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Treatment Benefit in the Enhanced External Counterpulsation Consortium

William E. Lawson John C.K. Hui Gudrun Lang

Division of Cardiology and Department of Surgery, SUNY at Stony Brook, N.Y., USA

Key Words

External counterpulsation · Angina · Assisted circulation · Noninvasive device

Abstract

The present study utilized a cohort of 2,289 consecutive patients enrolled in the Enhanced External Counterpulsation (EECP) Consortium to evaluate whether results of university studies showing EECP safety and effectiveness in treating angina can be generalized. EECP was found to be safe and well tolerated with a 4.0% rate of adverse experiences. Angina class improved in 74% of patients with limiting angina (Canadian Cardiovascular Society, CCS, functional class II–IV), with patients most impaired at baseline demonstrating the greatest improvement (39.5% of patients in CCS III and IV improved 2 or more classes). Efficacy was independent of provider setting or experience, women responded as well as men, and although younger patients demonstrated a greater likelihood of improvement, EECP was effective in patients ranging from 19 to 97 years. Extending the benefit of EECP treatment to a wider range of patients may be indicated based on these findings.

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Introduction

Enhanced External Counterpulsation (EECP) has been demonstrated to be a safe and effective therapy for angina refractory to medical therapy or revascularization. However, to date the published research studies have focused on selected patient cohorts in carefully controlled university hospital settings. Strict inclusion and exclusion criteria have been used. The cohorts studied have been small, comprised mainly of males, and in a relatively narrow age range. The general applicability of EECP in treating angina in a more diverse patient population and in the hands of community cardiologists has not been evaluated previously. To this end the EECP Clinical Consortium was organized in September 1995 to evaluate across a broad range of providers and patients, the practice, effectiveness and safety of EECP by consecutively tracking the results and side effects of EECP therapy at participating centers. Participation currently includes over 100 centers, treating patients with varied demographics, operating in diverse practice settings (hospital based, physician's office or rehabilitation facility) and with substantial differences in treatment experience with EECP.

Background and Methods

Background

The EECP device consists of three paired pneumatic cuffs that are applied to the lower extremities. The cuffs are sequentially inflated (applying 250–300 mm Hg of external pressure) during diastole, returning blood in the lower extremities to the central circulation, producing aortic diastolic augmentation, and increasing venous return and cardiac output. The cuffs are deflated in systole, reducing peripheral resistance to flow and providing left ventricular unload-

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William E. Lawson, MD
SUNY HSC T-17-020
Stony Brook, NY (USA)
Tel. + 1 516 444 1066, Fax +1 516 444 1054, E-Mail wlawson@ts.uh.sunysb.edu

Table 1. CCS grading of angina effort

Functional class	Effort associated with angina
I	Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina with strenuous or prolonged exertion at work or recreation.
II	Slight limitations of ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in cold or in wind, or under emotional stress, or only during the few hours after wakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions.
IV	Inability to carry on any physical activity without discomfort – anginal syndrome may be present at rest.

ing. Daily 1- to 2-hour treatment sessions are typically administered for a total treatment course of 35 h. In clinical practice, different treatment course lengths have been utilized, based primarily on patient response to therapy.

The efficacy of EECP in treating angina has been previously demonstrated in single center studies and a multicenter, prospective, randomized, masked, sham-controlled study (MUST-EECP). In the first US single center study, using radionuclide stress perfusion testing, an improvement in posttreatment stress perfusion imaging was reported in 78% of 18 angina patients and treadmill exercise duration on a Bruce protocol increased a mean of 1.58 min [1]. Exercise hemodynamics and tolerance, in addition to stress radionuclide perfusion imaging, were confirmed as being favorably influenced by EECP in a subsequent case control study of 27 patients [2]. Similar results were demonstrated in a single center group of 50 patients in which the effect of coronary disease extent on treatment benefit was assessed by radionuclide stress testing [3]. Overall 75% of patients demonstrated an improvement in radionuclide stress perfusion imaging after treatment. The lowest rate of response was noted in those patients with the most extensive disease and fewest proximally patent conduits, including both native coronary and bypass grafts. Clinical 3-year follow-up studies have demonstrated that in most patients treated with EECP there is a sustained improvement in stress myocardial perfusion and angina [4]. At 5-year follow-up a favorable effect on the incidence of major adverse cardiovascular events (death, myocardial infarction, revascularization) has also been demonstrated in patients showing improved perfusion after EECP treatment when compared with patients who failed to demonstrate improved perfusion after EECP treatment [5].

In the MUST-EECP study, 139 patients (13% women) with documented coronary artery disease, angina, and a stress test demonstrating significant ST segment depression were enrolled in seven participating university hospitals. Patients received treatment with active applied pressure (250 mm Hg) or low external pressure (75 mm Hg) EECP for a 35-hour course of treatment. Posttreatment evaluation demonstrated a significant increase in the time to ≥ 1 mm ST segment depression on stress testing in the active EECP-treated group compared to the low pressure control group ($p < 0.01$). There were also significant decreases in anginal episodes and nitroglycerin use in the active treatment group compared to the control group [6]. Quality of life follow-ups at 6 and 12 months have shown durable improvement in indices of quality of life in the actively treated patients and no benefit in the low pressure control group [7, 8].

The available data from academic center trials thus support the use of EECP as an effective treatment for chronic angina patients, including those refractory to medical or standard revascularization therapy. Post-EECP benefit has been consistently demonstrated in 70–80% of treated patients by diverse measures, including: time to ST segment depression, radionuclide stress perfusion imaging, functional tolerance, angina count, nitroglycerin use and quality of life measures. There is, however, a clear need to demonstrate whether these results can be generalized to include women, the broader clinical age range manifesting coronary artery disease and a more diverse group of providers and provider settings. Both women and the elderly are groups of special interest because they are underrepresented in most trials and because with surgical revascularization or angioplasty they are at increased procedural risk and may have less durable results [9, 10].

Methods

All consecutive patients undergoing EECP from January 1997 through March 2000 were enrolled at participating centers, which included university medical centers, hospitals, clinics, physician's offices and rehabilitation facilities. Patient benefit was assessed using the Canadian Cardiovascular Society (CCS) functional class of angina effort as listed in table 1. Any adverse consequences occurring during treatment were reported. Patient data recorded prior to treatment included: age, ethnicity, gender and history of prior EECP treatment. Functional class before and after EECP treatment and intervening major adverse cardiovascular events (myocardial infarction, stroke, angina requiring hospitalization or revascularization) were also recorded. The paired two-tailed Student's t test was used to evaluate the significance of improvement in anginal class with treatment.

Providers were grouped as hospital (tertiary or community) or ambulatory (office or clinic based). The profile of patients treated in different provider settings was compared using bivariate methods of analysis (comparing variables 2 by 2, but not controlling for any other factor). The effect of entry CCS functional class on mean treatment time and mean change in posttreatment functional class was compared using ANOVA.

Multivariate analysis was performed to evaluate the effects of age, gender, pretreatment CCS functional class, prior EECP treatment, duration of EECP treatment and treatment setting on response to EECP. Logistic regression was performed using posttreatment change in CCS functional class as the dependent variable and the other factors as control variables. CCS functional class I and II patients were grouped together to provide a reference for this analysis because they were unable to show further improvement in functional class with treatment. In performing multivariate analysis: prior EECP treatment was compared to the reference category of no prior treatment, hospital setting was compared to the reference category of no prior treatment, hospital setting was compared to a reference of office-based treatment, angina classes III and IV were compared to a

reference group of angina class I and II, treatment times <35 and >35 h were compared to the reference group receiving 35 h of treatment, males were compared to females as the reference group, the youngest 3 quartiles in age were compared to the oldest quartile of >74 years as a reference category.

Results

The EECP Clinical Consortium enrolled 3,788 patients from September 1997 through March 2000. This report is based on the completed follow-up available on 2,289 patients as of September 14, 1999, from 84 centers. Providers range from solo practitioners to large multidisciplinary groups and university hospitals. All patients had angina on entry, ranging from CCS functional classes I–IV. The enrolled patients were predominately white (92.4%), but included: African-American (2.7%), Asian (1.4%) and Hispanic (1%) patients; 79.7% were male. The average age was 65.8 ± 10.7 years (range 19–97 years). For 86% of the patients it was their first treatment with EECP. The average treatment time was 33.43 ± 12.3 h. Most (60.2%) patients received 35 h of EECP treatment. However, 21.0% of patients received less than 35 h and 18.2% received more than 35 h. EECP was chosen as treatment for diverse reasons, including: angina refractory to medical or surgical therapy, patient or physician preference, poor candidate for surgery due to lack of graft material or targets or operative risk.

There were 1,753 patients (76.6%) enrolled in 62 clinic sites including physician offices, freestanding centers, and within established rehabilitation facilities. On the other hand, 536 patients (23.4%) were enrolled in 22 participating hospital sites, including university medical centers. The pretreatment CCS functional class of patients entered from hospital and clinic sites did not differ (mean of 2.79 ± 0.88 vs. 2.78 ± 0.89, respectively, p = NS). There were no differences by treatment setting in the age of patients or in the hours of treatment administered. By univariate analysis, hospital-based centers had a higher proportion of female patients (25 vs. 19%; p = 0.005) and a greater change in posttreatment CCS functional class (1.05 vs. 0.95; p = 0.018). However, these differences were not confirmed on multivariate analysis.

There were rare reports of deterioration in anginal class during therapy, with 0.2% of patients worsening by 1 CCS class. The entire 2,991 patient registry was reviewed for safety and tolerability. A total of 91 adverse patient experiences were noted. The largest defined category was musculoskeletal and skin trauma with 23 adverse experiences including joint and muscle pain, leg swelling, bruising or abrasion. Noted cardiac events included: myocardial infarction (8 patients), angina, chest pain, or silent ischemia (4 patients), ECG changes (1 patient), arrhythmia (2 patients) and pulmonary edema (1 patient). There were 8 deaths listed, though none were reported as caused by EECP or related to treatment with EECP. The largest single category of adverse experiences included unrelated medical problems (e.g. gastrointestinal bleeding and pneumonia) and undefined events.

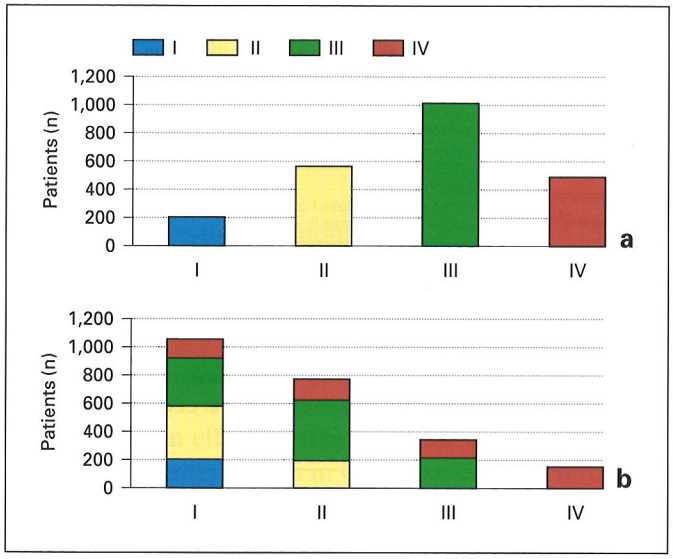
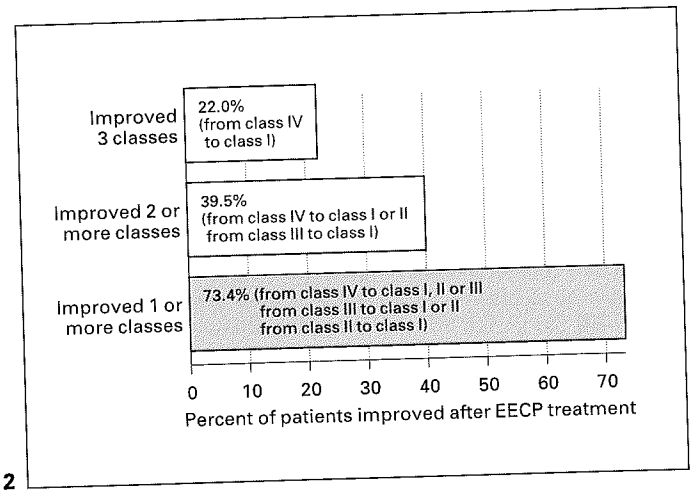


Fig. 1. a Distribution of patients in CCS angina class I–IV prior to treatment with EECP. **b** Distribution and change in CCS Angina class of patients after treatment with EECP.

The majority of patients limited by their angina (CCS functional classes II–IV) either improved their anginal class (1,531 – 73.4% of patients) or remained unchanged in functional class after EECP (554 – 26.5% of patients). Overall the average CCS anginal class before treatment of 2.78 improved to an average CCS class of 1.81 after EECP ($p < 0.001$; fig. 1). The mean change in CCS was significantly dependent on pretreatment CCS. Patients with greater degrees of impairment at baseline, CCS III and IV, were significantly more likely to demonstrate functional improvement and the average improvement was likely to be greater than for patients in pretreatment CCS functional classes I and II. Anginal class improved two or more functional classes in 48.9% of patients in pretreatment anginal class IV and in 34.9% of patients in pretreatment class III. The average anginal class of patients treated in functional classes II–IV decreased from 2.99 before treatment to 1.84 after treatment. The greatest functional



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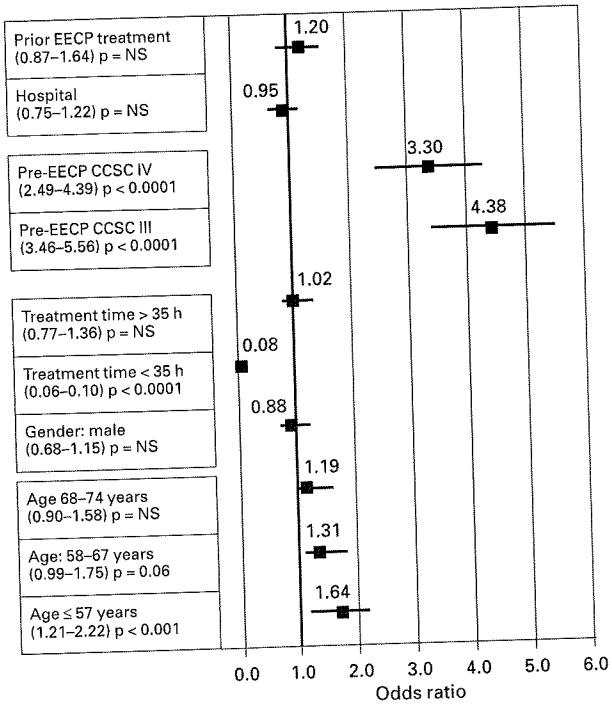

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Fig. 2. Change in CCS angina class after EECP treatment by pretreatment class.

Fig. 3. Multivariate analysis using logistic regression showing odds ratios, with 95% confidence intervals, of improvement with EECP treatment. Variables illustrated include: prior EECP treatment (compared to reference category of no prior treatment), hospital setting (compared to office), angina classes III and IV (compared to angina class I and II), treatment times < 35 and > 35 h (compared to 35-hour treatment), male sex (compared to females), youngest 3 quartiles in age (compared to oldest quartile of > 74 years).

improvement, on average, was seen in patients most impaired at baseline (fig. 2).

There were no significant differences in response to EECP based on provider type or experience, or by prior treatment with EECP. Mean treatment time varied significantly by pretreatment CCS functional class, with patients in lower CCS functional classes receiving fewer treatments were 20% less likely than those undergoing 35 h of treatment to demonstrate an improvement in CCS functional class. The group of patients undergoing treatments longer than 35 h did not demonstrate benefit over the standard 35-hour course of treatment. Gender had no significant influence on response to EECP. The likelihood of response to treatment with EECP was significantly related to patient age, with younger patients showing a significantly greater likelihood of benefit (fig. 3).

Discussion

Improvement in CCS functional class after EECP treatment was consistently seen across different providers, levels of provider experience, and treatment locations. Its robust efficacy was demonstrated in all settings, and a site- and operator-specific training effect was not demonstrable, supporting the postulation that the device is relatively user friendly. These results suggest that the broader use of EECP as a treatment alternative for angina may be appropriate.

The analysis of treatment duration and improvement in angina class is difficult to interpret. Patients in lower CCS functional classes are by definition less impaired and therefore have less room for improvement. This means that the starting functional class is an important factor to control for in assessing the impact of any other variable such as age or sex. Superficially the data support 35 h as the optimal treatment duration. Treatment for less than 35 h is associated with a diminished probability of benefit. Treatment for more than 35 h has comparable benefit to treatment for 35 h. The possible explanation, however, for the lack of improvement with short courses of EECP, includes both patient dropout for failure to improve and failure to improve due to patient dropout. Treatment beyond 35 h, by contrast, suggests a group of patients with less than the usual response at 35 h, perhaps achieving the usual response with additional treatment. The dose effects of EECP remain speculative. A prospective design of varying treatment lengths would be required to clarify the

dose response and perhaps determine the degree to which treatment should be individualized.

In examining subgroups, women and men respond equally well to EECP. The youngest patient quartile (the second youngest quartile was of borderline significance at $p = 0.06$), however, demonstrated a significant increase in the likelihood of improvement compared to the oldest patient quartile. Why the younger patients should be more likely to respond to EECP treatment is unclear. The baseline CCS functional class was similar between quartiles (CCS 2.80, 2.72, 2.76, 2.86 from youngest to oldest quartile, respectively). Possible other explanations include: more extensive disease in the elderly (increasing disease severity and decreasing transmission of augmented pressure and flow to the distal coronaries), a decrease in effective augmentation due to less lower extremity muscle mass and calcified non-compliant arterial walls (the lead pipe effect), an age-related decrease in the ability to recruit and/or develop collaterals. Further study will be necessary to investigate these possibilities.

Relieving anginal symptoms is one of the major objectives of CAD treatment. Chronic angina impacts on the utilization of health care resources, requiring repeated hospitalizations and revascularizations. It is a cause of chronic disability, often affecting patients (and their families) in their most productive years. While revascularization with coronary bypass surgery or angioplasty can provide rapid improvement in anginal symptoms, they are both costly procedures with associated morbidity and mortality. Medical therapy of angina can also be costly and requires long-term patient compliance. EECP is an emerging treatment alternative for angina that is both safe and effective in improving angina. In current practice it is often used when angina is refractory to medical or surgical treatment, though results suggest wider opportunities for its use.

Conclusions

Prior studies have demonstrated the utility of EECP in carefully controlled university settings. The present study confirms EECP as a safe and practical treatment for angina in general clinical practice. Its more widespread availability as a treatment alternative may prove beneficial to patient care.

1 EECP is an effective treatment for angina, with most (74% overall) patients in CCS classes II–IV improving their functional class with treatment and 39.5% in classes III–IV improving two or more anginal classes.
2 There was a low incidence of morbidity (4% mostly related to skin and musculoskeletal trauma) associated with the use of EECP in this study.
3 EECP is well tolerated by angina patients, including those in CCS functional class IV.
4 EECP is clinically effective across a broad range of providers and provider settings.
5 Women and men respond equally well to treatment with EECP.
6 While not limited by age, EECP treatment is more likely to be effective in younger patients.

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