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# Enhanced External Counterpulsation Improves Exercise Duration and Peak Oxygen Consumption in Older Patients With Heart Failure: A Subgroup Analysis of the PEECH Trial

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ORIGINAL PAPER

# Enhanced External Counterpulsation Improves Exercise Duration and Peak Oxygen Consumption in Older Patients With Heart Failure: A Subgroup Analysis of the PEECH Trial

*The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) trial demonstrated that enhanced external counterpulsation (EECP) therapy increased exercise duration and improved functional status and quality of life without affecting peak oxygen consumption. The authors present data from a prespecified subgroup of elderly patients (65 years or older) enrolled in the PEECH trial. The 2 co-primary end points were the percentage of subjects with a >60-second increase in exercise duration and the percentage of subjects with a >1.25-mL/kg/min increase in peak volume of oxygen consumption. At 6-month follow-up, the exercise responder rate was significantly higher in EECP patients compared with controls (P=.008). Further, in contrast to the overall PEECH study, the EECP group demonstrated a significantly higher responder rate for peak oxygen consumption (P=.017). The authors conclude that an older subgroup of PEECH subjects confirms the beneficial effect of EECP in patients with chronic, stable, mild-to-moderate heart failure. (CHF. 2006;12:307–311)* ©2006 Le Jacq

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Recent studies suggest that the number of patients older than 65 years is increasing and that there is an association between aging and the incidence of heart failure (HF).[1] In addition, the Acute Decompensated Heart Failure National Registry (ADHERE)[2] has demonstrated that in a community-based clinical setting, HF patients are considerably older than those enrolled in clinical trials. Therefore, it is reasonable to assess the effect of an HF trial on the subgroup of elderly patients.

Results of the Prospective Evaluation of Enhanced External Counterpulsation in the Treatment of Heart Failure (PEECH) trial[3] have recently been reported. The combination of protocol-mandated pharmacologic therapy (PT) and enhanced external counterpulsation (EECP) increased exercise duration and improved functional status when compared with PT alone in patients with clinically stable HF; however, EECP did not result in an increase in peak oxygen consumption. The mean age of patients enrolled in the PEECH trial was 63 years. Therefore, we assessed whether the effects of EECP in the overall PEECH population could also be observed in patients 65 years and older. This analysis was facilitated by the fact that patients enrolled in the PEECH study had been prospectively randomized within predefined strata based on etiology, age, sex, and medical therapy (use of angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II blockers [ARBs] and β-blockers). This analysis reports the impact of EECP therapy on the 2 co-primary exercise end points in a predefined elderly population.

## Methods

The design and rationale of the PEECH trial have been previously published.[4] Briefly, eligible patients were enrolled at 1 UK center and 28 US centers. Enrollment criteria included New York Heart Association (NYHA) class II or III symptoms secondary to either ischemic or nonischemic (idiopathic) cardiomyopathy, left ventricular ejection fraction ≤35%, and protocol-mandated PT consisting of an ACEI or an ARB and a β-blocker, unless they were not tolerated. Digoxin, diuretics, and other medications used to treat HF could be given at the investigator's discretion. Patients needed to be able to exercise for at least 3 minutes on a

**Table.** Characteristics of the Overall Study Population and Subgroup of Patients 65 Years or Older at Baseline

| | Subgroup (N=85) | | PEECH Overall (N=187) | |
|---|---|---|---|---|
| | EECP | PT | EECP | PT |
| No. of patients | 41 | 44 | 93 | 94 |
| Men, No. (%) | 35 (85.4) | 35 (79.6) | 72 (77.4) | 71 (75.5) |
| Caucasian, No. (%) | 36 (87.8) | 40 (90.9) | 76 (81.7) | 75 (79.8) |
| Age, mean (SD), y | 71.5 (5.2) | 72.0 (5.3) | 62.4 (11.7) | 63.0 (10.4) |
| Ischemic etiology, No. (%) | 35 (85.4) | 36 (81.8) | 64 (68.8) | 66 (70.2) |
| NYHA, No. (%) | | | | |
| Class II | 27 (65.9) | 24 (54.6) | 60 (64.5) | 62 (66.0) |
| Class III | 14 (34.2) | 20 (45.5) | 33 (35.5) | 32 (34.0) |
| LVEF, mean (SD), % | 26.1 (6.3) | 26.8 (6.3) | 25.9 (6.1) | 26.7 (6.5) |
| Patients completing exercise protocol, No. (%) | 37 (90.2) | 44 (100) | 80 (86.0) | 84 (89.4) |
| Exercise duration, s (SE) | 567.3 (39.0) | 529.0 (33.6) | 610.6 (27.8) | 570.9 (26.1) |
| Peak $Vo_2$, mL/kg/min (SE) | 13.6 (0.5) | 13.8 (0.5) | 14.7 (0.4) | 14.1 (0.4) |

Comparisons between groups were performed by analysis of variance for continuous variables or Fisher exact test for categoric variables. No significant between-group difference was observed. Percentages are relative to the subgroup population. PEECH indicates the Prospective Evaluation of Enhanced External Counterpulsation in the Treatment of Heart Failure trial; EECP, enhanced external counterpulsation; PT, protocol-mandated pharmacologic therapy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; and $Vo_2$, oxygen uptake volume.

standard treadmill exercise test (modified Naughton protocol) and not terminate the test for reasons of angina or claudication. Eligible patients were randomized in a 1:1 ratio to treatment with EECP in addition to PT or to PT alone. Patients assigned to EECP received 35 one-hour sessions during 7–8 weeks at a protocol-specified applied pressure of 300 mm Hg reached within 5 minutes of treatment initiation. Patients in both treatment groups were seen at 1 week, 3 months, and 6 months after completion of treatment. Subgroups defined in the study protocol included age, sex, etiology, and NYHA class at baseline.

The 2 co-primary end points were the percentage of subjects with at least a 60-second increase in exercise duration from baseline and the percentage of subjects with at least a 1.25-mL/kg/min increase in peak volume of oxygen consumption ($Vo_2$) from baseline to the 6-month follow-up visit. Peak $Vo_2$ was defined as the oxygen consumption observed at the maximum level of exercise during a standardized treadmill exercise test. Secondary end points included change in exercise duration, peak $Vo_2$, NYHA status, quality of life, and the occurrence of predefined cardiovascular clinical outcomes (death, acute myocardial infarction, exacerbation of HF that required intervention or hospitalization) during the treatment phase and the 6-month follow-up period. A core exercise laboratory, blind to treatment allocation and sequence, generated the results from raw exercise data used in this analysis. Sites were instructed to repeat tests when necessary to obtain a fully evaluable test. NYHA 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 Questionnaire (MLHFQ).[5] Lastly, an independent clinical end points committee classified adverse events.

Statistical methods applied to this subgroup analysis were the same as those applied in the study overall, with additional comparisons made between the subgroups. Primary analysis was by intent-to-treat with last observation carried forward, and results were verified in a secondary analysis using observed case data. The primary parameters were analyzed by logistic regression with treatment as a main effect. The baseline value of the parameter and the size were used as covariates. Other variables were analyzed using the Cochran-Mantel-Haenszel test adjusted for investigator. Continuous variables were analyzed using an analysis of variance, with treatment as a main effect and investigator as a blocking factor. The study was not powered prospectively for any of the subgroups considered, although these subgroup analyses were intended.

The study was approved by the Internal Review Boards of each participating center and was conducted according to the Declaration of Helsinki. All patients were enrolled in the trial after giving written informed consent.

## Results

**Study Population.** The PEECH study population has been previously described.[1] Baseline characteristics of the study population overall and of the subgroup of patients 65 years or older are provided in the Table. There were no significant differences between groups at baseline in the overall population. Characteristics of the 65 years and older subgroup were similar to the population overall, with the exception of older age (72 vs 63 years) and a higher likelihood of an ischemic etiology (83% vs 69%). Use of protocol-mandated cardiovascular medications was high (ACEI or ARB, 92.9%; β-blocker, 81.2%), consistent with the PEECH trial as a whole (ACEI or ARB, 95.5%; β-blocker, 85.4%), with

no difference observed between treatment groups in the subpopulation in the use of ACEIs or ARBs (data on file, Anabase International Corp). The median daily dose for ACEIs was 10 mg (enalapril equivalent) and for ARBs was 50 mg (losartan equivalent) in both the overall study population and in the subgroup. β-Blockers were used at lower doses in subjects aged 65 and older relative to the study population overall (median daily dose, 25 mg vs 50 mg [carvedilol equivalent], respectively).

**Exercise Duration.** The effect of EECP on exercise duration was assessed first by comparing the number of subjects who increased exercise duration by 60 seconds or more at follow-up compared with baseline ("responders"). In addition, the changes in exercise duration from baseline to follow-up were compared. The responder rate among subjects aged 65 years or older was significantly higher in the EECP group compared with the PT group at 6-month follow-up ($P=.008$) (Figure 1). Changes in exercise duration from baseline to follow-up were significantly greater in EECP compared with PT over the follow-up period. Between-group differences strengthened over time, as exercise duration increased at all time points in the EECP group, while it decreased progressively in control subjects (Figure 2).

**Peak $Vo_2$.** In contrast to the overall population in the PEECH trial, older subjects randomized to EECP demonstrated a significantly higher responder rate at 6-month follow-up ($P=.017$) (Figure 1). Changes from baseline were significant in older subjects treated with EECP compared with those receiving PT alone at 3- and 6-month follow-up ($P=.086$, $P=.020$, and $P<.001$ at 1 week, 3 months, and 6 months, respectively) (Figure 3).

**NYHA Class.** More subjects in the 65-or-older subgroup had improved NYHA class with EECP (35.1%, 40.5%, and 37.8%) compared with PT (9.8%, 9.1%, and 15.9%) at 1 week, 3 months, and 6 months, respectively, a difference that reached statistical significance at the 1-week and 3-month follow-up visits but not at the 6-month visit ($P=0.042$, $P=0.046$, and NS, respectively).

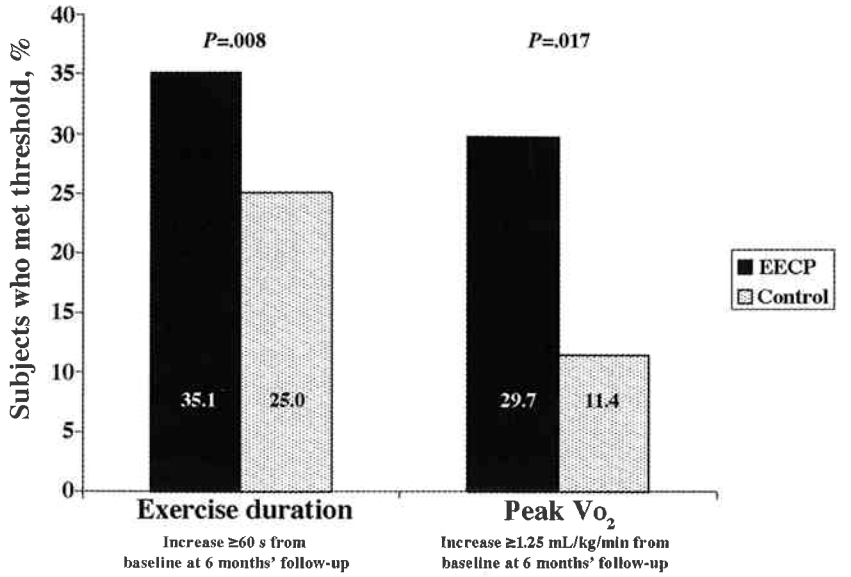


**Figure 1. The percentage of patients 65 years or older who had at least a 60-second increase from baseline in exercise duration, and the percentage of patients who had at least a 1.25-mL/kg/min increase from baseline at 6 months posttreatment (co-primary end points). EECP indicates enhanced external counterpulsation; control, protocol-mandated pharmacologic therapy; and $Vo_2$, oxygen uptake volume.**

**Quality of Life: MLHFQ.** Changes in MLHFQ total score did not differ statistically between treatment groups in the 65-or-older subgroup at any time point.

**Safety.** The safety profile of EECP in this subgroup of older subjects was internally consistent with the results in the overall study population. Specifically, nonserious adverse events were more frequent in the EECP group. This difference is directly related to skin and musculoskeletal adverse experiences, which are known to occur with EECP therapy. Serious adverse experiences tended to affect fewer subjects in EECP relative to PT (12 or 29.3% vs 16 or 36.4%, respectively) regardless of the attributed causality. One serious adverse experience was reported as definitely related to EECP: a worsening of HF in a 72-year-old man with ischemic HF. Clinical events adjudicated by the PEECH clinical events committee occurred at similar frequency in both study groups.

## Discussion

The results of this analysis showed that the addition of EECP therapy to protocol-mandated PT produced significant differences favoring EECP in both exercise duration and peak oxygen consumption response rates at 6-month follow-up in subjects aged 65 or older. In contrast, in the overall study population, the response rates were significantly different for exercise duration but not for peak oxygen uptake.

Changes from baseline of both exercise duration and peak oxygen consumption in patients 65 years or older demonstrated a trend at 1 week and were significant at 3- and 6-month follow-up visits. In the overall study population, the change in exercise duration was significant at all follow-up time points, while change in peak oxygen consumption showed a trend favoring EECP at 1 week, with no difference at 3 and 6 months.

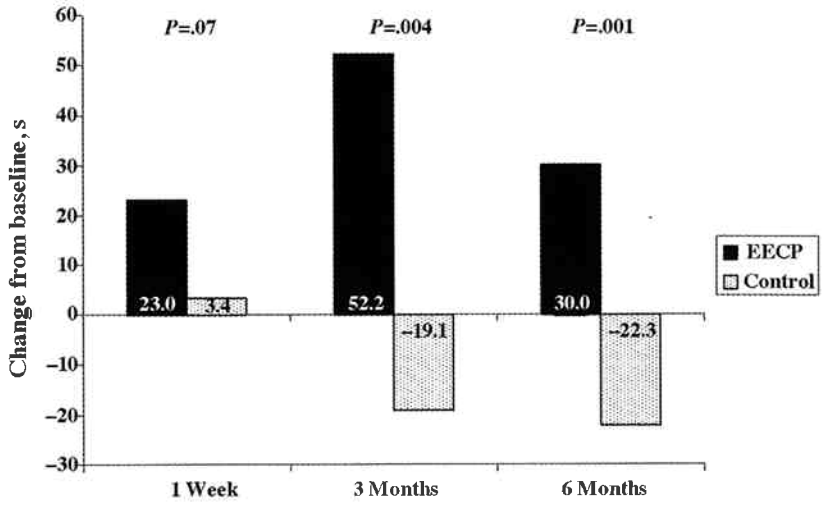


**Figure 2. Mean change in exercise duration in patients 65 years or older at 1 week, 3 months, and 6 months following completion of treatment compared with baseline. EECP indicates enhanced external counterpulsation; control, protocol-mandated pharmacologic therapy.**

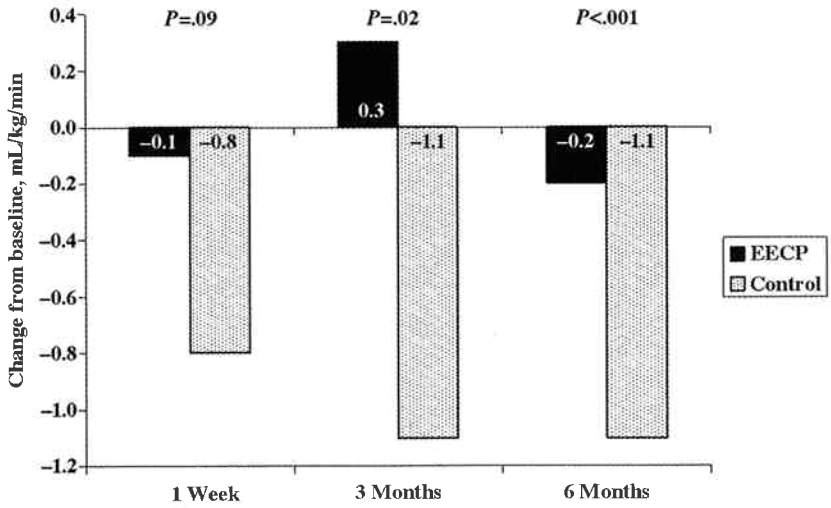


**Figure 3. Mean change in peak oxygen consumption in patients 65 years or older at 1 week, 3 months, and 6 months following completion of treatment compared with baseline. EECP indicates enhanced external counterpulsation; control, protocol-mandated pharmacologic therapy.**

Improvements in NYHA status in patients 65 or older were consistent with those seen in the overall study population (ie, significant differences favoring EECP were seen at all time points). Improvements in quality of life as assessed by MLHFQ scores were significant at 1 week and 3 months in the overall population, but were not significant in patients aged 65 or older. Lastly, no between-group differences were seen in the occurrence of serious adverse events, and the safety profile of EECP was similar when comparing the subgroup with the overall population in the PEECH study.

Thus, in contrast to the overall trial, more patients had improved peak $Vo_2$ in the EECP group than in the control group. Further, after 6 months of follow-up, EECP improved exercise duration and maintained peak oxygen consumption compared with the continuing deterioration observed in control subjects. These findings suggest an additional beneficial effect of EECP in older patients. Potential explanations for this difference in effect may be that the older patients had lower baseline exercise capacity (both in terms of time walked and peak $Vo_2$), thereby making it easier to demonstrate benefit of an intervention. Further, EECP patients in the older group, who had more ischemic heart disease than the overall study population, may have benefited disproportionately from treatment with EECP. Prior research, including recent investigations, has illustrated both cardiac and peripheral mechanisms through which patients with obstructive coronary artery disease may achieve symptomatic and functional improvements with EECP.[6–8]

Previous investigations have reported on the effects of EECP in patients with obstructive coronary disease and left ventricular dysfunction as well as in elderly patients undergoing EECP for treatment of angina. Soran and colleagues[9] showed that in patients with left ventricular dysfunction enrolled in the International EECP Patient Registry, EECP provided significant improvements in angina class, nitroglycerin use, and quality of life. During a 2-year follow-up, major adverse cardiovascular event-free survival was 70%, and 81% of patients reported no congestive HF event. Linnemeier and colleagues[10] compared results obtained in octogenarians enrolled in this registry with those obtained in younger patients and found that in the elderly patients, 76% achieved a reduction in angina class, while angina episodes decreased on average from 8 to 2 per week, and quality-of-life measures improved significantly. Patients in this elderly population were somewhat less likely to complete a full course of EECP compared with younger patients (76% vs 84%), but in those who completed therapy, benefit was sustained in 81% at 6 months and the rate of cardiac hospitalization was lower in the elderly group.

Few reports to date have focused on changes in exercise performance in older patients with chronic HF, particularly in those receiving current guideline-recommended medical therapy. Gullestad and associates[11] reported the effects of controlled-release/extended-release metoprolol on exercise tolerance in a substudy of the Metoprolol Randomised Intervention Trial in Heart Failure (MERIT-HF). Long-term treatment in patients with NYHA class II–IV HF and an ejection fraction ≤40% resulted in significant reductions in heart rate at peak exercise after 3 and 12 months of therapy compared with placebo, but peak $V_{O_2}$ appeared to decline slightly after 3 months and remained unchanged from baseline with no difference between groups at 1 year. O'Neill and colleagues[12] evaluated the effects of captopril as an adjuvant to diuretic and digoxin therapy in older HF patients and showed a trend but no significant changes in measures of walking performance, with no changes in oxygen consumption, ventilation, or ratio. More recently, perindopril improved 6-minute walking distance compared with placebo in patients with left ventricular systolic dysfunction in a randomized trial of elderly patients with NYHA class I–IV HF; however, while small improvements in quality-of-life questionnaire scores (36-item short form, MLHFQ) were seen in both active and control groups after the 10 weeks of treatment, they did not reach significance.[13]

The results of this subgroup analysis are consistent with the overall results of the PEECH trial. Both analyses show that EECP in addition to optimal PT provides functional benefits compared with PT alone in patients with chronic systolic HF; however, as a subgroup analysis, these data must be interpreted with caution. They are best used to further understand the totality of the PEECH results as well as to identify potential subgroups in which further study would be warranted.

In conclusion, this analysis of an older subgroup of PEECH subjects confirms the beneficial effect of EECP in patients with chronic, stable, mild-to-moderate HF. Further, it also appears as safe and well tolerated in this older group as in the overall PEECH population. The results of this subgroup analysis, consistent with prior experience, indicate that adjunctive use of EECP therapy in chronic, stable systolic HF provides functional benefit to older patients. Additional research in this targeted population would further elucidate its optimal role.

Disclosures: *Dr Varricchione is an employee of Vasomedical, Inc; Dr de Lame is a consultant for Vasomedical, Inc; and Drs Silver and Feldman have served as consultants for Vasomedical, Inc.*

*Appendix: The following centers and investigators participated in the PEECH trial: Steering Committee: A.M. Feldman (Chair); M.A. Silver; G.S. Francis; W.W. Parmley; P-A. de Lame; T. Varricchione. Data and Safety Monitoring Board: E. Rapaport (Chair); S. Goldstein; T. Ryan. Exercise Core Laboratory: M.B. Higginbotham. Clinical End Points Committee: M.A. Pfeffer. Data Coordination and Analysis: P-A. de Lame; M. Lemaire; D. Rom. Investigators: C.W. Abbottsmith; B.L. Fleishman; E.C. Lozner; J.C. Lafferty; J.G.F. Cleland; N.K. Vijay; O. Soran; M.A. Silver; C.A. Sueta; E.M. Guarneri; M.H. Yamani; N.H. Erenrich; A.L. Murphy; C.P. Fitzgerald; R.R. Arora; A.B. Raisingahani; B.A. Bart; B.F. Levy; S.W. Restaino; R.M. Siegel; A.C. Rabinowitz; K.M. Coy; K.D. Kronhaus; K.P. Newman; A.L. Heroux; G.C. Fonarow; H.H. Weitz; J.S. Simonson; A.L. Clavell. Study Coordinators: R.M. Kelly; K.S. Manzo; J.D. Furrow; L.S. Ferrara; J.F. Cook; M. Washam; C.A. Melegari; H.C. Lonergan-Thomas; L.L. Davis; D.M. Gilligan; S.M. Rydzinski; L.M. Herlan; V.M. Oehmann; B.B. Wall; C. Rogers; C.E. Judd; L.L. Berndt; K.A. English; M.M. Jones; B.D. Allen; P.A. Bielke; K.C. Minguez; S.A. Creamer; M. Nelson; C. Downer; J.W. Creaser; K. Keefe-McAllister; A.B. Antolick; A.L. McNallan.*

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