

Treatment Options for Refractory Angina Pectoris: Enhanced External Counterpulsation Therapy

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Opinion statement

Refractory angina pectoris, defined as angina refractory to maximal medical therapy and standard coronary revascularization procedures, remains a significant health problem in the United States and the world. Despite a panoply of recent therapeutic advances, patients with refractory angina pectoris are not adequately treated; therefore, scientists have been investigating new technologies to help these patients. The technique of counterpulsation, studied for almost half a century, is considered a safe, highly beneficial, low-cost, noninvasive treatment for these angina patients and now also for those with heart failure. Recent evidence suggests that enhanced external counterpulsation (EECP) therapy may improve symptoms and decrease long-term morbidity via several mechanisms, including improvement in endothelial function, promotion of collateralization, enhancement of ventricular function, improvement in oxygen consumption (V_{O_2}), regression of atherosclerosis, and peripheral “training effects” similar to exercise. Numerous clinical trials in the past two decades have shown EECP therapy to be safe and effective for patients with refractory angina, with a clinical response rate averaging 70% to 80%, which is sustained up to 5 years. This review summarizes the current evidence to support EECP’s use in treating refractory angina pectoris.

Introduction

An estimated 6.4 million patients in the United States suffer from symptomatic coronary artery disease, and about 400,000 new cases develop each year [1]. Despite optimal medical therapy and invasive procedures such as angioplasty and cardiac bypass surgery, an estimated 300,000 to 900,000 patients in the United States have refractory angina pectoris. About 25,000 to 75,000 new cases of refractory angina pectoris are diagnosed each year [1].

Daily tasks such as climbing a flight of stairs, walking a block, and dusting furniture become impossible without these difficult-to-treat patients experiencing chest pain. Many patients now are left to suffer from their symptoms, restrict their activities chronically, and anticipate a reduced life expectancy.

Current nonpharmacologic options for patients with refractory angina pectoris include neurostimu-

lation (transcutaneous electrical nerve stimulation and spinal cord stimulation), enhanced external counterpulsation (EECP) therapy, laser revascularization techniques, gene therapy, and newer interventional procedures such as percutaneous in situ coronary venous arterialization and percutaneous in situ coronary artery bypass [2,3]. Of these modalities, EECP therapy represents the only truly noninvasive technique for which a reduction in angina symptoms, improvement in objective measures of myocardial ischemia, and improvement in left ventricular function (both systolic and diastolic) have been shown [4–6].

This review summarizes the current evidence supporting the use of EECP therapy in patients with refractory angina pectoris.

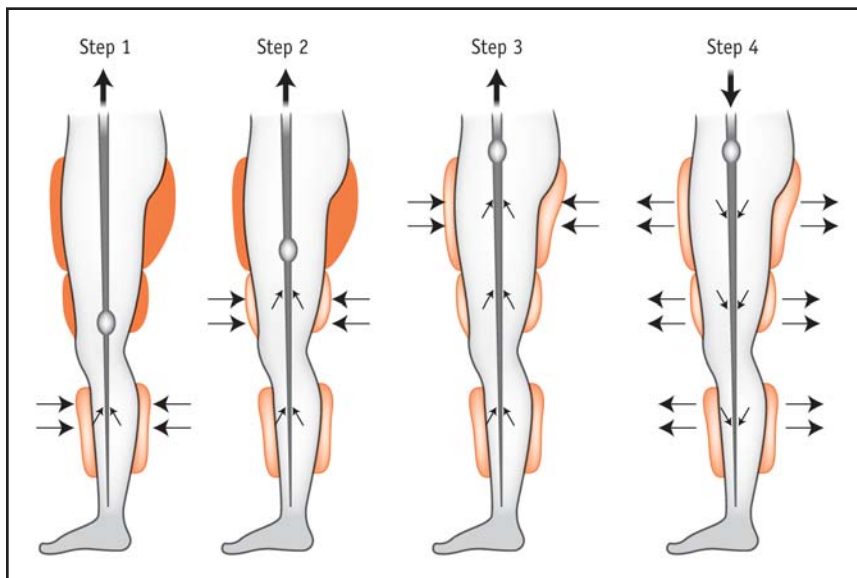


Figure 1. Technique of enhanced external counterpulsation (EECP) therapy. Three pairs of pneumatic cuffs are applied to the calves, lower thighs, and upper thighs. The cuffs are inflated sequentially during diastole, distal to proximal. The compression of the lower extremity vascular bed increases diastolic pressure and flow and increases venous return. The pressure is then released at the onset of systole. Inflation and deflation are timed according to the R wave on the patient's cardiac monitor. The pressures applied and the inflation–deflation timing can be altered by using the pressure waveforms and electrocardiogram on the EECP therapy monitor. (Adapted from Manchanda and Soran [3].)

WHAT IS EECP?

EECP therapy is a noninvasive outpatient therapy consisting of electrocardiography (ECG)-gated sequential leg compression, which produces hemodynamic effects similar to those of an intra-aortic balloon pump. However, unlike intra-aortic balloon pump therapy, EECP therapy also increases venous return.

Although the concept of counterpulsation was introduced in the United States in the early 1950s, it took more than 40 years for investigators to develop the effective technology that is currently being used [3,7,8]. Cuffs resembling oversized blood pressure cuffs—on the calves and lower and upper thighs, including the buttocks—inflate rapidly and sequentially via computer-interpreted ECG signals, starting from the calves and proceeding upward to the buttocks (Fig. 1) [3] during the resting phase of each heartbeat (diastole). This creates a strong retrograde counterpulse in the arterial system, forcing freshly oxygenated blood toward the heart and coronary arteries while increasing the volume of venous blood return to the heart under increased pressure. Just before the next heartbeat, before systole, all three cuffs deflate simultaneously, significantly reducing the heart's workload. This is achieved because the vascular beds in the lower extremities are relatively empty when the cuffs are deflated, significantly lowering the resistance to blood ejected by the heart and reducing the amount of work the heart must do to pump oxygenated blood to the rest of the body [3].

A finger plethysmogram is used throughout treatment to monitor diastolic and systolic pressure waveforms. A typical therapy course consists of 35 treatments administered for 1 hour a day over 7 weeks.

EECP AND REFRACTORY ANGINA PECTORIS

Several nonrandomized and randomized trials have demonstrated a consistently positive clinical response

among patients with refractory angina pectoris treated with EECP [9–15]. Benefits associated with EECP therapy include reduction in angina and nitrate use, increased exercise tolerance, favorable psychosocial effects, and enhanced quality of life as well as prolongation of the time to exercise-induced ST-segment depression and an accompanying resolution of myocardial perfusion defects [16–20].

Most studies on EECP therapy cannot be double-blind and lack good control groups because of technical limitations, drawbacks that have frequently raised questions regarding operator bias. However, the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), a randomized double-blinded placebo-controlled trial, did document a clinical benefit from EECP therapy in patients with chronic stable angina and positive exercise stress tests [14]. Moreover, a MUST-EECP substudy demonstrated a significant improvement in quality-of-life parameters in patients assigned to active treatment, and this improvement was sustained during a 12-month follow-up [21].

Although randomized (including placebo-controlled) and nonrandomized studies have shown beneficial effects of EECP therapy, investigators saw the need to assess EECP's effectiveness in real-world settings, leading them to develop the International EECP Patient Registry (IEPR) under the management of the University of Pittsburgh [22]. More than 5000 patients were enrolled in phase I and another 2500 patients enrolled in phase II of the study, and more than 90 centers participated. Results from the IEPR [19,23] and the EECP Clinical Consortium [24] have demonstrated that the symptomatic benefit observed in controlled studies translates to the heterogeneous patient population seen in clinical practice. Moreover, follow-up data indicate that the clinical benefit may be maintained for up to 5 years in patients with a favorable initial clinical response [19,25,26].

EECP therapy in refractory angina pectoris with left ventricular dysfunction

- When providing EECP therapy to patients with heart failure, the initial researchers were concerned primarily that the increased venous return resulting from EECP therapy might precipitate pulmonary edema in angina patients with severe left ventricular dysfunction (SLVD).
- Using outcomes data from 363 patients enrolled in the IEPR, Soran et al. [15,27] evaluated the safety and efficacy of EECP therapy in those with refractory angina pectoris and SLVD (ejection fraction [EF] < 35%). They concluded that EECP therapy for angina is safe and effective in patients with SLVD who are not considered good candidates for revascularization by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) [15]. After the patients completed therapy, there was a significant reduction in angina severity: 72% improved from severe angina to no or mild angina. Fifty-two percent of the patients stopped using nitroglycerin. There was also a significant increase in quality of life. At 2-year follow-up, angina reduction was maintained in 55% of patients, the survival rate was 83%, and event-free (death/myocardial infarction [MI]/PCI/CABG) survival was 70%. Forty-three percent had no cardiac hospitalization; 81% had no congestive heart failure event [15].
- Lawson et al. [28] evaluated refractory angina pectoris patients with preserved left ventricular function (PLV; EF > 35%) and with SLVD (EF ≤ 35%) who were treated with a 35-hour course of EECP. Bioimpedance measurements of cardiovascular function were obtained before the first and after the 35th hour of EECP therapy. Twenty-five patients were enrolled, 20 with PLV and 5 with SLVD. Angina class improved similarly in both groups. The SLVD group, in contrast to the PLV group, had increased cardiac power (ie, mean arterial pressure × cardiac output/451), stroke volume, and cardiac index and decreased systemic vascular resistance with treatment. This study suggests that EECP may benefit patients experiencing coronary artery disease with SLVD directly by improving cardiac power and indirectly by decreasing systemic vascular resistance [28].
- Patients with refractory angina pectoris and left ventricular dysfunction (LVD) exert an enormous burden on health care resources, primarily because of the number of recurrent emergency department visits and hospitalizations. Improvements in symptoms and laboratory assessments in these patients may not correlate with a reduction in emergency room visits and hospitalizations. Soran et al. [29•] assessed the impact of EECP therapy on emergency department visits and hospitalization rates at 6-month follow-up. In this prospective cohort study, clinical outcomes, number of all-cause emergency department visits, and hospitalizations within the 6 months before EECP therapy were compared with those at 6-month follow-up. The mean number of emergency department visits per patient decreased from 0.9 ± 2.0 before EECP to 0.2 ± 0.7 at 6 months ($P < 0.001$), and hospitalizations were reduced from 1.1 ± 1.7 to 0.3 ± 0.7 ($P < 0.001$) [29•].

Mechanism of EECP

- Upon diastole, cuffs inflate sequentially from the calves, raising diastolic aortic pressure proximally and increasing coronary perfusion pressure. Compression of the vascular beds of the legs also increases venous return. Instantaneous decompression of all cuffs at the onset of systole significantly

unloads the left ventricle, thereby lowering vascular impedance and decreasing ventricular workload. This latter effect, when coupled with augmented venous return, raises cardiac output. In summary, EEC therapy increases venous return, raises cardiac preload, increases cardiac output, and decreases systemic vascular resistance [30,31].

- Mode-of-action studies have shown that EEC therapy increases angiogenesis factors such as human growth, basic fibroblast growth, and vascular endothelial growth factors. Enhanced diastolic flow increases shear stress, increased shear stress activates the release of growth factors, and augmentation of growth factor release activates angiogenesis [32].
- EEC therapy improves endothelial function and enhances vascular reactivity. As with athletic training, the vascular effects of EEC therapy may be mediated through changes in the neurohormonal milieu. Wu et al. [33] showed that EEC therapy has a sustained, dose-related effect in stimulating endothelial cell production of the vasodilator nitric oxide (NO) and in decreasing production of the vasoconstrictor endothelin. In another study, Qian et al. [34] showed that the NO level increased linearly in proportion to the hours of EEC treatment.
- Masuda et al. [16] demonstrated that EEC therapy increased myocardial perfusion and enhanced dipyridamole-induced coronary vasodilation. On exercise testing, the time to 1-mm ST-segment depression was increased significantly with a similar trend in exercise duration. After the EEC treatment course, NO levels measured at rest were increased, whereas human atrial natriuretic peptide and brain natriuretic peptide (BNP) levels were decreased.
- Urano et al. [4] further showed that plasma BNP levels decreased after EEC therapy and were positively correlated with left ventricular end diastolic pressure and negatively correlated with peak filling rate. They concluded that EEC therapy reduces exercise-induced myocardial ischemia in association with improved left ventricular diastolic filling in patients with coronary artery disease.
- Another possible mechanism explaining EEC's mode of action is that it may effect changes in ventricular function independent of changes in cardiac load. Gorcsan et al. [5] evaluated the effects of EEC therapy on left ventricular function in New York Heart Association (NYHA) class II or III heart failure patients with an EF less than 40%. Their results showed that EEC treatment was associated with improvements in preload adjusted maximal power, a relatively load-independent measure of left ventricular performance and EF, along with a decrease in heart rate in these heart failure patients.
- A recently published randomized controlled study examining the effect of EEC therapy on inflammatory and adhesion molecules in patients with coronary artery disease with refractory angina pectoris indicated that EEC therapy has an anti-inflammatory effect in patients with angina pectoris. Patients were randomly assigned to receive active EEC or sham treatment. Plasma tumor necrosis factor- α , monocyte chemoattractant protein-1, and soluble vascular cell adhesion molecule-1 were measured before and after a full course of 35 1-hour sessions of EEC or sham treatment. Patients in the EEC group demonstrated reductions in tumor necrosis factor- α and monocyte chemoattractant protein-1 after treatment, whereas those in the sham therapy group showed no changes. EEC therapy decreased circulating levels of proinflammatory biomarkers in patients with symptomatic coronary artery disease [35••].

US Food and Drug Association–cleared indications

- Labeled indications for the use of EECP include treatment of patients with:
 - Stable or unstable angina pectoris
 - Congestive heart failure
 - Acute MI
 - Cardiogenic shock

Which group of patients may benefit from EECP therapy?

- Candidates for EECP therapy include patients with angina or angina-equivalent symptoms such as shortness of breath and/or fatigue who:
 - Have coronary anatomy unsuitable for surgical or catheter-based revascularization
 - Inadequately respond to optimum medical therapy
 - Are considered inoperable or at high risk of operative/interventional complications
 - Have comorbid conditions that increase the risk of revascularization procedures, such as diabetes, heart failure, pulmonary disease, and renal dysfunction
 - Are unwilling to undergo additional invasive revascularization procedures
 - Have stable (NYHA class II or III) heart failure; patients with any evidence of decompensation should not be treated until they are stable with the use of medical therapy
 - Have ischemic or idiopathic cardiomyopathy
 - Have LVD (EF < 35%)

Side effects

- EECP's side effects include:
 - Skin abrasion or ecchymoses
 - Bruises (especially in patients using warfarin in whom the international normalized ratio [INR] is not adjusted)
 - Paresthesias
 - Leg or waist pain
 - Worsening of heart failure in patients with severe arrhythmias

Contraindications

- Contraindications to EECP are:
 - Moderate to severe aortic insufficiency (regurgitation would prevent diastolic augmentation)
 - Arrhythmias that may interfere with EECP system triggering (uncontrolled atrial fibrillation or flutter or very frequent premature ventricular contractions)
 - Coagulopathy with an INR or prothrombin time greater than 2.5
 - Severe hypertension: greater than 180/110 mm Hg (the augmented diastolic pressure may exceed safe limits)
 - Cardiac catheterization or arterial puncture (risk of bleeding at femoral puncture site) within the past 2 weeks
 - Decompensated heart failure

- Severe peripheral arterial disease (reduced vascular volume and muscle mass may prevent active counterpulsation)
- Aortic aneurysm (≥ 5 mm) or dissection (diastolic pressure augmentation may be deleterious)
- Pregnancy or being of childbearing age (effects of EECp therapy on the fetus have not been studied)
- Venous disease (phlebitis, varicose veins, stasis ulcers, prior or current deep vein thrombosis or pulmonary embolism)
- Severe chronic obstructive pulmonary disease (no safety data in pulmonary hypertension)

Hypotheses currently of interest

- *Erectile dysfunction*: Studies looking at EECp therapy and erectile dysfunction have shown a 200% increase in penile artery flow and reported improvement in erectile function [36–38].
- *Hepatorenal syndrome*: Werner et al. [39] assessed the potential role of EECp therapy in diuresis and increased urinary flow in patients with end-stage liver disease awaiting a transplant. They found that EECp therapy increased mean arterial pressure as well as urinary production (urinary flow rate) in patients with end-stage cirrhosis and hepatorenal syndrome.
- Studies involving larger sample sizes are necessary to confirm the effectiveness of EECp therapy in erectile dysfunction and hepatorenal syndrome.
- Recent study results have shown that EECp therapy significantly improves vascular endothelial function in coronary artery disease patients with refractory angina. A new study is under way to explore the role of EECp therapy in primary and secondary prevention of coronary artery disease.

Disclosure

No potential conflict of interest relevant to this article was reported.

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