Case Report

Noninvasive Revascularization by Enhanced External Counterpulsation: A Case Study and Literature Review

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Nearly 8 million people in the United States suffer from symptoms of coronary artery disease (CAD). Unfortunately, the population of patients with ischemic coronary disease that is not readily amenable to surgical or percutaneous revascularization continues to grow. For patients who are not candidates for standard revascularization procedures and in whom aggressive medical therapy fails to control symptoms, enhanced external counterpulsation (EECP) is a new, noninvasive outpatient method to improve quality of life by decreasing ischemic symptoms and permit increased activity. We report the case of a 56-year-old woman with severe, symptomatic CAD receiving maximal medical therapy who underwent a course of EECP therapy because she was not a good candidate for other forms of revascularization. She demonstrated dramatic improvement in her anginal symptoms and complete resolution of myocardial ischemia on repeat nuclear stress imaging. This case suggests that EECP is a safe and effective method for reducing symptoms of myocardial ischemia in patients for whom standard percutaneous or surgical revascularization is not suitable treatment.

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CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiographic; EECP = enhanced extended counterpulsation

The standard treatment options for patients with symptomatic coronary artery disease (CAD) currently include pharmacologic therapy (β-blockers, calcium channel blockers, nitrates), percutaneous coronary intervention, and surgical revascularization.[1-4] The limitations of each of these strategies include procedure-related mortality and morbidity, adverse effects of medication, restenosis after percutaneous coronary intervention, and time-dependent graft attrition after coronary artery bypass graft (CABG) surgery. Although most patients are candidates for medical therapy, many do not experience complete symptom relief with medications alone. In addition, a growing number of patients are not appropriate candidates for standard revascularization options. Comorbid conditions, poor distal coronary artery targets, and patient preference may limit revascularization options. In patients who have had previous surgical revascularization and require repeat procedures, the morbidity and mortality associated with repeat procedures are significantly higher, often excluding them from consideration for further revascularization. These patients, therefore, did not have optimal symptom relief.

Recently, therapeutic options have been introduced to provide further benefit to such patients, including transmyocardial revascularization[5,6] or percutaneous myocardial revascularization by laser,[7] minimally invasive coronary bypass surgery,[8-12] transcutaneous electrical nerve stimulation,[13,14] and percutaneous CABG surgery.[15,16] A variety of therapeutic efforts that involve growth factor technology have also been used.[17]

All the newer treatment modalities are still in experimental stages, or only a small number of human studies have been conducted. Many of the new devices are invasive and carry a considerable risk of complications. Enhanced external counterpulsation (EECP) has been introduced as a noninvasive, atraumatic procedure for the outpatient treatment of patients with CAD.[18-20] Based on the principle of diastolic augmentation, EECP increases coronary perfusion pressure and reduces the myocardial oxygen demand. We report a patient treated with EECP and also review the literature regarding the current status of EECP.

REPORT OF A CASE

History

A 56-year-old postmenopausal woman with hypertension, hyperlipidemia, and a 10-year history of insulin-requiring diabetes mellitus presented with refractory Canadian Cardiovascular Society Class IV angina despite optimal antianginal medications, including diltiazem (sustained release), 300 mg/d; atenolol, 100 mg/d; and oral nitrates, 60 mg/d. She had severe CAD with typical anginal symptoms since 1996 and had undergone coronary angiography with percutaneous intervention of the right coronary artery. Due to persistent angina and severe CAD in other distributions, she underwent CABG surgery in July 1996, with a left internal mammary graft to the mid-left anterior descending artery and vein grafts to the first

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obtuse marginal, intermediate, and distal right coronary arteries.

After 1 year, exertional angina recurred. Angiography demonstrated native left main and 3-vessel disease with occluded vein grafts to the intermediate and the first obtuse marginal arteries. The left internal mammary artery graft to mid-left anterior descending artery was widely patent. An 80% lesion in the body of the vein graft to the right coronary artery was successfully treated with coronary stenting.

Within 2 months of the procedure, she had progressive exertional and rest angina, and within a year of coronary intervention, she was hospitalized with unstable angina. She reported frequent episodes of chest pain that occurred at rest and with minimal exertion. She took 1 to 4 sublingual nitroglycerin tablets every day. An adenosine (140 μg • kg^{-1} • min^{-1} for 6 minutes) thallium perfusion imaging demonstrated a fall in systolic blood pressure on stress, accompanied by chest pain and electrocardiographic (ECG) changes. The perfusion images demonstrated medium-sized apical, inferior, and inferoseptal defects consistent with abnormal flow reserve. Repeat coronary angiography revealed 50% diameter stenosis of the distal left main artery and 75% stenosis of the proximal left anterior descending artery. Disease had progressed in both the vein grafts and the native coronary arteries, including severe disease of the native left anterior descending artery distal to the graft insertion and native right coronary disease. The graft to the right coronary artery was occluded. Echocardiography showed normal left ventricular systolic function. Repeat percutaneous or surgical revascularization was not considered an option due to the severe distal native vessel disease. Despite aggressive medical therapy with aspirin, nitrates, angiotensin-converting enzyme inhibitors, β-blockade, statins, and vitamins E and C, she remained symptomatic, with frequent episodes of typical angina at rest and with minimal exertion. Further increase in her medical therapy was not possible because her blood pressure was borderline (90/70 mm Hg), and she had sinus bradycardia. She was referred for EECP.

EECP Treatment Protocol

All potential EECP patients have a detailed medical history taken and physical examination that focuses on symptoms, previous revascularization procedures, and documentation of symptomatic CAD (Table 1). Specific precautions are taken to screen patients for any contraindications to this procedure (Table 2).

EECP involves sequential inflation and deflation of compressible cuffs wrapped around the patient's calves, lower thighs, and upper thighs. Inflation and deflation of cuffs are activated by events in the cardiac cycle via microprocessor-interpreted ECG signals (Figure 1). This process augments the aortic diastolic pressure and subsequently increases coronary perfusion pressure. Patients are typically treated for 1 hour daily for a total of 35 hours over 7 weeks.

Table 1. **Enhanced External Counterpulsation Treatment Indications**

Marked symptoms of coronary ischemia (Canadian Cardiovascular Society Class III-IV) despite optimal medical therapy
Not candidate for surgical or percutaneous revascularization
Evidence of coronary artery disease documented by
Angiographic evidence of >70% stenosis in at least 1 major epicardial coronary artery and/or surgical conduit, *or*
Nuclear or echocardiographic imaging consistent with myocardial infarction and/or myocardial ischemia, *or*
Documented history or electrocardiographic evidence of myocardial infarction

Treatment and Follow-up

The EECP therapy was initiated without incident. During the early phase of therapy, the patient needed help getting to her treatment sessions because of her limiting angina. Over the course of therapy, she noticed a marked decrease in her angina, accompanied by a marked increase in her physical activity (Table 3). At the end of the 7-week course of therapy, she was fully active without limitation, including 60 minutes of bicycle or treadmill exercise per day. She continued to take the same antianginal medications as before EECP.

At follow-up, there was improvement in perfusion, as demonstrated by an adenosine thallium study that showed no objective evidence of ischemia or infarction (Figure 2). Nine months after the completion of treatment, the patient remained active with anginal episodes occurring less frequently than once per month and relieved promptly with rest or sublingual nitroglycerin.

Table 2. **Relative Contraindications to Enhanced External Counterpulsation**

Ongoing, persistent ischemia
Overt congestive heart failure
Severe valvular heart disease
Uncontrolled blood pressure (>180/110 mm Hg)
Dysrhythmia interfering with electrocardiographic trigger
Severe, symptomatic peripheral vascular disease
History of phlebitis, deep vein thrombosis, severe varicose veins, or stasis ulcers
Bleeding diathesis, including ongoing warfarin use with international normalized ratio >2.0
Increased bleeding risk (within 7 d of coronary angiography or other invasive procedure)
Pregnant women or women of childbearing potential who do not use a reliable contraceptive method to avoid possible danger to fetus

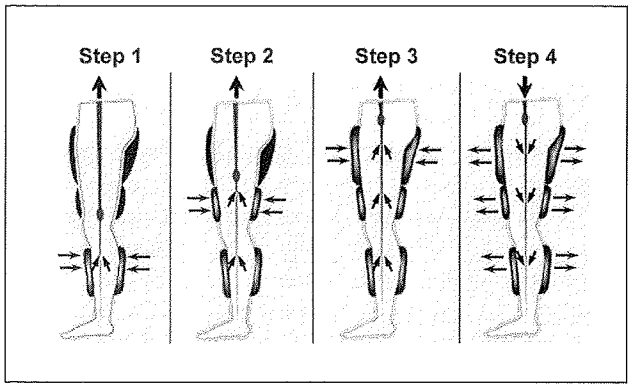

Figure 1. Mechanism of diastolic augmentation and systolic afterload reduction using enhanced external counterpulsation. Note the electrocardiographically-gated sequential diastolic activation to "milk" lower extremity venous and arterial blood from the periphery to the central vasculature (steps 1-3). All cuffs deflate simultaneously immediately prior to systole (step 4).

Table 3. **Clinical Course During Treatment**

Week 1
1 Anginal episode at rest
Physical activity limited to sitting in hotel room
Week 3
1 Anginal episode at rest
Walking in hotel room
Week 5
2 Brief episodes of angina with slight exertion
Beginning gentle exercise program
Week 7
No angina
Walking/biking 60 min/d

DISCUSSION

This case report offers a dramatic example of the potential of EECP therapy in reducing symptoms of myocardial ischemia. At the onset of therapy, this patient was essentially bedridden because of severe exertional angina. After a 7-week course of EECP, she was able to exercise daily without symptoms and had complete resolution of myocardial ischemia at the time of repeat nuclear perfusion imaging. This clinical benefit has been maintained with 9 months of follow-up.

Used as a treatment for angina for 2 decades, external counterpulsation has a growing body of literature supporting its effectiveness.[18-22] The procedure, first proposed by Kantrowitz and Kantrowitz,[23] is noninvasive and atraumatic and increases diastolic pressure and coronary perfusion pressure, as well as left ventricular unloading, in a manner analogous to the invasive intra-aortic balloon pump.[24-26] These early cumbersome hydraulic counterpulsation devices have been modified over the years and now include computerized, ECG-gated pneumatic compression cuffs placed over the lower extremities, improving diastolic augmentation and reproducibility of effect. Newer EECP devices have been shown to provide long-term symptom relief and improved quality of life in a heterogeneous group of patients with ischemic heart disease.[20]

EECP in Angina

Several studies reported their experience of EECP in patients with angina refractory to medical therapy.[18-22] These patients were not candidates for either percutaneous or surgical revascularization. These studies reported consistent improvement in anginal status as determined by

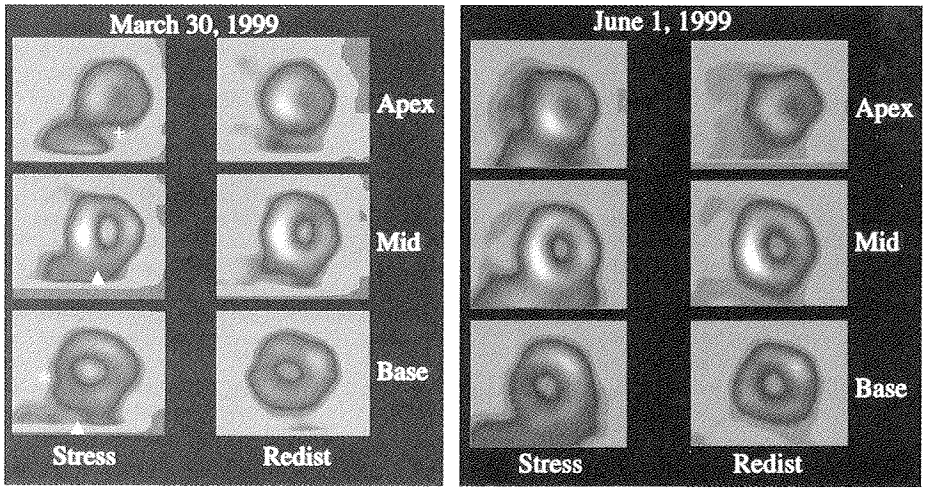

Figure 2. Matched stress and rest perfusion images obtained before (left) and after (right) external counterpulsation treatment. Note the improvement after treatment in adenosine-induced inferior (arrowhead), inferoseptal (asterisk), and apical (plus sign) ischemia noted on the pretreatment images. Redist = redistribution.

Table 4. **Results of Early, Nonrandomized Studies of the Clinical Effect of EECP***

Author	No. of patients	EECP treatment sessions (h)	Angina relief (%)	Improvement in thallium test (%)
Zheng et al,[21] 1983	200	12	97	NA
Lawson et al,[19,20] 1992, 1995	18	36	100	78
Karim et al,[22] 1995	38	36	86	78

*EECP = enhanced external counterpulsation; NA = not available.

Canadian Cardiovascular Society Classification, decrease in daily use of nitroglycerin tablets, improvement in exercise tolerance, and improvements in objective measures of ischemia (Table 4). The drawbacks with these initial studies were the small number of patients involved and the lack of sham controls, prohibiting the exclusion of a placebo effect as the primary mode of action.[19,20] In a recent multicenter, randomized, placebo-controlled trial of EECP, 139 patients with angina and documented coronary ischemia were randomized to active vs hemodynamically inactive counterpulsation.[18] Active counterpulsation patients demonstrated significantly improved time to ST-segment depression on exercise testing, as well as significantly improved exercise duration. The number of angina episodes was also significantly reduced in the treatment group but not in the control group (Table 5). There were no serious complications, and treatment effects on quality of life were sustained at 1-year follow-up.

Nuclear perfusion imaging studies have demonstrated reduction or resolution in the size of ischemic defects after a course of EECP,[19,22] and EECP may increase the perfusion from baseline as evidenced by ammonia positron emission tomography.[27]

Mechanisms of Action

The exact mechanism by which EECP improves symptoms in patients with chronic angina and other syndromes remains undefined. The acute hemodynamic effect is similar to that seen with the intra-aortic balloon pump and is due to a reduction in afterload and in the diastolic augmentation of central aortic pressure. Additionally, preload may be augmented.[24] Recent advances in the understanding of coronary arterial physiology and response have provided insight into possible modes of effect and an explanation for the benefits seen with EECP. In the setting of an ischemic substrate, increased coronary blood flow and shear forces induced by diastolic aortic pressure augmentation may be sufficient to promote angiogenesis and collateral formation.[27-30] In vitro, increased shear stress activates the tyrosine kinase pathway in the endothelium. The tyrosine kinase receptor causes phosphorylation in a group of submembranous proteins, which in turn induces changes in the actin cytoskeleton. This modification of the actin cytoskeleton is the key factor in endothelial and smooth muscle cell migration, potentially resulting in new vessel formation to ischemic areas of the myocardium.

Apart from angiogenesis and collateral formation, the increased vascular shear forces created both centrally and peripherally during EECP therapy may be instrumental in improving vasomotor function. Endothelial shear stress has been shown to augment endothelium-derived relaxing factor/nitric oxide production.[27] Down-regulation of endothelin-1 levels by pneumatic external pulsations was recently demonstrated.[28] Down-regulation of endothelin-1 levels may improve coronary vasodilation and coronary perfusion. This may also contribute to the anti-ischemic effects of EECP. These factors thus play a central role in coronary smooth muscle response and vasodilation. There is also participation of various growth factors, in particular vascular endothelial growth factor.[30] These changes are considered important in promoting angiogenesis and collateral formation and could explain the sustained benefit even after stopping EECP therapy.

Table 5. **Exercise Tolerance Test Changes in MUST-EECP***

Parameter	Control group No.	Control group Mean (SE) change (s)	EECP-treated group No.	EECP-treated group Mean (SE) change (s)	*P*
Exercise duration	58	26 (12)	57	42 (11)	.30
Time to ST depression	56	−4 (12)	56	37 (11)	.01

*MUST-EECP = Multicenter Study of Enhanced External Counterpulsation.[18]

Conclusions

Recent studies suggest that EECP is a novel, potentially beneficial adjunctive therapy in the treatment of angina secondary to CAD. It is safe and noninvasive and without major adverse effects. This can be offered to patients with angina refractory to antianginal medications who are not suitable candidates for conventional revascularization procedures. The data are still limited, however, and long-term prospective studies are unavailable. Currently, protocols are being developed to describe the mechanisms of action and provide long-term clinical follow-up information.

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