Clinical Reviews: Focused

Enhanced External Counterpulsation: An Innovative Physical Therapy for Refractory Angina

Debra L. Braverman, MD

The prevalence of refractory angina in the United States is 600,000 to 1.8 million. Improved pharmacological, invasive, and surgical therapies for cardiovascular diseases during the last few decades have led to an increase in life expectancy of such individuals. Despite treatment with multiple medications and invasive procedures, these patients remain symptomatic and functionally limited. Enhanced external counterpulsation (EECP) is a safe, noninvasive, well-tolerated, and clinically effective outpatient physical therapy for many patients with refractory angina. Numerous trials demonstrate positive clinical responses among at least 80% of patients undergoing EECP, including reductions in angina and nitrate use, increases in exercise tolerance, and enhanced quality of life. Several mechanisms, including the promotion of collateral blood flow, improvement in endothelial function, reduction in inflammation, and the production of peripheral training effects similar to exercise, are thought to be responsible for the clinical benefits of this therapy. Despite the marked success rates EECP achieves with appropriately selected patients who have end-stage coronary artery disease, the treatment remains largely unknown, particularly among physiatrists. This review will summarize the current evidence for the use of EECP and spark a better understanding of the potential role of this treatment in cardiac rehabilitation.

INTRODUCTION

Approximately 9.1 million Americans have angina pectoris, with 500,000 new cases developing annually. Direct and indirect costs of coronary heart disease approach $156.4 billion per year [1]. Improved drug therapy and invasive procedures have increased the life expectancy of these patients. However, some remain severely disabled by angina despite exhausting these treatments. The prevalence of refractory angina in the United States is 600,000 to 1.8 million [2]. For these individuals, daily activities such as walking, climbing steps, carrying a bag of groceries, making the bed, or mowing the lawn are impossible without chest pain, shortness of breath, or considerable fatigue.

What remains beyond conventional surgically invasive and pharmacological treatments is enhanced external counterpulsation (EECP). It is an innovative noninvasive therapy for coronary artery disease and angina for which a reduction of symptoms, improvement in objective measures of myocardial ischemia, and improvement in left ventricular function have been shown. There are more than 100 peer-reviewed articles cited by the U.S. National Library of Medicine documenting the safety and efficacy of EECP, yet this physical therapy remains largely unknown, particularly among physiatrists. This review will summarize the current evidence for the use of EECP and spark a better understanding of the role of this treatment in cardiac rehabilitation.

BACKGROUND

Historical Perspective

More than half a century ago researchers at Harvard University conducted experiments with counterpulsation demonstrating that this technique markedly reduces the work-
load, and thus oxygen consumption, of the left ventricle. In 1953, Kantrowitz described diastolic augmentation as a means of improving coronary blood flow. Birtwell did pioneering work toward the development of this technique and was the first to apply this concept by developing the initial arterial counterpulsator in the United States. Zheng et al reported the benefits of external counterpulsation in the 1980s by using a pneumatic counterpulsation technique.

Figure 1. A patient receiving EECP treatment.

Figure 2. Schematic of EECP cuffs. The procedure consists of sequential leg compression by the EECP cuffs at 50-ms intervals during early diastole followed by simultaneous cuff deflation at the onset of systole.
Interest in EECP grew in the United States when multiple open-label studies in the 1990s showed resolution of coronary perfusion defects associated with improvement in exercise tolerance on stress tests. In 1995 the U.S. Food and Drug Administration approved the EECP device to treat stable angina, cardiogenic shock, and acute myocardial infarction and, in 1999, the Centers for Medicare and Medicaid Services approved coverage of EECP for Medicare recipients with disabling angina. Because of its effects on the venous system, EECP therapy initially was considered contraindicated in patients with heart failure. However, recent studies showed the safety and effectiveness of the system in heart failure treatment which subsequently led the Food and Drug Administration to expand its approval of the EECP device to treat congestive heart failure in 2002 [4-7].

Hemodynamic Effects of EECP

During EECP the patient’s lower extremities are wrapped in 3 compressive pneumatic cuffs applied to the calves, lower thighs, and upper thighs (Figure 1). Electrocardiogram (ECG)-gated sequential leg compression occurs as these cuffs are inflated from distal to proximal in early diastole and then rapidly deflated at the onset of systole (Figure 2), analogous to the intra-aortic balloon pump (IABP). The rapid inflation increases diastolic pressure (diastolic augmentation) by 93%, increasing coronary perfusion pressure and myocardial perfusion. Peak coronary flow velocity increases by 109%. The rapid cuff deflation promotes lower extremity arterial “runoff” and leads to a decrease in systolic pressure (systolic unloading) by 15% in the aorta and coronary arteries and improved ventricular unloading [8]. Unlike the IABP, EECP also increases venous return, further promoting an increase in cardiac output.

DISCUSSION

Mechanism of Action

There are several possible mechanisms of action of EECP (Figure 3) put forth by numerous studies (Table 1) [9-15]. Initially, the prevailing theory was that EECP increased cor-
Mechanism of Action of EECP

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Methods</th>
<th>Results</th>
<th>Mechanism of Action of EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stys et al 2002 (9)</td>
<td>175 patients had baseline maximal radionuclide perfusion treadmill stress test (RPST) and follow-up RPST within 6 mos of completing course of EECP (97 had same level RPST and 78 had maximal RPST).</td>
<td>Improved perfusion and 12% improvement in exercise duration with maximal RPST; same level RPST had even larger improvement in perfusion and 5% lower double product.</td>
<td>EEC leads to expanded myocardial perfusion via increased collateralization and decrease in myocardial oxygen demand.</td>
</tr>
<tr>
<td>Zhang et al 2007 (10)</td>
<td>35 pigs in 3 groups (high-cholesterol diet; high-cholesterol diet plus EECP; usual diet): histopathological and immunohistochemical analyses of coronary arteries and aortas.</td>
<td>EECP increases arterial shear stress; intimal hyperplasia in high-cholesterol pigs and intima-to-media area ratio decreased 42% in EECP group; high-cholesterol pigs had attenuated endothelial nitric oxide synthase and enhanced phosphorylation of extracellular signal-regulated kinases 1 and 2 which were reversed by EECP.</td>
<td>Chronic exposure of vascular endothelial cells and vascular smooth muscle cells to high physiological shear stress during EECP has antiproliferative and vasoprotective effects.</td>
</tr>
<tr>
<td>Akhtar et al 2006 (11)</td>
<td>Plasma nitrate and nitrite (NOx) and endothelin-1 (ET-1) levels measured serially in 13 EECP patients.</td>
<td>After 36 hrs EECP there was a 62±17% increase in NOx and a 36±8% decrease in ET-1. At 3 mos, NOx remained 12±11% above baseline and ET-1 remained 11±10% below baseline.</td>
<td>Neurohormonal evidence that EECP improves endothelial function.</td>
</tr>
<tr>
<td>Bonetti et al 2003 (12)</td>
<td>Reactive hyperemia-peripheral arterial tonometry (RH-PAT) measured in 23 patients before, during, and after a course of EECP.</td>
<td>RH-PAT index increased after each treatment, and at one month follow-up in those patients who experienced clinical benefit from EECP.</td>
<td>EEC increases peripheral endothelial function.</td>
</tr>
<tr>
<td>Nichols et al 2006 (13)</td>
<td>Radial artery pressure waveforms recorded by applanation tonometry and central aortic pressure waveforms generated using a mathematical transfer function in 20 EECP patients.</td>
<td>Reflected wave amplitude decreased from 13±7.1mmHg to 8.7±6.8mmHg (p&lt;.001) causing a significant decrease in central aortic augmentation index from 18±9.6mmHg to 12±8.4mmHg (p&lt;.001).</td>
<td>EEC improves wave reflection characteristics and reduces arterial stiffness by 30%.</td>
</tr>
<tr>
<td>Casey et al 2008 (14)</td>
<td>12 EECP patients vs 9 sham patients; Plasma tumor necrosis factor-α (TNF), monocyte chemotactic protein-1 (MCP), and soluble vascular cell adhesion molecule-1 (VAM) were measured before and after course of EECP.</td>
<td>EECP patients had a 29% reduction in TNF (6.9±2.7 vs. 4.9±2.5 pg/ml, p &lt; 0.01) and a 19% reduction in MCP (254.9±55.9 vs. 190.4±47.6 pg/ml, p&lt;.01) as compared to control. No change in VAM for either group. EECP increased EPC number by 75% (10.2 to 17.8/10^6 mononuclear cells; p &lt; .05), and CFUs by 214% (3.5 to 11.0; p=.01). These parameters in the control group did not change.</td>
<td>EEC decreased circulating levels of proinflammatory biomarkers.</td>
</tr>
<tr>
<td>Barsheshet et al 2008 (15)</td>
<td>25 EECP patients vs 10 controls; number of endothelial progenitor cells (EPCs) positive for CD34 and kinase insert domain receptor (KDR) determined by flow cytometry and number of colony-forming units (CFUs) assessed in a 7-day culture, before and after course of EECP.</td>
<td>EECP increased EPC number by 75% (10.2 to 17.8/10^6 mononuclear cells; p &lt; .05), and CFUs by 214% (3.5 to 11.0; p=.01). These parameters in the control group did not change.</td>
<td>EEC is associated with increased number and colony-forming capacity of circulating EPCs.</td>
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</tbody>
</table>

Recent advances in the understanding of vascular homeostasis include an understanding that the endothelium plays a critical role. Basic science research in a pig model showed an even greater improvement in post-EECP perfusion. At the same cardiac workload, they achieved a lower double product (5%, P < .05), reflecting a decrease in myocardial oxygen demand. This is analogous to peripheral vascular conditioning found with exercise, in which improved vasomotor tone decreases the blood pressure response to exercise [9].

An illustration of this was observed in a study in which patients underwent maximal radionuclide perfusion treadmill stress tests (RPSTs) before and after EECP that showed significant improvement in exercise duration (12%, P < .0001) after EECP without change in the double product. The improvement in RPST was not caused by an alteration in myocardial oxygen demand but by expanded myocardial perfusion (increased supply by collateralization). Another group of patients underwent RPSTs at the same level of exercise before and after EECP that showed an even greater improvement in post-EECP perfusion. At the same cardiac workload, they achieved a lower double product (5%, P < .05), reflecting a decrease in myocardial oxygen demand. This is analogous to peripheral vascular conditioning found with exercise, in which improved vasomotor tone decreases the blood pressure response to exercise [9].

Recent advances in the understanding of vascular homeostasis include an understanding that the endothelium plays a critical role. Basic science research in a pig model...
documented that increased peak diastolic arterial wall shear stress during EECP (107%, \( P < 0.001 \)) reduces endothelial damage in coronary artery disease. This augmented sheer stress also mitigates cellular changes by arresting vascular smooth muscle cell proliferation and migration, decreasing proliferating cell nuclear antigen proliferative index, suppressing extracellular matrix formation, and inhibiting intimal hyperplasia and the development of atherosclerosis by activating endothelial nitric oxide synthase [10].

Endothelial dysfunction is known to be an early step in atherogenesis and is characterized by impaired bioavailability of endothelium-derived nitric oxide (NO), which has vasodilatory, antiproliferative, anti-inflammatory, anti-thrombotic, and antiplatelet properties. Endothelial dysfunction also is marked by an increase in production of endothelin-1 (ET-1), a vasoconstrictor with prothrombotic, proinflammatory, and mitogenic effects. This imbalance between vasodilators and vasoconstrictors leads to impaired endothelium-dependent vasodilation, the functional characteristic of endothelial dysfunction. There is neurohormonal evidence that EECP improves endothelial function in humans. After 36 hours of EECP, there was a 62% increase in plasma NO and a 36% decrease in ET-1 compared with baseline. Three months later, NO remained 12% above and ET-1 remained 11% below baseline [11]. Patients who experienced a favorable clinical response with EECP demonstrated a significant increase (25%, \( P < 0.05 \)) in their endothelial function as measured by reactive hyperemia-peripheral arterial tonometry index after 1 hour of treatment and at 1-month follow-up [12].

The likely mechanism of improvement from EECP is that it mimics the vascular effects of aerobic exercise. The repetitive inflation and deflation of the cuffs echoes the cyclic strain on leg arteries from intermittent skeletal muscle contraction and relaxation, although the EECP effect is more dramatic as the applied circumferential pressure of the cuffs is 260–20 mm Hg. Also, both aerobic exercise and EECP increase arterial blood flow and wall shear stress. Together the cyclic strain and increased shear stress improve endothelial function, stimulate NO release, and cause vasodilation. Such changes in arterial wall properties from EECP decrease arterial stiffness by 30% (\( P < .001 \)), resulting in a decrease in left

### Table 2. Published Trials of EECP in Patients with Stable Angina

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Year</th>
<th>N</th>
<th>Treatment Duration (h)</th>
<th>Angina (% ≥ 1 CCS Class)</th>
<th>Nitrate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al [16]</td>
<td>1983</td>
<td>200</td>
<td>12</td>
<td>↓ (97)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lawson et al [17]</td>
<td>1992</td>
<td>18</td>
<td>36</td>
<td>↓ (100)</td>
<td>↓</td>
</tr>
<tr>
<td>Lawson et al [18]</td>
<td>1996</td>
<td>27</td>
<td>35</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lawson et al [19]</td>
<td>1996</td>
<td>50</td>
<td>35</td>
<td>↓ (100)</td>
<td>↓</td>
</tr>
<tr>
<td>Lawson et al [20]</td>
<td>1998</td>
<td>60</td>
<td>35</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Arora et al [21]</td>
<td>1999</td>
<td>139</td>
<td>35</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lawson et al [22]</td>
<td>2000</td>
<td>33</td>
<td>35–36</td>
<td>↓ (100)</td>
<td>↓</td>
</tr>
<tr>
<td>Lawson et al [23]</td>
<td>2000</td>
<td>2,289</td>
<td>35</td>
<td>↓ (74)</td>
<td>N/A</td>
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<tr>
<td>Urano et al [24]</td>
<td>2001</td>
<td>12</td>
<td>35</td>
<td>N/A</td>
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</tr>
<tr>
<td>Masuda et al [25]</td>
<td>2001</td>
<td>11</td>
<td>35</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Stys et al [26]</td>
<td>2001</td>
<td>395</td>
<td>35</td>
<td>↓ (88)</td>
<td>N/A</td>
</tr>
<tr>
<td>Barsness et al [27]</td>
<td>2001</td>
<td>978</td>
<td>35</td>
<td>↓ (81)</td>
<td>↓</td>
</tr>
<tr>
<td>Stys et al [9]</td>
<td>2002</td>
<td>175</td>
<td>35</td>
<td>↓ (85)</td>
<td>N/A</td>
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<tr>
<td>Fitzgerald et al [28]</td>
<td>2003</td>
<td>4,454</td>
<td>35</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Tartaglia et al [29]</td>
<td>2003</td>
<td>25</td>
<td>35</td>
<td>↓ (93)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lawson et al [30]</td>
<td>2005</td>
<td>746</td>
<td>32</td>
<td>↓ (72)</td>
<td>↓</td>
</tr>
<tr>
<td>Lawson et al [31]</td>
<td>2006</td>
<td>1,458</td>
<td>35</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Novo et al [32]</td>
<td>2006</td>
<td>25</td>
<td>35</td>
<td>↓ (84)</td>
<td>N/A</td>
</tr>
<tr>
<td>Loh et al [33]</td>
<td>2006</td>
<td>58</td>
<td>35</td>
<td>↓ (86)</td>
<td>↓</td>
</tr>
<tr>
<td>Petterson et al [34]</td>
<td>2006</td>
<td>55</td>
<td>35</td>
<td>↓ (79)</td>
<td>↓</td>
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<tr>
<td>Soran et al [35]</td>
<td>2007</td>
<td>450</td>
<td>35</td>
<td>↓ (72)</td>
<td>↓</td>
</tr>
<tr>
<td>Casey et al [14]</td>
<td>2008</td>
<td>21</td>
<td>35</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Barshehet et al [15]</td>
<td>2008</td>
<td>25</td>
<td>35</td>
<td>↓</td>
<td>N/A</td>
</tr>
<tr>
<td>Loh et al [36]</td>
<td>2008</td>
<td>1,427</td>
<td>33</td>
<td>↓ (78)</td>
<td>↓</td>
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</tbody>
</table>

CCS = Canadian Cardiovascular Society; ED = emergency department; EECP = enhanced external counterpulsation; EPCs = endothelial progenitor cells; HR = heart rate; PUMPERS = candidates for percutaneous coronary intervention and/or coronary artery bypass graft and chose enhanced external counterpulsation as initial revascularization treatment; pts = patients; PVR = peripheral vascular resistance.
ventricular afterload, myocardial oxygen demand, and number of angina episodes [13].

Cardiovascular disease is associated with chronic inflammation, and studies suggest that inflammation can be suppressed under conditions of high endothelial shear stress. EECP reduces levels of the circulating proinflammatory biomarkers tumor necrosis factor-α (TNF-α, -29%, \(P < .01\)) and monocyte chemoattractant protein-1 (MCP, -19%, \(P < .01\)) in patients with angina. Interestingly, the percentage reduction in TNF from EECP is similar to what has been reported with exercise in cardiovascular disease. Increased TNF and MCP predict future coronary events and, therefore, a reduction may have clinical significance with regard to reducing forthcoming risk [14]. Another marker of cardiovascular disease risk is the number of circulating endothelial progenitor cells (EPCs). The improvement of angina after EECP treatment is associated with an increased number (by 75%, \(P < .05\)) and colony-forming units (by 214%, \(P = .01\)) of circulating EPCs [15], again linking EECP to improved vascular health and diminished vascular risk.

Because the similarities between exercise and EECP are substantial, one might argue that EECP is not necessary because exercise itself can achieve these desired outcomes. However, most of these patients are so symptomatic and functionally limited that they cannot exercise to the degree it would take to achieve the aforementioned cardiovascular benefits. They use EECP as a bridge to regain an active lifestyle. EECP provides passive exercise, making patients feel better, and allowing them to engage in a more intense active exercise program thereafter.

**Clinical Studies**

Numerous trials (Table 2) [16-36] demonstrate positive clinical responses among approximately 80% of patients undergoing EECP, including reductions in angina and nitrate use, increase in exercise tolerance, enhanced quality of life, improved exercise stress tests, and resolution of myocardial perfusion defects (Figure 4). In 1999, Arora et al. [21] published the first randomized, placebo-controlled, double-
Criteria for Patient Selection for EECP

The overall data support the use of EECP in patients with coronary artery disease with CCS functional class III-IV angina or angina equivalent syndrome, who are not candidates for surgical revascularization, and who are receiving optimal pharmacological management [38]. The American Heart Association recommends EECP as a Class IIb intervention for the treatment of refractory angina pectoris (level of evidence: B indicates data from randomized trials with high false-positive [alpha] or high false-negative [beta] errors) [39]. In particular, patients who have had incomplete or unsuccessful revascularization and have persistent angina or significant silent ischemic burden have favorable outcomes with EECP. Symptomatic individuals who are unable to undergo invasive revascularization as the result of high risk co-morbid states (i.e., renal failure, advanced pulmonary disease, elderly and frail, diabetes, and advanced heart failure) or anatomic constraints making them unsuitable for surgical or catheter-based revascularization likewise do well with EECP. Patients with New York Heart Association function class II-III heart failure caused by ischemic heart disease who are stable, well-compensated, and in a euvoletic state also derive benefit from EECP.

The procedure is safe and well-tolerated for most patients. Infrequent side effects include discomfort, skin abrasions, ecchymoses, and/or paresthesias in the lower extremities (overall incidence 0.8%), angina or silent ischemia (incidence 0.2%), arrhythmia (0.07%), and pulmonary edema (0.03%) [23]. Contraindications for EECP include arrhythmias that interfere with machine triggering, bleeding diathesis or warfarin therapy with an international normalized ratio ≥ 3.0, current or recent (within 2 months) lower-extremity thrombophlebitis or deep venous thrombosis, severe lower-extremity peripheral vascular disease with rest claudication or nonhealing ischemic ulcers, aortic aneurysm requiring surgical repair, pregnancy, severe pulmonary hypertension, decompensated heart failure, uncontrolled systemic hypertension, and severe aortic insufficiency [38].

Providing and Monitoring Patients During EECP

The typical course of treatment is 35 sessions of 1 hour in duration, once a day, 5 days per week over the course of 7 weeks. EECP generally is provided by a nurse or cardiac technician, and each procedure is performed under direct physician supervision. Before beginning the program, each patient should have a comprehensive cardiac assessment, including noninvasive testing to evaluate left ventricular function, valvular competence, and myocardial ischemic burden. Once in the EECP program, patients are clinically assessed daily before and after treatment and vital signs are recorded. During the treatment hour, the magnitude of he-
modynamic change is estimated noninvasively several times by measuring the diastolic-to-systolic effectiveness ratio via the use of finger plethysmography. Upon completion of the therapy course, patients may undergo repeat nuclear stress testing to document the objective benefits of EECP. EECP is covered by Medicare under the HCPCS (Healthcare Common Procedure Coding System) code GO166 with the ICD-9 (International Statistical Classification of Diseases and Related Health Problems) code 413.9 for other and unspecified angina pectoris. The treatment is also reimbursed by most private insurers.

EECP is painless for most patients. Some individuals, such as those with severe peripheral vascular disease and advanced degenerative lumbosacral spine and hip disease, might experience pain or discomfort during treatment. This pain can usually be managed with individualized padding and positioning techniques that often alleviate the soreness and allow for favorable clinical outcomes [40].

The Future of EECP

As patients live longer with coronary artery disease, they have more complex comorbidities and are at greater risk for invasive procedures, making EECP an attractive treatment alternative. As a noninvasive modality, it should perhaps be considered as first-line treatment with invasive revascularization reserved for EECP failures. Patients who choose EECP as first-line therapy have similar favorable results compared with those who were previously revascularized and then have EECP [28]. Because the scientific evidence of EECP efficacy is growing, it should be considered to be integrated into cardiac rehabilitation programs as a jump-start to enable these patients to attain their maximal functional capacity.

Looking beyond angina, it is known that EECP increases blood flow throughout the body, not only to the heart. As such, there are numerous conditions associated with circulatory compromise where EECP may play a therapeutic role. Further investigation is warranted in this arena [40].

As the basic science and clinical research of EECP continues to grow, physician acceptance of this unique physical therapy will expand and allow access for more patients to this valuable outpatient treatment that provides long-term relief of anginal symptoms and improved quality of life for those with symptomatic ischemic heart disease.

REFERENCES


Braverman DL. Heal Your Heart with EECP. Berkeley, CA: Celestial Arts, 2005.