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A Review of Enhanced External Counterpulsation Clinical Trials

GEORGE A. BELLER, M.D., MACC

Cardiovascular Division, University of Virginia, Charlottesville, Virginia, USA

Summary: A variety of clinical trials of enhanced external counterpulsation (EECP) have been conducted since the 1960s. The vast majority of these studies have investigated the use of EECP in patients with angina pectoris. Only one of these trials was randomized. These clinical trials have demonstrated the benefits of EECP in terms of reduction in anginal episodes, increased exercise times, and improvement in health-related quality of life scores. The International EECP Patient Registry, through its phase I and II enrollment, is expanding the data set on outcomes after EECP treatment.

Key words: angina pectoris, coronary artery disease, enhanced external counterpulsation, health-related quality of life, International EECP Patient Registry

Introduction

Since the development of enhanced external counterpulsation (EECP) in the 1960s, several important clinical trials have been conducted and published. These studies have demonstrated the value of EECP in patients with coronary artery disease (CAD) and angina not amenable to conventional therapy. Even with this advancing knowledge, some limitations remain regarding these published clinical studies. At present, there has been only one randomized study of EECP, which did not use a "pure" placebo. There have also been no studies of repeat or extended treatment with EECP. The precise mechanisms by which EECP confers benefit remain unclear. As clinical studies continue, a better means of identifying which patients may benefit the most from EECP is needed.

Address for reprints:

George A. Beller, M.D., MACC
Chief, Cardiovascular Division
University of Virginia Health System
P.O. Box 800158
Charlottesville, VA 22908-0158, USA
e-mail: gbeller@virginia.edu

Early Clinical Studies

Banas and colleagues published one of the first papers on the use of external counterpulsation in 1973.[1] The trial enrolled 21 patients with the majority having class III (6) and class IV (14) angina pectoris. External counterpulsation was given for 1 h each day for a period of 5 days. Of the 21 patients participating in the study, 18 experienced significant diastolic augmentation (75.3 ± 1.8 vs. 123.3 ± 2.7 mmHg). All but one of these 18 patients were pain free by Day 4. After 1 month, 10 patients were upgraded to class I, and 8 patients were upgraded to class II, indicating significant decreases in angina class. When angiograms were performed in 11 patients, 5 showed increases in vascularity.

Lawson looked at 18 patients with chronic, refractory angina.[2] Of those enrolled, eight had 19 prior revascularization attempts and seven had 14 prior myocardial infarctions. Each subject underwent 36 1-h treatment sessions. Pre- and post-EECP thallium stress tests were performed to the same exercise times. In addition, separate, post-treatment maximal routine treadmill stress tests were obtained.

At the conclusion of this case study, all of the patients (100%) reported improvement in angina symptoms. No angina during usual activities was reported in 16 (89%) of these patients. Twelve (67%) had resolution of reversible perfusion defects, while 2 patients (11%) showed improvement of reversible perfusion defects. Four patients (22%) had no change in stress perfusion defects. All 18 patients were positive for reversible defects prior to their EECP. After EECP, 4 patients still had positive reversible defects, while 11 patients had no reversible defects. The three other patients showed partial improvement. A 3-year follow-up was conducted using radionuclide stress perfusion imaging.[3] Of the four patients still positive for redistribution, two had events and two remained unchanged. Of the remaining 14 patients,

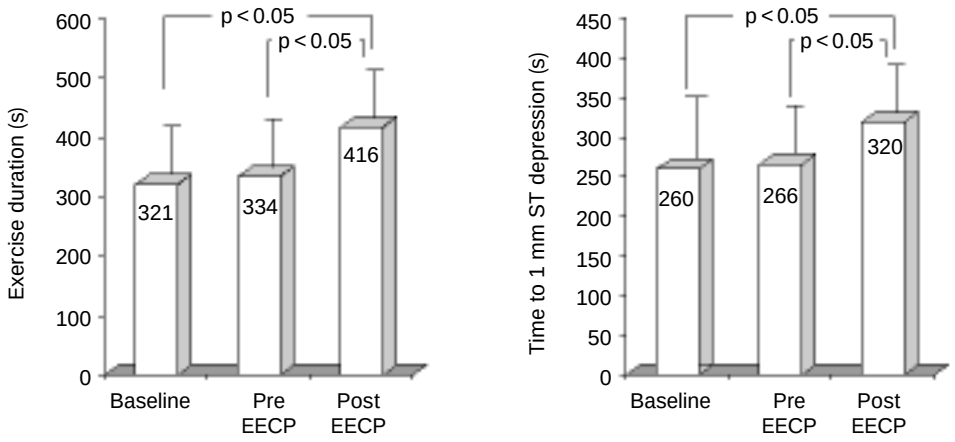

FIG. 1 Exercise duration and time to ST depression before and after enhanced external counterpulsation (EECP) (n = 12). Adapted from Ref. No. 4 with permission.

8 were unchanged, 2 had reversible defects, 2 had events, and 2 were lost to follow-up.

A variety of other case series have also been published. They were nonrandomized observational studies of patients with angina pectoris undergoing exercise tolerance testing (ETT), some with radionuclide imaging. Endpoints were angina class, treadmill time, quality of life (QOL), and nitroglycerin use. These case series came from all parts of the world, including Germany, Ireland, England, and Japan. Several came from the U.S. All results were consistent with the findings of Lawson.[2]

Recent Clinical Studies

In 2000, Urano *et al.* conducted a study of EECP in 12 patients with coronary artery disease (CAD), looking specifically at exercise tolerance, exercise-induced myocardial ischemia, and left ventricular diastolic filling.[4] After EECP, the number of normal scans increased significantly, while the number of abnormal scans decreased significantly, from 50 to 33%. As expected, there was no change in fixed perfusion defects. Figure 1 shows exercise tolerance test results by exercise duration and by time to ST depression. After EECP, both outcomes improved significantly.

In 2001, Masuda *et al.* also conducted a study of EECP in 11 patients with chronic stable angina.[5] They evaluated patients using (13)N-ammonia positron emission tomography (PET). Most patients had either prior anterior myocardial infarctions or ischemic events related to left arterial descending CAD. Even though there was a significant improvement in the time to 1-mm ST depression, there was no significant change in the double product at peak exercise. This raised the possibility of some peripheral rather than central effects that would increase the time to the ischemic ST depression. Positron emission tomography showed significant improvement at peak stress only in the anterior wall, but no changes in perfusion in the septum, and nonsignificant blood flow increases in the lateral and inferior walls (Fig. 2).

The first randomized study of EECP was reported in 1999, 26 years after the first observational study was performed. Arora *et al.* conducted a multicenter study of EECP (MUST-EECP) and its effect on exercise-induced myocardial ischemia and anginal episodes.[6] This study was designed to confirm the efficacy and safety of EECP using a randomized, sham-controlled, double-blind protocol.

A total of 139 outpatients at seven university hospitals participated. All had angina, documented CAD, and a positive exercise treadmill test. Subjects were randomized to receive either active or inactive counterpulsation for 35 h over a 4- to 7-week period. This was not a pure sham study, as the control group may have experienced an increase in venous return.

Exercise duration was greater in the active group than with the sham group (see DeMaria for specific study results). The time to ST depression was also increased in the active group, while decreasing by 4 s in the sham group. These exercise test results were similar to those repeated in observational studies. There was also a significant change in daily episodes of angina in the active group.

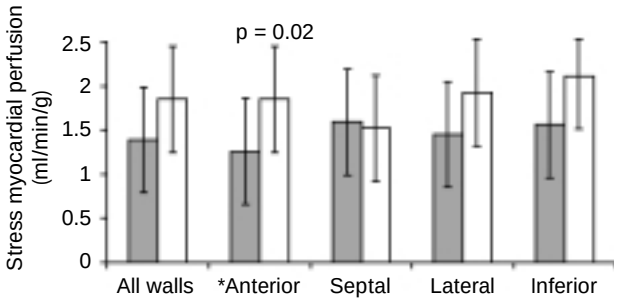

FIG. 2 Myocardial perfusion in all walls after enhanced external counterpulsation (EECP) as measured by (13)N-ammonia positron emission tomography (n = 11). Adapted from Ref. No. 5 with permission. ■ = Baseline, □ = post EECP. *Area of interest.

TABLE I Adverse experiences considered by investigator as probably, possibly, or definitely device-related in the MUST-EECP trial

	Sham (n = 66)	EECP (n = 71)	P Value
Paresthesia	1	2	p > 0.5
Edema	0	2	p = 0.5
Skin abrasion, bruise, blister	2	13	p = 0.005
Pain in leg or back	7	20	p = 0.01
Total	10	37	p < 0.001
No. of patients reporting AEs	17 (25.8%)	38 (54.9%)	p < 0.001
Withdrawal due to AE	1	7	

Abbreviation: AE = adverse event.
Adapted from Ref. No. 6 with permission.

Changes in on-demand nitroglycerin were also measured in the protocol using both per-protocol and intention-to-treat analyses. There was no controlling for long-acting nitrates or for prophylactic use. Patients could receive either nitroglycerin patches or long-acting nitroglycerin. Nitroglycerin trended lower in the active counterpulsation (CP) group but did not change in the inactive CP group. The between-group difference was not significant. Patients in the active EECP group experienced a variety of adverse effects (Table I). These included skin abrasions, bruises, and blisters. Seven patients in the active group withdrew because of these adverse experiences.

In a substudy of the MUST EECP trial,[7] in which health-related QOL outcomes were measured out to one year beyond treatment, all QOL parameters were greater in the active CP group compared with the inactive CP group (Fig. 3). These included the ability to perform activities of daily living, maintain employment, and engage in social activities with family and friends.

An analysis of the potential benefits of EECP has also been conducted in a registry cohort of 2,289 consecutive patients enrolled in the EECP Consortium.[8] This consortium study preceded the International EECP Registry (IEPR). Patients received their EECP at more than 100 centers, including university medical centers, hospitals, clinics, physicians' offices, and rehabilitation centers. They were assessed using the Canadian Cardiovascular Society angina classification system (class 1–IV). As shown in Figure 4, patients who were most impaired at baseline demonstrated the greatest improvement after treatment. The effectiveness of EECP was independent of the patient's gender or provider setting. Younger patients, however, had the greatest likelihood of improvement. There was a 4.0% rate of adverse experiences.

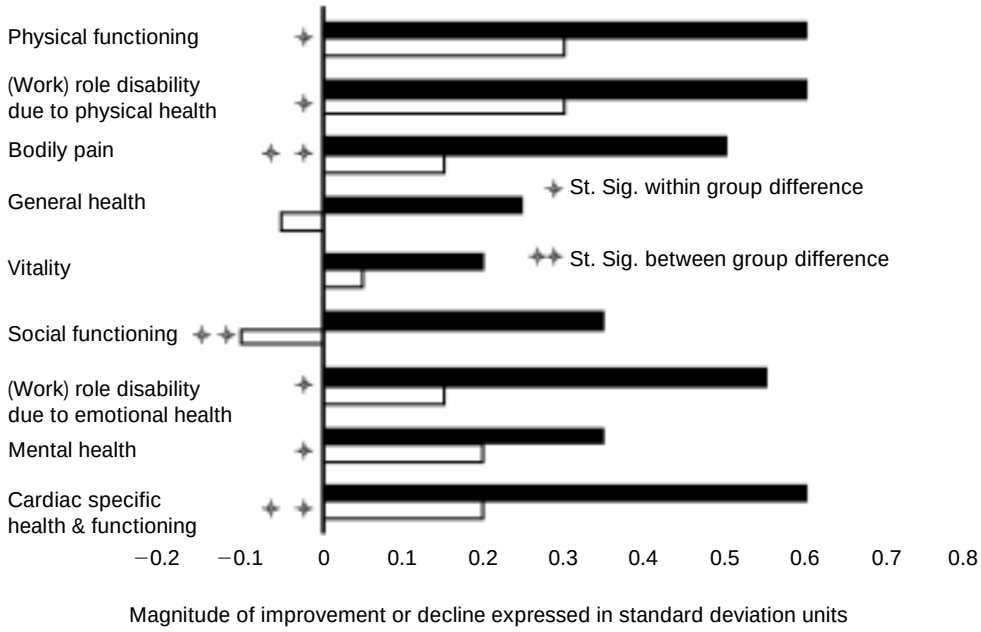

FIG. 3 Health-related quality of life changes 12 months after enhanced external counterpulsation (EECP) treatment in a substudy of the MUST-EECP trial. Adapted from Ref. No. 7 with permission. ■ = Active CP, □ = inactive CP. St. Sig. = statical significance.

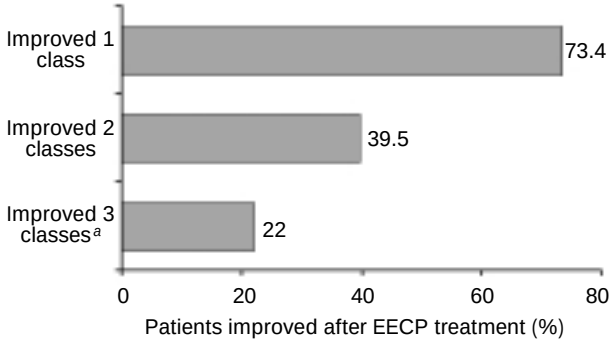

FIG. 4 Improvement in angina class for patients enrolled in the enhanced external counterpulsation (EECP) Consortium (n = 2,289). [a] Canadian Cardiovascular Society (Angina) Class. Adapted from Ref. No. 8 with permission.

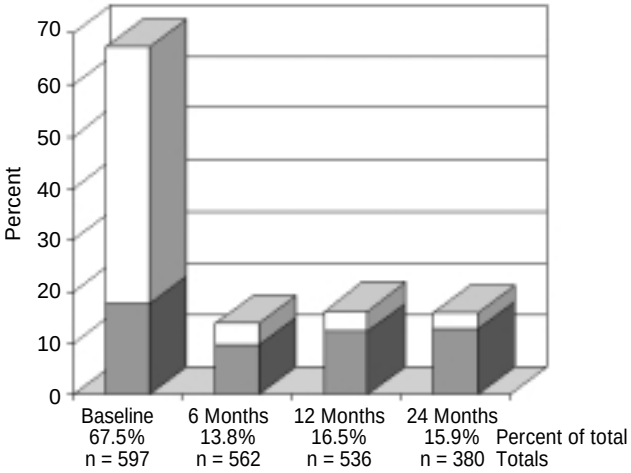

FIG. 5 Change in angina class for patients participating in the International EECP Patient Registry (n = 597). Courtesy of the Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh (Ref. No. 9). □ = CCSC III, ■ = CCSC IV.

The International EECP Patient Registry

Organized in 1998, the IEPR was developed to document the safety, efficacy, and patterns of the use of EECP in a consecutive series of patients.[9] The registry was open to all centers using EECP for treatment of patients with angina pectoris. As a voluntary registry, no payments were made to patients or centers.

The first phase enrolled more than 5,000 consecutive patients with follow-up for a minimum of 3 years. At present, 92 centers are participating, including 82 from the U.S., 5 from Europe, and 5 from other international locations. An analysis was conducted of the first 5,222 patients enrolled, amounting to 5,718 courses of EECP therapy. The mean age of participants was 66 years (±11), with a male-to-female ratio of 74 to 26. The time since diagnosis was 9 years, with 78% having multivessel disease. Prior diagnoses and procedures were congestive heart failure (27%), myocardial infarction (64%), angioplasty/coronary artery bypass graft (80%), and angioplasty alone (60%).

Figure 5 shows the long-term 24-month changes in angina class in a subject of 597 patients from the registry. Only 2% of patients experienced worsening of angina. Among all patients, 30% experienced nonexclusive cumulative adverse events. The two most common events were cardiac hospitalization and repeat EECP. Death occurred in 7% of patients over the 2-year period. Prior to EECP, most of these individuals were excluded from revascularization. Quality of life, health, and satisfaction parameters were also measured. At the end of 24 months, there was a trend toward QOL to decrease, although it was still significantly better than at baseline.

Conclusion

A number of conclusions can be made from the one randomized trial of EECP, several clinical observational studies, and the registry data. First, there is a consistent reduction in anginal episodes, approximately 70%, through the use of EECP. Second, there appears to be sustained improvement in angina class beyond the 7 weeks of treatment. There is also improvement in time to ischemia, greater exercise workload, and fewer stress-induced reversible perfusion defects. More research must be conducted in the radionuclide perfusion area really to determine whether ischemic defects truly do decrease and by how much. Finally, EECP contributes to a better health-related QOL. More studies of EECP are needed, including randomized trials, to investigate several unresolved issues, such as mechanism, extended treatment, and which patients benefit the most.

Discussion

Participant: We use EECP at our facility, which is located on a Caribbean Island. Since we are not in the U.S., we do not have to worry too much about the FDA. So we have been freely treating lots of patients post stroke and those with renal insufficiency, although this has not been done in a scientific way. My impression is that, especially in patients post stroke, it seems like the recovery is better in some patients. I would be very interested to know whether EECP also prevents stroke. When I purchased the machine, I heard that, especially in China, they use it for treating strokes. I have never seen any studies or data on this.

DeMaria: We have Dr. Zeng in attendance, who really pioneered the device in China. They have reported, as you said, that EECP increases the rapidity and the degree of recovery from stroke. Maybe Dr. Zeng could address your question more fully.

Zeng: In China, we have used EECP since 1976. It increases perfusion to the brain, the heart, and all organs in the body. We try to use EECP on patients with stroke if the problem is an ischemic stroke. We found a lot of improvement in patients with ischemic stroke.

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