

Treating Heart Failure With Enhanced External Counterpulsation (EECP): Design of the Prospective Evaluation of EECP in Heart Failure (PEECH) Trial

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ABSTRACT

Background: Enhanced external counterpulsation (EECP) treatment can improve exercise tolerance in patients with ischemic heart disease; however, the possible benefits of EECP in patients with stable heart failure (HF) and left ventricular dysfunction (LVD) are unclear. An open pilot study showed significant increases in exercise tolerance in HF patients undergoing EECP. Thus a larger, controlled study of EECP in patients with stable HF (New York Heart Association [NYHA] classes II and III) and LVD was undertaken.

Methods and Results: The PEECH trial is a controlled, randomized, single-blind, parallel-group, multicenter study of 187 patients with symptomatic but stable HF (NYHA classes II and III) and an LV ejection fraction $\leq 35\%$ was designed to assess the efficiency of EECP in patients with stable HF. Medical therapy is optimized in all patients based on the recommendations of the Heart Failure Society of America ("Usual Care"), and then randomized between 2 treatment groups; UC or EECP (35 hours over 7 weeks).

Conclusion: Efficacy measures include standard exercise tolerance tests on a treadmill (modified Naughton protocol), with measurements of peak oxygen uptake and exercise duration time; quality of life questionnaires; NYHA classification; and neurohormonal markers of HF.

Key Words: Enhanced external counterpulsation, heart failure, clinical trial.

Heart failure is a disease of epidemic proportions in the United States, affecting more than 5 million patients and causing nearly 500,000 deaths each year.¹ Although standard therapy has substantially decreased 1-year mortality and hospitalization rate, this disease is still associated with a substantial morbidity and mortality.¹

Recently, enhanced external counterpulsation (EECP) improved exercise tolerance in patients with angina and normal left ventricular function.² However, a subsequent voluntary patient registry including nearly 5000 subjects suggested that EECP was also beneficial in patients with compromised left ventricular function.³ Furthermore, a small pilot study

in patients with heart failure secondary to both ischemic and nonischemic dilated cardiomyopathy demonstrated an improvement in exercise capacity, quality of life, and functional status with few adverse effects.⁴ Thus the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) trial was designed to test the efficacy of this novel therapy in a single-blind, randomized, controlled clinical trial.

This article describes the design and discusses the methodology of the PEECH trial.

Study Design

The PEECH trial is designed to evaluate EECP as an adjunctive therapy to guideline-mandated medical care. It is a controlled, randomized, single-blind, multicenter study of patients with symptomatic mild-to-moderate heart failure (New York Heart Association [NYHA] class II-III) and a left ventricular ejection fraction (LVEF) of 35% or less. Subjects must be clinically stable, with minimal or no edema, and, before enrolling, must be receiving heart failure therapy in compliance with the Practice Guidelines of the Heart Failure Society of America.⁵ Before enrolling, all study candidates must be taking an angiotensin-converting enzyme inhibitor and a β -blocker for at least 1 and 3 months, respectively,

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unless these drugs are not tolerated. Eligible patients are randomized in a 1:1 ratio between EECP (active group) and “Usual Care” (UC) (ie, continuation of baseline treatment compliant with Heart Failure Society of America guidelines as discussed previously). Follow-up visits occur at 1 week, 3 months, and 6 months after treatment in the EECP group. UC subjects are seen at the same time points, starting 8 weeks after randomization to keep all study subjects on the same timeline (Fig. 1).

The PEECH trial is being conducted in compliance with the Declaration of Helsinki and applicable regulations. All subjects sign an informed consent before any study procedure being performed.

Study Procedures

Eligibility criteria are summarized in Table 1.

Treatment Assignment

Eligible subjects are randomized by the coordinating center. Subjects are stratified according to etiology of heart failure (ischemic or idiopathic), age, gender, treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and treatment with a β -blocker. Subjects assigned to EECP undergo 35 hours of therapy, in 35 1-hour sessions over 7 to 8 weeks. EECP uses 3 sets of pneumatic cuffs wrapped around the lower limbs and buttocks. The cuffs are inflated sequentially upward at the onset of diastole, and released rapidly and simultaneously at the onset of systole. The protocol-specified applied pressure is 300

mm Hg, to be reached within 5 minutes of the initiation of treatment. Pulse oximetry is monitored continuously during the treatment session, and the subject’s clinical condition must be reevaluated if oxygen saturation drops by 4% or more. Treatment is continued if the investigator is satisfied that the subject’s clinical status is satisfactory. Subjects assigned to UC are instructed to contact study personnel at any time regarding their condition and scheduled to return for their first follow-up visit 8 weeks after randomization.

Exercise Tolerance Testing

The exercise tolerance test is standardized across all participating centers, and study sites must complete 2 qualifying exercise tests successfully before enrolling study patients. Subjects undergo testing using a modified Naughton protocol on standard, calibrated treadmill equipment with cardiopulmonary testing capability.

A 12-lead electrocardiogram and vital signs are monitored throughout the exercise tolerance test, and oxygen uptake is measured continuously. Oxygen is sampled on a breath-by-breath basis, and peak oxygen uptake is measured. Peak oxygen uptake (peak VO_2) is defined as the oxygen consumption observed at the maximum level of exercise that a given subject can achieve. Criteria are established to ensure that exercise tests reach the maximum capacity for each subject, including respiratory ratio >1 , Borg scale at 14 or above (on a 6 to 20 scale), and observation of the anaerobic

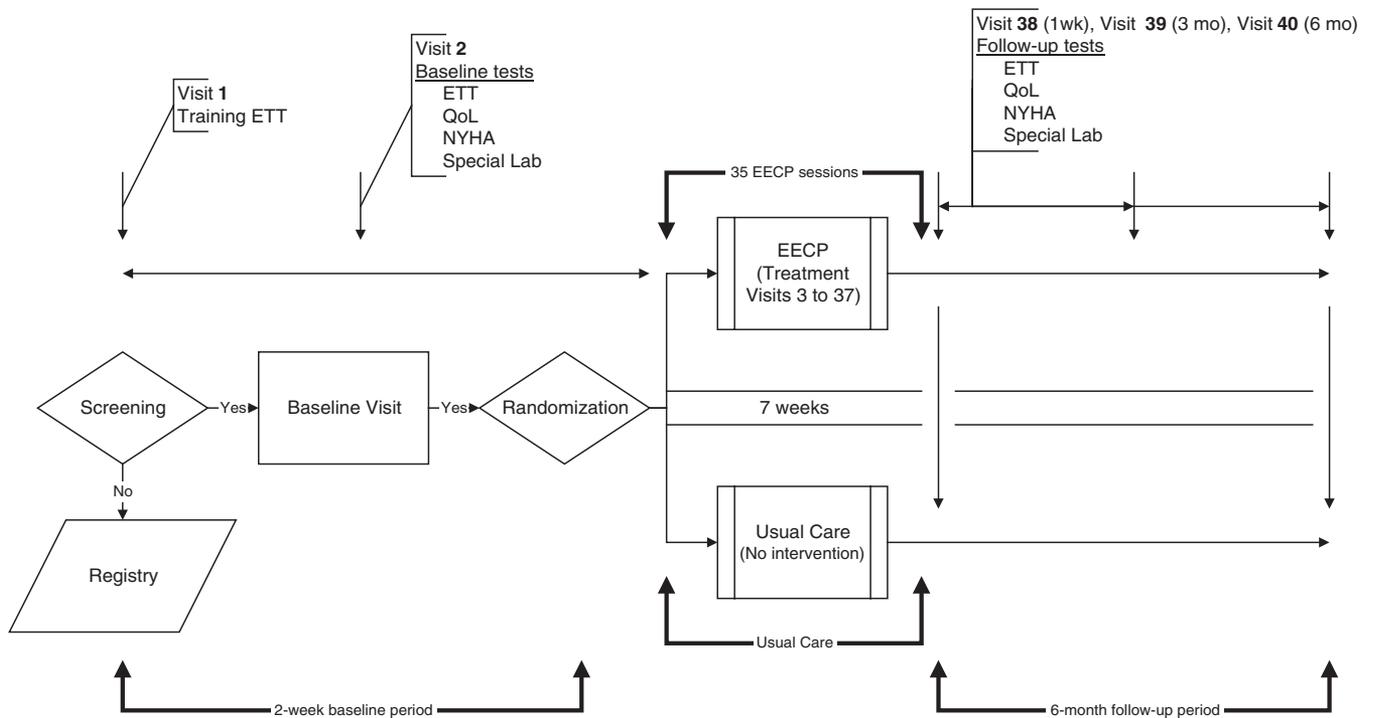


Fig. 1. Study design and flowchart.

Table 1. Eligibility Criteria**Inclusion Criteria**

Heart failure secondary to ischemic heart disease or idiopathic dilated cardiomyopathy, with LVEF $\leq 35\%$ as assessed within 3 months prior to enrollment. NYHA class II or III.

Ability to exercise for 3 minutes or more, the exercise being limited only by symptoms of heart failure.

Clinically stable condition as shown by no change in heart failure medication for 2 weeks prior to randomization.

Less than 1+ edema, no more than trace/ankle edema.

If applicable, digoxin level ≤ 1.75 nanogram/ml.

Serum creatinine ≤ 2.5 mg/dl.

Treated with ACE inhibitor for ≥ 1 month prior to enrollment.

Treated with a stable dose of beta-blocker for ≥ 3 months prior to enrollment.

Exclusion Criteria

Acute coronary syndrome < 6 weeks prior to enrollment.

Non-bypassed left main coronary with a luminal stenosis $\geq 50\%$.

CABG < 3 months, PCI < 6 months prior to enrollment.

Cardiac catheterization < 2 weeks prior to enrollment.

Arrhythmias that would significantly interfere with the triggering of the EECF device.

COPD with a forced expiratory volume at 1 second (FEV1) ≤ 1.5 L.

Clinically significant valvular heart disease, acute myocarditis.

ICD if it has been triggered < 3 months prior to enrollment.

History of deep vein thrombosis, phlebitis, stasis ulcer and/or pulmonary embolism, aortic aneurysm.

INR ≥ 2.5 .

Uncontrolled hypertension (SBP ≥ 180 mmHg, DBP ≥ 110 mmHg).

Any medical, psychological, cognitive, social or legal condition that would interfere with the ability of the patient to give an Informed Consent and/or his or her capacity to comply with all study requirements, including the necessary time commitment.

Participation as a subject in any clinical intervention study, in the past 30 days.

Women who are pregnant, or are of childbearing potential and do not follow a medically valid method of contraception.

Prohibited Medications

In idiopathic cardiomyopathy: calcium channel blockers

In ischemic cardiomyopathy: calcium channel blocker if initiated < 1 month or withdrawn < 3 months prior to enrollment, beta blocker if blockers if initiated or withdrawn < 3 months prior to enrollment.

Ongoing or expected treatment with injectable inotropic agents including dobutamine.

threshold before exercise completion. All data analysis is performed by a core exercise laboratory.

Other Parameters

Quality of life is assessed using the SF-36⁶ and Minnesota Living With Heart Failure⁷ instruments. NYHA classification is assessed by a blinded investigator who also performs physical examinations at each evaluation visit (baseline and follow-up). Modifications in medical therapy and adverse experiences are collected. Adverse experiences defined as PEECH study outcomes, including worsening of heart failure, acute coronary syndromes, stroke, resuscitated sudden death, and death, are evaluated by a clinical endpoint committee. Selected circulating markers and standard safety laboratory tests are performed at baseline, and at 1 week and 6 months after treatment.

Blinding

Staff members responsible for evaluating study subjects at baseline and follow-up visits are blinded to treatment allocation, as are the various core laboratories. Each study site must designate blinded investigators before study initiation. Study files are also organized to preserve blinding at the study site. Other personnel, including study coordinators, are defined as "open investigators." Study coordinators are

responsible for monitoring compliance with study procedures, including blinding. Open coinvestigators are responsible for pre- and posttreatment clinical examinations, for assessing adverse experiences, and for providing needed medical care. No direct contact between blinded personnel and study subjects is to occur outside of the evaluation. Core laboratories, in particular the exercise core laboratory, are kept unaware of the site, subject, and sequence of the exercise tests.

Subjects assigned to EECF are seen every treatment day during the treatment period, whereas those assigned to UC are not. To prevent this imbalance from affecting the interpretability of the study results, and to ensure that all study subjects are treated equally in regard to medical care during that period, study coordinators refrain from volunteering medical advice to EECF subjects. Study coordinators also contact UC subjects weekly to afford them opportunities for reporting on their condition and interacting with study personnel. Patients are also instructed not to inform the investigator of their study group.

Statistical Considerations

The primary time point for analysis will be at the 6-month follow-up. Secondary analyses will be conducted to assess changes from baseline to the 1-week follow-up and

changes from baseline to the 3-month follow-up. All statistical tests will be 2-sided with a significance level of 0.05, unless stated otherwise.

Efficacy Parameters

The primary parameters include the percent of subjects with at least 1.25 mL/min/kg increase in peak VO_2 , and percent of subjects with at least a 60-second increase in exercise duration from baseline. Secondary parameters consist of change in peak VO_2 , in exercise duration and in submaximal exercise parameters, in quality of life scores and NYHA class, in circulating markers, in selected cardiovascular medications, and in the occurrence of cardiovascular clinical outcomes.

Analytical Methods

The primary population for efficacy analysis will be the intent-to-treat population. A secondary analysis will be conducted on the per-protocol population. Patients who drop out of the study will be handled in 2 ways. The primary analysis will be on data carried forward from all postbaseline visits (last observation carried forward analysis). A secondary analysis will not replace missing data (observed case analysis).

For categorical variables, efficacy parameters will be analyzed using the Cochran-Mantel-Haenszel test, adjusted for investigator. Continuous variables will be analyzed using an analysis of variance, with treatment as a main effect and investigator as a blocking factor. Treatment by investigator interaction will be tested at the 0.1 level of significance and, if found significant, the nature of the interaction will be explored further. If it appears that the assumptions of homogeneity of variance or normality are not met, nonparametric tests will be used instead of the analysis of variance. The treatment comparison of the 2 primary parameters (peak VO_2 and exercise duration) will be made according to Hochberg's closed testing procedure, with control of the overall type one error at 0.05. A secondary analysis using O'Brien's global test procedure will be done on the changes from baseline in peak VO_2 , exercise duration, and quality of life (SF-36 and Minnesota Living With Heart Failure total scores).

Sample Size and Power Statement

A sample size of 72 patients per group will give 90% power for a statistically significant difference at the 0.025 level of significance, assuming that 60% of subjects treated with EECP will have at least a 1.25 mL/min/kg increase in peak VO_2 compared with 30% of UC patients. This sample size also provides 90% power to detect a statistically significant difference between EECP and UC subjects in exercise

duration increase from baseline, assuming that 50% of EECP patients will have at least a 60-second increase from baseline compared with 20% of UC patients. To account for a 20% dropout rate, about 90 patients per group will be enrolled.

Study Organization

A steering committee oversees the overall direction of the study and manages the project from a clinical and scientific standpoint. The coordinating center provides day-to-day supervision of all aspects of this multicenter study, including randomization procedures, data collection and management, and site monitoring. Centralized core laboratories are used for exercise testing, safety laboratory tests, and circulating markers. A data safety monitoring board oversees all safety aspects of the study and is informed immediately of any adverse effect considered serious by the investigator or the centrally based clinical monitor. The data safety monitoring board can recommend changes to the protocol and withdrawal of individual patients, and establishes rules under which the trial may be halted on safety grounds. An independent clinical endpoints committee classifies adverse effect information into clinical outcomes and this classification is reviewed by the clinical monitor before being entered into the database.

Discussion

An important issue that arose in designing the PEECH trial was identification of the appropriate treatment strategy for the control group. In an earlier study of EECP in patients with coronary artery disease (ie, MUST-EECP),² the "control" population received sham EECP, "sham" being defined as suboptimal counterpulsation (75 mm Hg applied pressure, which is too low to reduce afterload). However, sham EECP was believed to be contraindicated in a heart failure population. First, there was a potential risk of causing symptoms of right heart failure or pulmonary edema as a result of sham EECP increasing venous return to the right heart without an accompanying decrease in afterload. Second, because of increased awareness among patients regarding the treatment protocols for EECP and the availability of a significant amount of information for the lay public on EECP-related web sites, it was felt that patients would be able to recognize whether or not they were receiving active therapy. Finally, studies have suggested that even low-pressure inflation could produce changes in vascular function and platelet activation, resulting in some salutary benefits at a suboptimal level of inflation. Taken together, these findings led to the use of a UC group as the control population. However, this approach required careful blinding of the investigational team.

The challenge created by choosing a UC group as the control population for the PEECH trial raised issues that

were not dissimilar from those that arose in the design of recent studies assessing the efficacy of devices in the heart failure population, including resynchronization therapy and implantable cardiac defibrillators.⁸ However, unlike studies that assessed the efficacy of implantable devices, we blinded the study investigators to the treatment randomization of each patient by separating the clinical team that provided the protocol-mandated study assessment from the physician team providing routine cardiac care. Such blinding was far more difficult in patients receiving device therapy, because each patient receiving the device had an obvious surgical scar. In the multicenter device studies, the primary endpoint was mortality or hospitalization, objective endpoints that could not be biased by individual physician investigators. By contrast, the endpoints of the PEECH trial required physician input or could be influenced by inherent bias on the part of study personnel at the time of exercise testing, so that a more conservative blinding protocol was required and provided. However, the study design cannot ensure that patients do not inform the investigator of their study group or the frequent visits have an impact or a “placebo” effect, both of which might bias the results of the study. Therefore, we will interpret the data from the study with caution. In addition, to further balance against potential bias, we will carefully assess all secondary study endpoints as part of the overall evaluation of this study. These secondary endpoints will include changes in medical therapy and change in the expression of neurohormonal markers and will thus provide objective data that should not be influenced by a placebo effect—particularly over the 6-month follow-up period.

A final concern was that patients not assigned to EECp treatment seemed unlikely to accrue any form of benefit from their enrollment in the PEECH trial. However, each patient was carefully evaluated to ensure that their care was optimized before their enrollment (ie, that they were receiving all guideline-recommended medications for the care of patients with chronic heart failure).⁵ Furthermore, each patient in the UC arm underwent frequent study visits and was routinely contacted by the study nurse—disease management strategies that have been found to be of benefit in patients with heart failure. Thus patients enrolled in the UC arm of the study received a level of care that was in all likelihood superior to that which they might receive outside the context of the study.

In summary, PEECH is a multicenter, randomized, single-blind, controlled trial assessing the utility of EECp as adjunct treatment in the management of patients with heart failure secondary to both ischemic and nonischemic dilated cardiomyopathy. PEECH was designed to provide a substantive evaluation of the efficacy of EECp in improving functional performance and quality of life in a group of patients with mild to moderate symptoms of heart failure despite optimal medical therapy. Important elements of the PEECH

Trial design include randomization, use of objective primary endpoints, blinding of clinical evaluators, independence and blinding of core laboratory evaluators, rigorous selection criteria for subjects, and the optimization of UC to guideline-mandated medical therapy.

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Appendix

Steering Committee

A. Feldman (chair), W. Parmley (retired), M.A. Silver, G.S. Francis, T. Varricchio (sponsor’s representative), P.-A. de Lame (coordinating center representative)

Data Safety Monitoring Board

E. Rapaport (chair), S. Goldstein, T. Ryan

Clinical Event Committee

M. Pfeffer

Coordinating Center

Anabase International Corp., P.-A. de Lame (clinical monitor), M. Lemaire (clinical operations), D. Rom (biostatistics)

Core Laboratories

M. Higginbotham (exercise testing), ICON (safety laboratory), M. Rousseau (special laboratory tests), J. Gorcsan (echocardiography)