Enhanced External Counterpulsation in Unrevascularizable Patients

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Enhanced external counterpulsation (EECP) is a noninvasive outpatient therapy for the treatment of chronic angina. EECP treatment produces an acute hemodynamic effect that is similar to that produced by the invasive intra-aortic balloon pump. Three sets of cuffs on the upper thigh, lower thigh, and calves of each leg are inflated with compressed air during the diastolic phase of the cardiac cycle and are deflated in early systole. This rapid inflation and deflation raises diastolic aortic pressure, increases coronary perfusion pressure, and provides improved afterload reduction and increased venous return with a subsequent increase in cardiac output.

Enhanced external counterpulsation has been shown to provide long-term symptom relief in patients with ischemic heart disease in several case series, as well as in a randomized trial. Up to 80% of patients selected for treatment have a positive clinical response, and an associated objective improvement has been demonstrated by functional imaging in several case series. A treatment course consists of 35 1-hour sessions over a 7-week period and is generally well tolerated with a low risk of adverse events. Development and enhancement of collateral channels, as well as peripheral conditioning and neurohumoral effects, may play a role in providing symptomatic relief. Studies are ongoing to determine the mechanism of action and to further define subsets of patients who might benefit.

Introduction

More than six million patients have symptomatic coronary artery disease in the United States, and an estimated 350,000 new cases develop each year [1]. As this population of patients continues to grow, so does the cohort of patients who remain symptomatic despite optimal medical therapy. Although percutaneous intervention or coronary bypass grafting may provide additional symptomatic relief, as many as 2.4 million symptomatic patients are not candidates for standard revascularization procedures because of personal preference, multiple previous revascularization attempts, or unsuitable coronary anatomy. The therapeutic options for such patients are distinctly limited, and there is a growing need for novel methods of symptom relief.

Enhanced external counterpulsation (EECP) has been used abroad as a treatment for angina for over two decades. Recent technical improvements and a growing body of literature to support its effectiveness have reinvigorated interest in EECP as a therapeutic modality in this country. EECP is a noninvasive, atraumatic, outpatient procedure providing long-term relief of angina symptoms and improved quality of life in a heterogenous group of patients with ischemic heart disease. Based on reports of efficacy in a variety of clinical states, the United States Food and Drug Administration has approved this procedure for the treatment of chronic or unstable angina as well as for heart failure and acute myocardial infarction.

Procedure

Diastolic blood pressure augmentation was first proposed as a means of improving coronary perfusion nearly 50 years ago [2]. EECP was developed as a noninvasive method of providing this diastolic augmentation through pressure applied to the lower extremities. Although providing modest diastolic augmentation, early EECP devices were cumbersome and relied on relatively slow and ineffective hydraulic actuation of single-chamber bladders placed over the lower extremities.

Newer devices provide an improved and more reproducible acute hemodynamic effect through more responsive ECG-gated pneumatic compression of the lower extremities via cuffs on the calf, lower thigh, and upper thigh of each leg. These cuffs are sequentially inflated with compressed air during the diastolic phase of the cardiac cycle, effectively "milking" blood centrally from the lower extremities. Rapid deflation of the cuffs in early systole promotes systolic aortic runoff (Fig. 1). This rapid inflation and deflation of the cuffs raises diastolic aortic pressure, increases coronary perfusion pressure, and provides improved left ventricular unloading in a manner analogous to that of the invasive intra-aortic balloon pump (Fig. 2). In addition to this diastolic augmentation and systolic afterload reduction, EECP also promotes increased venous return with a subsequent increase in cardiac output [3]. A standard treatment course consists of 35 1-hour sessions over a 7-week period.

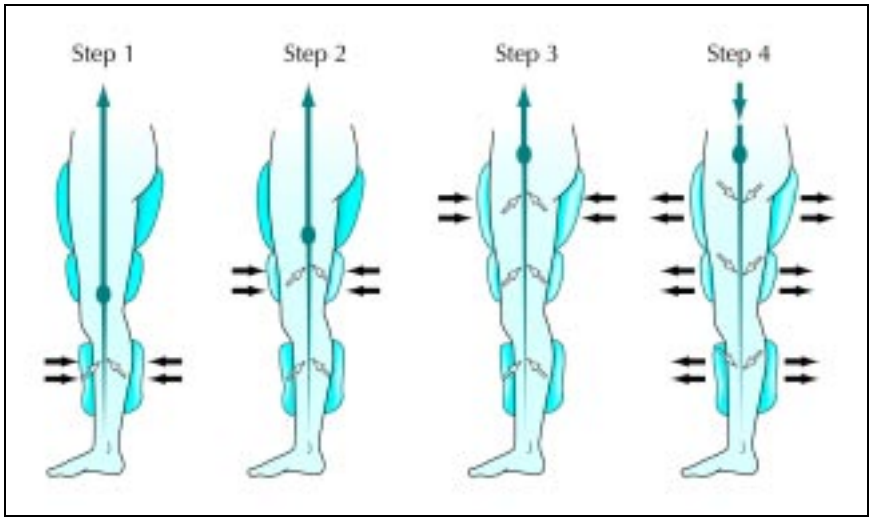

Figure 1. Mechanism of diastolic augmentation and systolic afterload reduction during enhanced external counterpulsation (EECP). Electrocardiography-gated sequential activation of the lower extremity cuffs results in "milking" of the lower extremity blood pool to the central vasculature during diastole (steps 1–3). All cuffs deflate simultaneously immediately prior to systole for systolic afterload reduction (step 4). *Horizontal arrows* indicate inflation of cuffs (squeezing) and deflation of cuffs. *Slanted arrows* indicate blood movement due to squeezing. (*From* Singh *et al.* [3].)

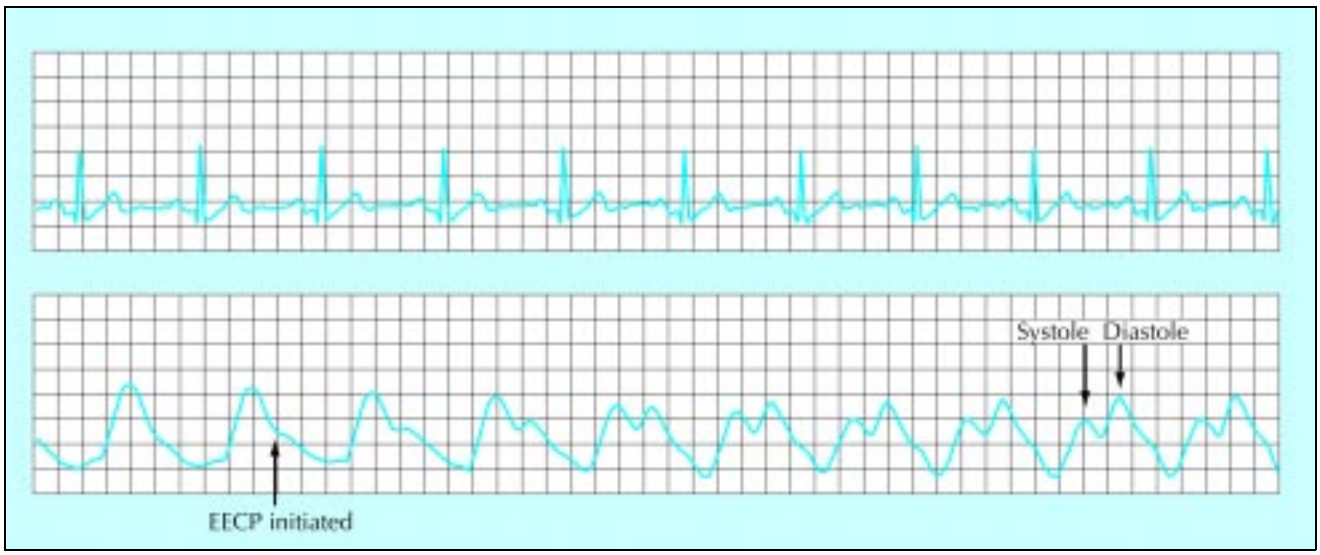

Figure 2. Plethysmographic evidence of increased diastolic pressure and reversal of the usual systolic to diastolic blood pressure ratio during initiation of enhanced external counterpulsation (EECP). EECP increases diastolic perfusion pressure analogous to intra-aortic counterpulsation.

Results

Several case series [4–15,16•] and a recent randomized trial [17••] demonstrated the safety and efficacy of EECP therapy in reducing symptoms of angina. Anecdotal reports and EECP treatment registries have consistently reported a positive clinical response in up to 80% of patients selected for treatment (Table 1). Observed benefits have included reductions in angina [4–13,16•,17••] and nitrate use [6,9,11,12,17••], as well as improved exercise tolerance [4,6,8,10,12–15,17••] and improvement in objective measures of ischemia, such as prolonged time to exercise-induced ST segment depression [13–15,17••] and perfusion defect resolution [4,6,8–12,14,15].

Positive exploratory studies performed in China in the early 1980s using sequential pneumatic external counterpulsation [5] led to the prospective evaluation of a series of patients at the State University of New York (SUNY) at Stony Brook [6]. Eighteen patients with chronic symptomatic coronary disease and exercise-induced myocardial perfusion defects underwent a 35-hour course of EECP therapy. All patients reported improvement in symptoms, and 16 of 18 patients reported no angina with activities of daily living. Exercise-induced thallium perfusion defects resolved completely after the treatment course in 12 patients and improved in an additional two patients [6]. These treatment effects persisted, with 13 patients remaining pain free at 3 years [7]. Other investigators have now reported similar early improvement in symptomatic and objective measures of ischemia, with long-term follow-up pending [12,13,15].

These reports, although illustrating the potential benefit of EECP in ischemic coronary disease, were generally small or retrospective studies without adequate control populations. The prospective Multicenter Study of Enhanced Exter-

Table 1. Uncontrolled clinical studies of EECP treatment of angina

Study	Patients, *n*	Angina relief, %	Improvement in perfusion, %	Exercise time improvement, %
Zheng *et al.* [5]	200	97	—	—
Lawson *et al.* [6]	18	89	78	94
Karim *et al.* [8]	38	86	86	78
Lawson *et al.* [9]	33	100	79	—

EECP—enhanced external counterpulsation.

nal Counterpulsation (MUST-EECP) confirmed the clinical benefit of EECP in a randomized, double-blind, placebo-controlled trial involving 137 patients with chronic, stable angina and positive exercise studies [17••]. Patients were randomized to 35 sessions of active EECP therapy or "sham" sessions of reduced-pressure, inactive counterpulsation. Patients and physicians were blinded to the treatment assignment and patient-patient contact was minimized in an effort to diminish the possibility that patients would surmise their assigned treatment group. Prior to treatment, both groups had similar mean daily angina counts (0.76 ± 0.15 and 0.76 ± 0.13, respectively) and similar treadmill exercise duration (426 ± 20 seconds and 432 ± 22 seconds, respectively). After treatment, the 71 patients undergoing active EECP therapy had fewer angina episodes per day than the 66 patients randomized to inactive counterpulsation (0.55 vs 0.77, $P < 0.05$). Although exercise duration (Fig. 3) increased in both groups after treatment (44 seconds and 32 seconds, respectively), only active counterpulsation was associated with improved time to ST-segment depression (42 seconds vs -4 seconds, $P = 0.01$).

A quality of life substudy to MUST-EECP [18,19] provided insight into additional effects of EECP and confirmed previous findings of the psychosocial benefit associated with this therapy [20]. In MUST-EECP, active as compared with inactive counterpulsation was associated with marked improvement in numerous quality of life measures at both 6 [18] and 12 months [19] after treatment completion. Although both groups had similar quality of life scores at baseline, only patients treated with active counterpulsation demonstrated statistically significant improvement on all measured scales at 6 months [18]. Patients in the active counterpulsation cohort also experienced improved measures of physical functioning ($P = 0.04$), emotional well-being ($P = 0.01$), and general health status ($P < 0.01$) compared with the inactive counterpulsation cohort. Preliminary follow-up suggests that these quality of life benefits are sustained at 1 year [19].

Several ongoing registries have corroborated the beneficial impact of EECP therapy. The International EECP Patient Registry (IEPR) was initiated in 1997 to collect short- and long-term outcome data in a heterogenous group of consecutive patients treated with EECP [16•]. As opposed to the MUST-EECP experience, this registry focuses on the "real-world" experience of EECP delivery and outcome. Data is collected at baseline, after treatment, and at 6, 12, 24, and 36 months. Baseline characteristics gathered confirm the severity of underlying risk factors and cardiac disease present in this population, including advanced age (mean 66.2 years), diabetes mellitus (40%), hypertension (68%), hyperlipidemia (75%), history of tobacco abuse (71%), history of myocardial infarction (68%), and history of heart failure (28%).

Among the first 978 registry patients, most had undergone previous revascularization procedures (81%) and were felt by the referring physician to be poor candidates for conventional revascularization strategies (69%), due to anatomic considerations or significant comorbidities. The initial clinical results associated with EECP have been favorable in this high-risk cohort, with improvement in Canadian Cardiovascular Society (CCS) angina class in 72% of 2204 patients enrolled in the registry as of April 2000. A total of 40% of patients have experienced improvement of at least two CCS classes (Fig. 4) (Kennard, Personal communication).

Although extensive long-term follow-up data is lacking, initial reports suggest a prolonged benefit among patients with an initial positive response. Lawson *et al.* [9] have reported the 5-year follow-up results of 33 patients treated with EECP at SUNY-Stony Brook [9]. After a course of treatment, 26 patients (79%) experienced symptomatic improvement and had improvement or resolution of ischemic changes on stress perfusion imaging. Despite significant adverse clinical characteristics at baseline, 64% of the total cohort remained free of significant adverse events at 5 years. In the group with an initial positive response to EECP, only six patients (23%) suffered a significant clinical event over the ensuing 5 years, including death (one patient), repeat revascularization (two patients), myocardial infarction (one patient), recurrent angina (one patient), and aortic valve replacement (one patient). Patients enrolled in the IEPR have also experienced clinical benefit persisting beyond the first year after treatment. Among 579 patients with 12-month follow-up, 79% indicate no increase in angina since completion of EECP treatment, with less than 18% of these patients experiencing CCS class III or IV angina (Kennard, Personal communication).

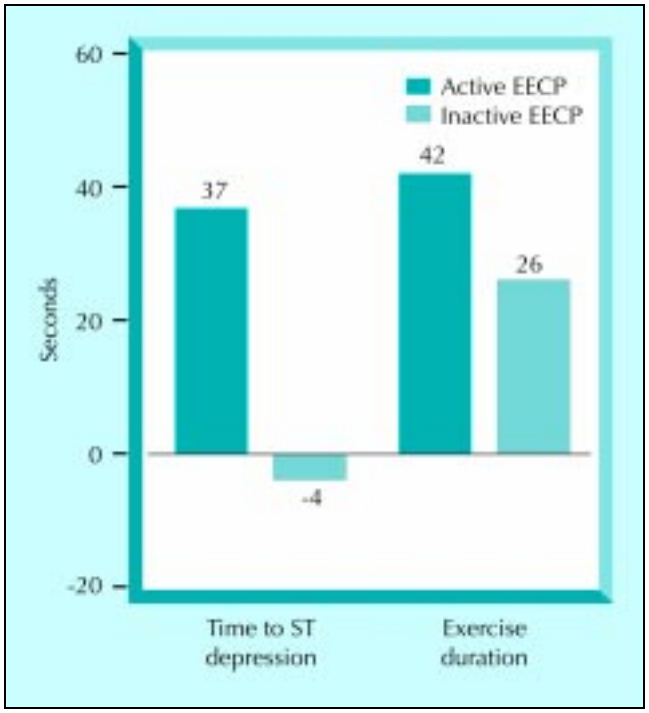

Figure 3. Exercise tolerance test changes in the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP). (*From* Masuda *et al.* [15].)

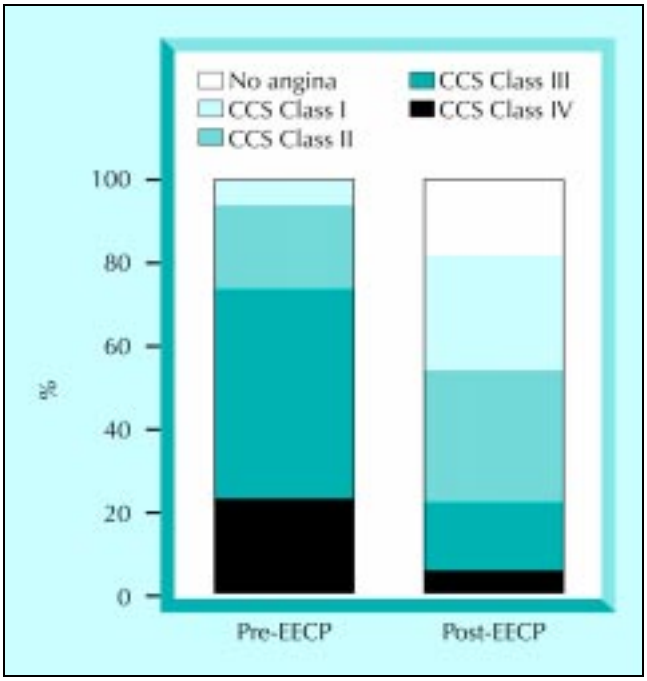

Figure 4. Change in clinical angina status after completion of treatment among 2204 consecutive patients enrolled in the International EECP Patient Registry. CCS—Canadian Cardiovascular Society; EECP—enhanced external counterpulsation.

Mechanism

The mechanism of benefit attributable to EECP remains uncertain and underexplored. Despite the growing body of evidence supporting the safety and symptomatic benefit associated with EECP therapy, it is unclear whether central or peripheral effects, or a combination of factors, predominate. The acute hemodynamic effect is similar to invasive intra-aortic balloon counterpulsation [3], including aortic diastolic pressure augmentation and systolic unloading. EECP action on the venous system also promotes increased venous return, resulting in a measurable improvement in cardiac output of 10% to 25% [3,21]. Under fully applied EECP, diastolic to systolic pressure ratios may approach 1.5 or greater (Fig. 2), and in the absence of obstructive arterial disease, increased diastolic perfusion pressure theoretically translates into increased distal arterial flow [22,23]. Increased diastolic flow has, in fact, been demonstrated in a variety of arterial beds during EECP, including the renal [24,25], carotid [25], internal mammary [26], and coronary arterial systems [12,25], with left main coronary diastolic flow increasing up to 42% [12].

This hemodynamic impulse may act directly on vascular channels or indirectly through endothelial mediators to improve coronary perfusion. Increased diastolic flow may directly open preexisting channels and encourage new channel development, as capillary density has been shown to increase acutely in experimental infarction models treated with EECP [27]. It is also believed that the repeated increases in diastolic pressure and flow create intravascular shear stress, a recognized stimulant of growth factor expression and vasculoneogenesis. In vitro, increased shear stress activates the tyrosine kinase pathway in the endothelium, causing phosphorylation of submembrane proteins and modification of the actin cytoskeleton. In the setting of an ischemic substrate, this may promote smooth muscle cell migration and stimulate the growth of collateral vessels, thereby improving blood flow to the myocardium and providing a possible mechanism for the observed long-term benefits of this short-term therapy.

There is additional circumstantial clinical evidence to implicate collateral development as a factor in symptomatic improvement. As noted previously, several case series have reported improvement in perfusion defects after EECP [4,6,8–12], as well as improvement in coronary flow as measured by rest and stress positron emission tomography images [14,15], although this has not been entirely consistent [28]. Lawson *et al.* [11] provide further indirect evidence, reporting a retrospective evaluation of 50 consecutively treated patients with symptomatic coronary disease. In this series, patients were categorized according to the extent of unrevascularized coronary disease. Blinded review of matched nuclear perfusion images identified a correlation between procedural success and residual 1- or 2-vessel disease. Patients with native 3-vessel disease and without a patent bypass conduit received significantly less improvement in perfusion, indicating less benefit when increased diastolic pressure is not translated into increased distal flow and shear forces due to obstructive proximal coronary disease. Perfusion defect resolution occurred in

95% (18 of 19), 90% (17 of 19), and 42% (five of 12) of patients with residual 1-, 2-, or 3-vessel disease, respectively ($P < 0.01$). Similarly, a retrospective analysis of patients enrolled in the randomized MUST-EECP trial found that among those patients receiving active counterpulsation, less residual obstructive coronary disease (1- or 2-vessel) was associated with more improvement in exercise duration ($P = 0.04$) and time to ST-segment depression with exercise ($P = 0.038$) [29]. Finally, increased vascular endothelial growth factor (VEGF) expression has been demonstrated after a course of therapy. Werner *et al.* [12] found a significant increase in plasma VEGF levels among five of nine patients experiencing marked symptomatic improvement compared with those experiencing only modest symptomatic improvement after a course of EECP. These studies appear to lend credence to the hypothesis that the outcome of EECP is dependent upon patent arterial flow to areas adjacent to ischemic territories and that shear-induced collateral development and improvement in flow to ischemic areas may be operative in the observed clinical response. This mechanistic hypothesis will be explored in an upcoming controlled trial evaluating perfusion defect changes after a course of EECP.

Apart from collateral formation, hemodynamic forces may be instrumental both centrally and peripherally in improving vasomotor function through the enhanced expression of vasoactive factors [15,30–32]. Potential markers of improved vasoreactivity were explored in a larger series of 43 patients with coronary artery disease [30]. The authors demonstrated a dose-related (time-dependent) increase in nitric oxide levels that were sustained at 3-months post treatment. This was associated with a significant and parallel decrease in endothelin-1 levels throughout the period of testing. Similarly, Qian *et al.* [31,32] examined nitric oxide production and lipid peroxidation in 104 patients, including 35 normal volunteers and 69 patients randomized to EECP treatment or continued medical therapy for chronic ischemic coronary disease. Baseline nitric oxide levels were significantly greater in the control group than the diseased group. However, the authors again found a dose-related increase in nitric oxide levels among patients treated with EECP, with a dramatic and statistically significant increase after 36 hours of treatment. By the end of treatment, nitric oxide levels exceeded those measured in the control groups. Patients randomized to medical therapy had a small increase in nitric oxide levels over the course of the study, but the levels did not approach those of the "normal" control group. Lipid peroxidation rates were reduced in parallel to improvements in nitric oxide expression among treated patients [32]. The promotion of these and other factors may contribute to the anti-ischemic effects of EECP and help to explain the observed sustained benefits.

Additional benefit may occur due to peripheral "training" and neurohormonal effects associated with treatment. Much of this effect may be described as "passive exercise." It is intriguing that the hemodynamics of exercise have been described in terms of a form of counterpulsation, with heartbeat and step entrainment noted in highly trained athletes [33]. In addition, although exercise training has been shown to improve outcome in patients with coronary disease, the exact mechanism of benefit remains unclear. Exercise has been shown to improve endothelial function in patients with underlying atherosclerotic coronary disease, possibly contributing to the improvement associated with exercise in this population [34]. In a similar way, the vascular shear forces induced during EECP therapy may be involved in improving vasomotor function and altered exercise hemodynamics. The maintenance of a stable peak exercise double product, despite increased exercise duration and improved perfusion imaging among EECP responders, has been described as evidence of a peripheral "training" effect that may coexist with and enhance the central cardiac effects of the therapy [10,14,15]. As noted, EECP has been shown to increase peripheral nitric oxide levels [15,31] while decreasing endothelin-1 [30] and lipid peroxidation rates [32], indicating a possible effect of EECP therapy on central and peripheral vascular smooth muscle regulation and response.

The vascular and fibrinolytic milieu may be altered by this therapy as well. Intermittent lower extremity pneumatic compression, often employed as deep venous thrombosis prophylaxis in surgical and immobilized patients, may exert an antithrombotic effect through increased venous flow and stimulation of the endogenous fibrinolytic cascade. Although results are not consistent across trials [35,36], as little as 120 minutes of this low activity venous compression has been shown to acutely stimulate endogenous fibrinolysis through decreased plasminogen activator inhibitor–1 activity in both normal and post-thrombotic states [35]. As with improved endothelial function, favorable effects on thrombotic homeostasis may play a beneficial role in the reduction of symptoms, as well as cardiac events.

Although the mechanism of action is not fully established, collateral recruitment, neurohormonal mechanisms, and peripheral conditioning effects probably contribute to any physiologic effect. It is also true that other nonspecific factors, often referred to as the "placebo effect," can have a significant role in subjective improvement, particularly in the population of patients with chronic disease [37,38]. Symptomatic improvement may occur as a result of increased medical attention associated with prolonged contact, close adherence to treatment guidelines among interested practitioners, and increased attention to other aspects of an "evidence-based approach" in the treatment of chronic ischemic coronary disease. These effects can have an impressive impact on registry data as well as randomized trials. The recent DIRECT trial (DMR in Regeneration of Endomyocardial Channels Trial) of direct percutaneous laser revascularization highlighted this effect, with 42% of patients in the placebo cohort achieving a reduction of two CCS angina classes by 3 months (Leon, Paper presented at Transcathe-

Table 2. Relative contraindications to EECP treatment

Increased bleeding risk (*eg*, within 10 days of femoral-access coronary angiography or other invasive procedure)
Bleeding diathesis (*eg*, warfarin use with international normalized ratio > 2.0)
Dysrhythmia interfering with electrocardiographic trigger
Uncompensated congestive heart failure
Severe valvular heart disease
Severe, symptomatic peripheral vascular disease
History of thrombophlebitis or increased risk
Severe, medically resistant hypertension (> 180/110)
Pregnant women or women of childbearing potential without reliable contraception

EECP—enhanced external counterpulsation.

Table 3. Adverse experiences related to counterpulsation in MUST-EECP

	Control group, % (*n* = 66)	Active counterpulsation, % (*n* = 71)	*P*
Paresthesia	1	2	NS
Edema/swelling	0	2	NS
Skin trauma	2	13	0.005
Leg/back pain	7	20	0.01

MUST-EECP—Multicenter Study of Enhanced External Counterpulsation; NS—not significant.
(*From* Arora *et al.* [17••].)

ter Cardiovascular Therapeutics, Washington, DC, 2000). In contrast, although some of the proposed benefit of EECP therapy may occur independently of recognized physiologic factors, the randomized MUST-EECP trial found a significant difference in objective measures of improvement between active and placebo treatment, as well as a significant and consistent benefit in quality of life measures. The reproducibility of these findings awaits further study.

Risks

Enhanced external counterpulsation therapy is generally well tolerated. Due to the vigorous compression applied to the lower extremities, certain factors may theoretically predispose patients to complications, including a bleeding diathesis, severe valvular disease, uncompensated heart failure with significant peripheral edema or pulmonary hypertension, or a high likelihood of venous thrombotic disease (Table 2). The most common side effects are mild headache after treatment, mild dizziness, and muscle aches. In approximately 10% of patients, pressure sore or bruising may develop in the lower extremities as the direct result of cuff inflation (Table 3). This may necessitate discontinuation or a brief respite in treatment in a small minority of patients [17••].

Conclusions

The need to treat a growing number of unrevascularizable patients with chronic angina refractory to optimal medical therapy has led to the investigation of a wide range of new therapeutic modalities. EECP represents a safe, nontraumatic, outpatient alternative for relief of chronic, symptomatic ischemic coronary disease. Thirty-five hours of therapy over a 7-week period has been shown to provide persistent relief of angina in numerous case series and anecdotal reports. Although the weight of evidence supporting the efficacy of EECP includes a randomized trial demonstrating significant symptomatic improvement compared with placebo, the mechanism of effect and verification of long-term benefits awaits further study.

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