HF symptoms in patients with NYHA functional class II and III HF who were receiving PT but did not improve peak Vo_2. Because patients were not blinded to therapy, these benefits of EECP may be attributable to a "placebo" effect. However, the usefulness of EECP by physicians must be individualized based on their assessment of the totality of EECP data. Further studies may help elucidate both the mechanism of action and the overall effects of EECP therapy.

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APPENDIX

For a list of the investigators participating in the PEECH study, please see the online version of this article.

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