

“No-option” Patients—Role of Enhanced External Counterpulsation

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A 69-year-old diabetic man underwent coronary artery bypass graft (CABG) in 1990 for chronic stable angina. He required a repeat CABG in 2000 and percutaneous transluminal coronary angioplasty (PTCA) with stent implantation to graft the left circumflex artery (LCX) and native right coronary artery (RCA). Debilitating angina continued despite maximally tolerated doses of anti-anginals, and a check angiogram done in 2005 revealed that all the stents were blocked with native diffuse triple vessel disease. Surgeons and interventional cardiologists refused to intervene further and advised the patient to continue with medical therapy. What should be done now?

The last three decades have witnessed enormous advances in the treatment of coronary artery disease (CAD), including medical, interventional (PTCA/stent) and surgical (CABG) techniques. However, despite these developments, nearly 5–15% of patients with CAD may not be good candidates for current revascularization techniques.¹ Such patients continue to have limiting symptoms, despite maximally tolerated medical therapy; they do not have the option of revascularization due to one of the following problems.

1. Unsuitable coronary anatomy, such as diffuse coronary sclerosis.
2. One or several previous CABGs and/or PTCAs, which exclude the possibility of benefit from further revascularization, or even the feasibility of such an operation.
3. The presence of extra-cardiac disease, such as renal insufficiency and pulmonary disease, which increases preoperative/postoperative morbidity or mortality.

Pharmacological agents like nicorandil and trimetazidine have not been found to be of much help in such cases. Of the non-pharmacological options available, like trans-myocardial laser therapy, spinal cord stimulation, stem cell therapy and enhanced external counterpulsation (EECP), transmyocardial laser therapy has fallen out of favor due to the dismal long-term results. Stem cell and other gene therapies are still at the experimental stage and it may take some time for them to become commercially available. There is a significant

body of data to suggest that EECP is an effective noninvasive technique for patients with refractory angina.^{2–4} Besides, its use for the treatment of such patients has been approved by the Food and Drug Administration (FDA).

WHAT IS EECP?

Enhanced external counterpulsation is a non-invasive technique in which three pairs of pneumatic cuffs are applied to the calves, lower thighs and upper thighs, and an electrocardiographic trigger is used to sequentially inflate the cuffs, starting at the calves, at the onset of diastole. All the cuffs are deflated simultaneously before the onset of systole. The patient receives this treatment as an outpatient, for one hour a day for a period of 35 days.

Just like the intra-aortic balloon pump, EECP leads to an augmentation of aortic pressure during diastole. This process of generating a pressure waveform during the counter or reverse phase of normal cardiac pulsation in diastole has been termed ‘counterpulsation.’ During systole, the pressure in the cuffs is relieved suddenly. This has a suction-like effect, which reduces afterload and is called ‘systolic unloading’ of the left ventricle (Figure).

Mechanism of Action

A combination of mechanisms is understood to be responsible for the benefits of EECP. These can be categorized into central effects, peripheral effects, or both. Hemodynamically, EECP augments diastolic blood flow in multiple vascular beds and reduces cardiac afterload. The effects achieved are tabulated (Table 1).

Effect on Coronary Blood Flow

The inflation of the cuffs increases the venous return and hence, the diastolic pressure. This augments the coronary blood flow, which leads to the development of collaterals in the long run. The shear stress generated results in the release of angiogenic growth factors.⁵ Michaels *et al.* made direct measurements of left ventricular and intracoronary

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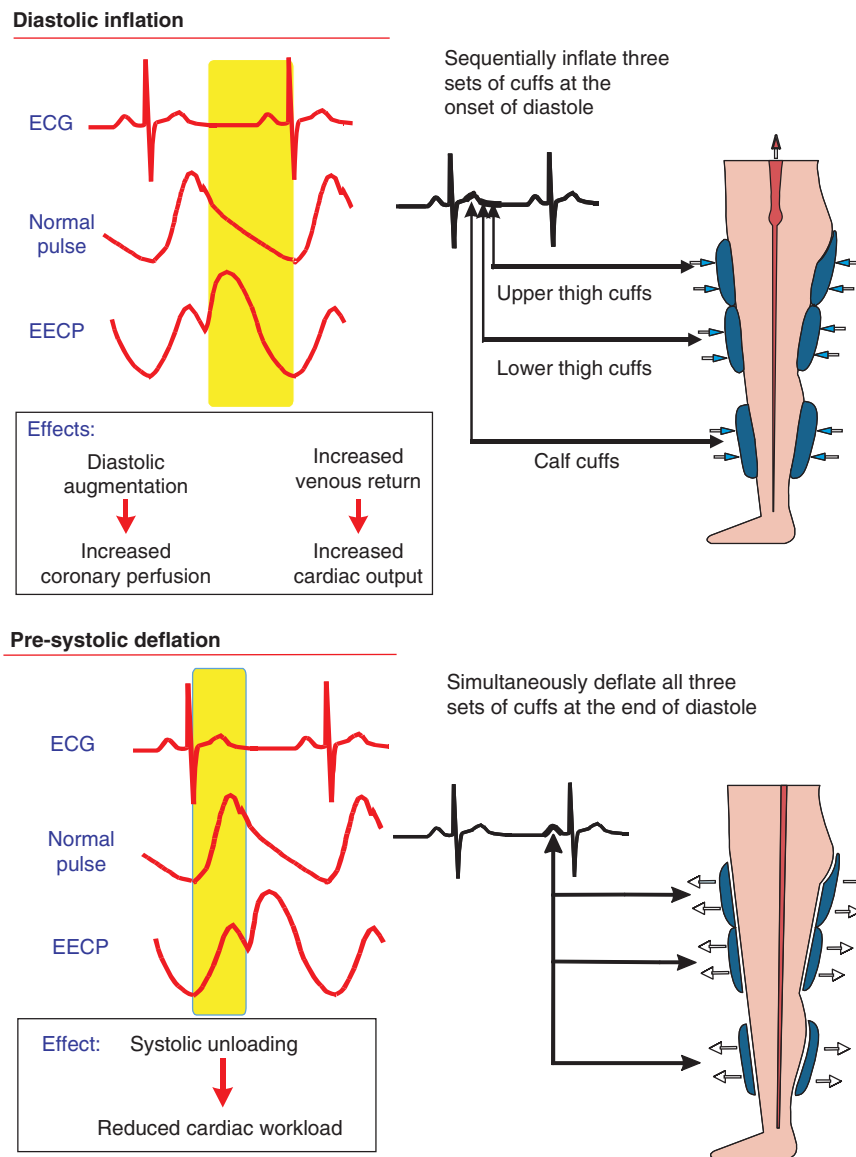


Figure. The EECP technique. ECG: electrocardiogram; EECP: enhanced external counterpulsation.

hemodynamics in patients undergoing EECP.⁶ These measurements showed that EECP led to a 93% increase in diastolic and 16% increase in mean intracoronary pressure. The corrected thrombolysis in myocardial infarction (TIMI) frame count on angiography revealed a 28% increase in coronary flow.

EECP AND MYOCARDIAL PERFUSION

Nuclear studies have demonstrated an increase in myocardial perfusion with EECP therapy. Patients with greater diastolic augmentation have a greater reduction in angina class⁷ and greater improvement of wall motion abnormalities on dobutamine stress echocardiography following EECP.⁸ On the basis of this, it can be hypothesized that EECP may

recruit preformed collaterals, resulting in improved myocardial perfusion. The clinical benefits of this are an improvement in the quality of life, a decrease in the symptoms of angina and a reduction in nitrate requirement.

The other mechanisms thought to be responsible for the improvement of symptoms are as follows:

- Enhancement of endothelial function—Flow-mediated vasodilatation of the brachial artery (FMD), was shown to improve with a seven-week course of EECP. The assessment was carried out with the help of high-resolution ultrasonography, which reflects endothelium-dependent vasodilator function. No such improvement was seen in the control group. The study also demonstrated that there is no increase in FMD following the administration of exogenous nitric oxide

Table 1. Effects of EECP

| Acute Effects | Chronic Effects | Objective Evidence | Clinical Benefits |
|--|--|--|--|
| Increased coronary blood flow | Increased TMPG → Open dormant collaterals | Increased myocardial perfusion (nuclear perfusion, PET scan) | ↓ Symptoms |
| Increased coronary flow velocity | Shear stress | Improved dobutamine | → Improved quality of life |
| Increased diastolic pressure | Increased VEGF → Arteriogenesis and angiogenesis Increased HGF → Increased FGF → | Wall motion score induced Improved LVEF | ↓ Nitrate intake |
| Inflation of cuffs Increased venous return Increased cardiac output | Improved endothelial function → Increased NO Decreased endothelin | Increase in time to ST-segment depression Increased FMD Increased RH (PAT) | → May improve morbidity and mortality |
| Deflation of cuffs Decreased left ventricular afterload Decreased myocardial oxygen consumption | Peripheral training effect similar to exercise ↓ Left ventricular wall stress | ↓ Systemic vascular resistance ↓ BNP | → Improved tolerance (independent) effects |

EECP: enhanced external counterpulsation; TMPG: TIMI myocardial perfusion grade; VEGF: vascular endothelial growth factor; HGF: hepatocyte growth factor; FGF: fibroblast growth factor; NO: nitric oxide; LVEF: left ventricular ejection fraction; PET: positron emission tomography; FMD: flow-mediated dilatation; RH: reactive hyperemia; PAT: peripheral arterial tonometry; BNP: brain natriuretic peptide.

Table 2. Trials of enhanced external counterpulsation in patients with stable angina

| Reference | No. of Patients | Percentage with ≥1 CCS* Angina Class Change | Nitrate Use | Exercise Tolerance (%) | Cardiac Perfusion (%) |
|--------------------------------------|-----------------|---|-------------|------------------------|-----------------------|
| Zheng <i>et al.</i> ¹¹ | 200 | Decrease (97) | NA | NA | NA |
| Lawson <i>et al.</i> ¹² | 60 | Decrease | NA | Increase | Increase (75) |
| Arora <i>et al.</i> ² | 139 | Decrease | Decrease | Increase | NA |
| Lawson <i>et al.</i> ³ | 33 | Decrease (100) | Decrease | NA | Increase (79) |
| Stys <i>et al.</i> ¹³ | 395 | Decrease (88) | NA | NA | NA |
| Barsners <i>et al.</i> ¹⁴ | 978 | Decrease (81) | Decrease | NA | NA |

*CCS = Canadian Cardiovascular Society

(NO), suggesting that improved endothelial function is related to endogenous production of and improved response to NO.⁹ The mechanism by which EECP improves endothelial function remains largely unknown. The most prominent theory is that the regulation of factors affecting endothelial function is modulated by the arterial shear forces that are increased by diastolic augmentation. Fluid shear stress induces phosphorylation and activates endothelial NO synthetase, leading to vasodilation.

- Improvement in ventricular function.
- Peripheral effects similar to those seen with physical exercise.¹⁰
- Several non-specific placebo effects may also be operational.

Evidence of Benefit

Several controlled and uncontrolled trials have investigated the use of EECP therapy in patients with refractory angina. The results are summarized in Table 2.

The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial conducted by Arora *et al.* was the first prospective, randomized, blinded, sham-controlled trial of EECP in the management of patients with chronic stable angina and a positive exercise treadmill test.² In this trial, conducted in seven centers, 139 outpatients with angina, documented CAD and a positive exercise treadmill test were randomly assigned to receive 35 hours of active ($n = 72$) or inactive ($n = 67$) counterpulsation, over a period of 4–7 weeks. The former group had a significant (15%) increase in time to ≥ 1 mm ST-segment depression ($p = 0.01$) and 25% fewer anginal symptoms per week ($p < 0.035$). These effects were not seen in patients in the sham-controlled arm. Follow-up analysis after one year showed greater improvement in health-related measures of quality of life among those who had received active counterpulsation.

Several uncontrolled studies have reported benefits from the use of EECP, and have found the technique to be reasonably safe. A long-term follow-up study, which evaluated 1097 patients from the International EECP Patient Registry (IEPR),⁴ found that immediately after EECP, 73% of the

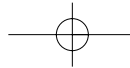


Table 3. Predictors of improvement in angina class after EECP treatment¹⁵

| Variable | Odds ratio |
|-------------------|------------|
| CCS class II | 2.17 |
| CCS class III | 5.29 |
| CCS class IV | 6.69 |
| Treatment hours | 3.47 |
| Diabetes mellitus | 0.67 |
| History of CHF | 0.81 |
| Prior CABG | 0.76 |

CCS: Canadian Cardiovascular Society; CHF: congestive heart failure; CABG: coronary artery bypass graft.

patients improved by at least one Canadian Cardiovascular Society angina class. This was maintained at two years' follow-up. Improvements were also noted in the weekly anginal episodes and sublingual nitroglycerine use. In addition, there was an improvement in the patients' health status, quality of life and satisfaction with life.

The potential for improvement upon undergoing EECP treatment is greater among patients with more severe disease, particularly in terms of their functional angina class. The treatment produces better results if there is good augmentation and at least one artery is patent. Single vessel disease and toleration of complete therapy are other factors that improve the results. Table 3 shows the independent predictors of improvement in angina class after EECP.

EECP treatment produces better results if:

- i. There is good augmentation;
- ii. At least one artery is patent;
- iii. There is single vessel disease; and
- iv. Patient tolerates complete therapy.

Side-Effects of EECP

The following side-effects, though rare, have been reported with EECP therapy.

1. Skin abrasions, bruises and blisters
2. Myalgia and leg pain
3. Precipitated heart failure
4. Pulmonary embolism

CONTRAINDICATIONS

Absolute

1. Decompensated heart failure, usually class III to IV (EECP results in an increase in venous return)
2. Greater than moderate aortic insufficiency (regurgitation would prevent diastolic augmentation)
3. Severe hypertension >180/110 mmHg (the augmented diastolic pressure may exceed safe limits)
4. Aortic aneurysm or dissection (diastolic pressure augmentation may be deleterious)

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5. Pregnancy (the effects of EECP on the fetus have not been studied)
6. Venous disease (phlebitis, varicose veins, stasis ulcers, prior or current deep vein thrombosis or pulmonary embolism)

Relative

1. Initiation of therapy within two weeks of cardiac catheterization or arterial puncture (risk of bleeding at femoral site of puncture)
2. Arrhythmias that may interfere with triggering of EECP system (atrial fibrillation, flutter and very frequent premature ventricular contractions)
3. Severe peripheral arterial disease (reduced vascular volume and muscle mass may prevent effective counterpulsation, increased risk of thromboembolism)
4. Anticoagulants or severe coagulopathy (to avoid risk of hematoma with high cuff pressures)
5. Severe chronic obstructive pulmonary disease (no safety data in pulmonary hypertension)

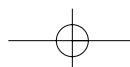
CONCLUSION

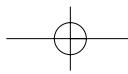
Refractory angina is growing in prevalence and has become an increasingly challenging problem in clinical practice. While various forms of treatment have been tried, results from clinical studies suggest that EECP therapy has the most favorable risk/cost-benefit profile. This therapy is the only FDA-approved non-pharmacological approach to refractory angina that has been supported by sham-controlled data. It is recommended by the American Heart Association as a potential therapy for refractory angina as a class IIb indication (its usefulness/efficacy is relatively less well established).¹⁶ Given the rapid development of EECP over the past few years, it is hoped that the use of this modality will soon receive greater priority than at present. In the future, more patients are expected to benefit from this innovative treatment for angina and other cardiovascular conditions.

The patient mentioned at the beginning of their article underwent 35 cycles of EECP and reported an improvement in his overall quality of life. Objectively, the grade of angina improved from class III to class I, and the distance covered in the six-minute walk from 400 to 1220 feet.

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