Enhanced External Counterpulsation: An Innovative Physical Therapy for Refractory Angina

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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-

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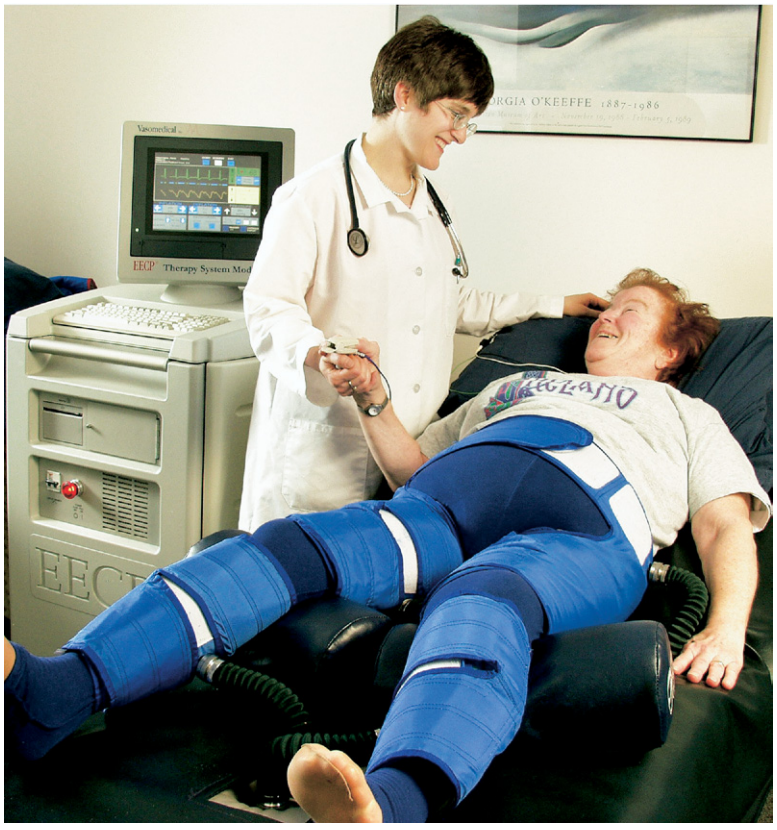

Figure 1. A patient receiving EECP treatment.

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

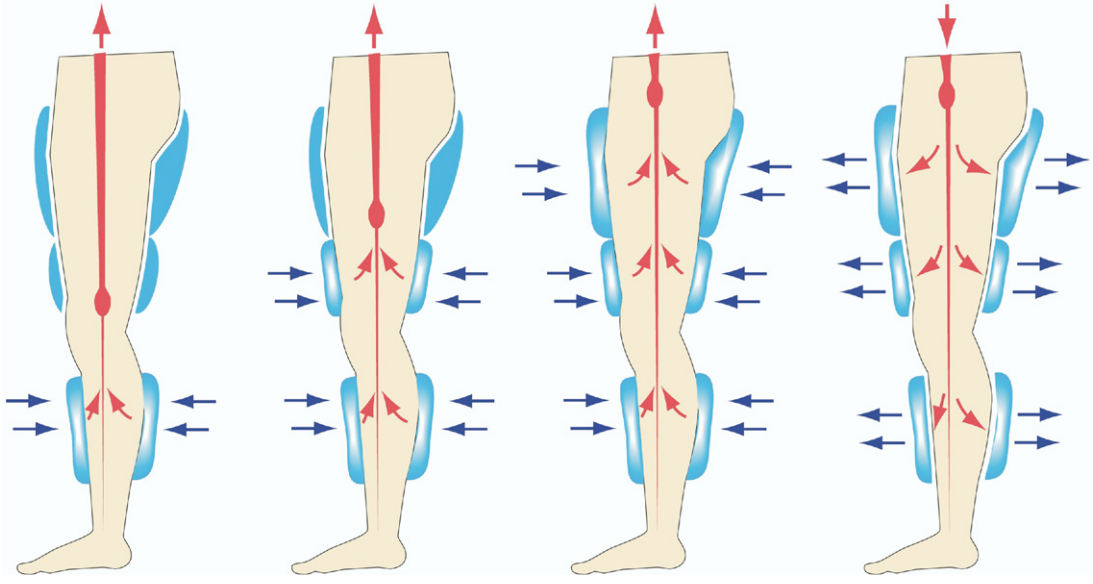

Figure 2. Schematic of EECP cuffs. The procedure consists of sequential leg compression by the EECP cuffs at 50-ms intervals during early diastole followed by simultaneous cuff deflation at the onset of systole.

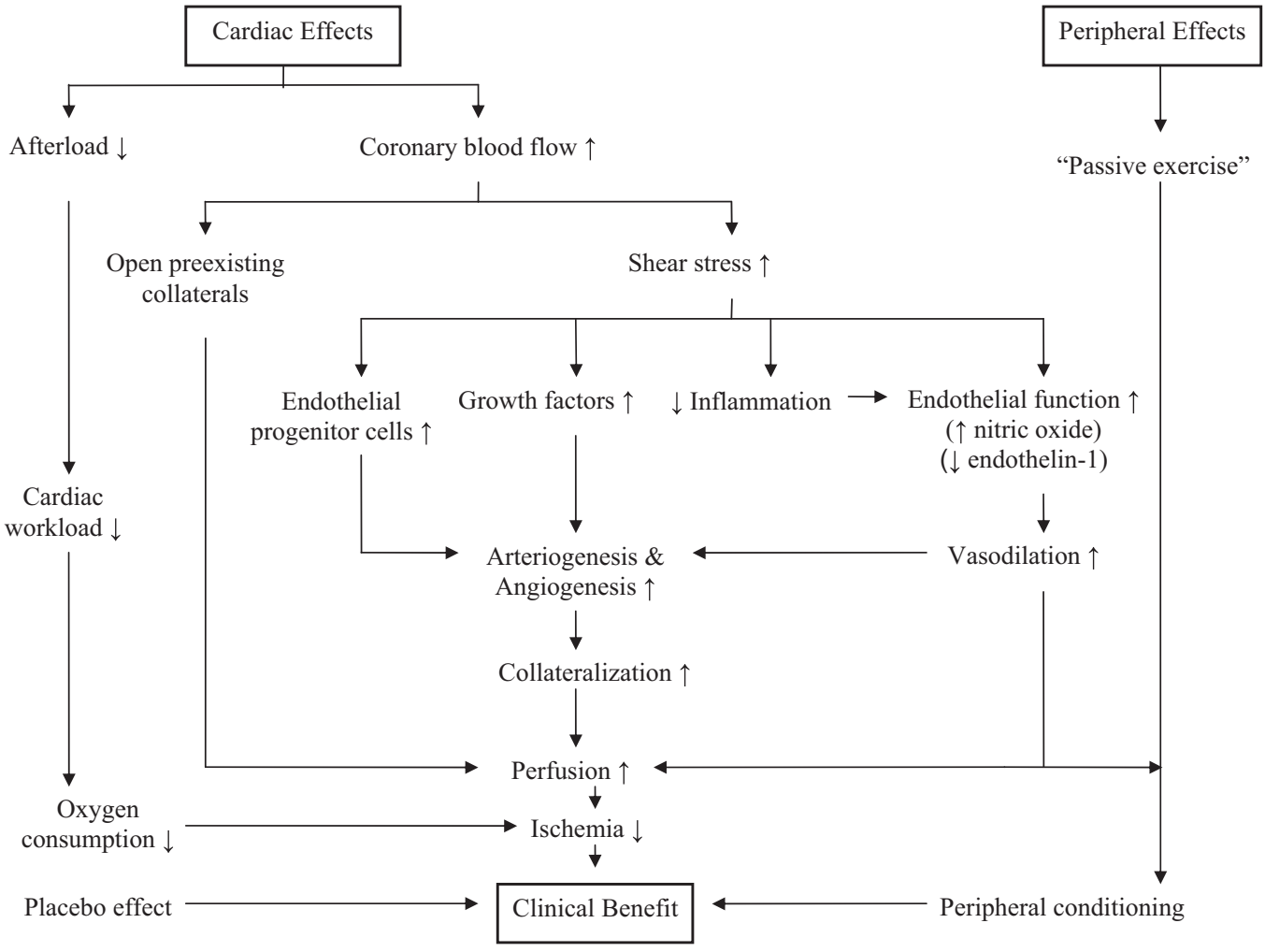

Figure 3. Mechanism of action of EECP.

device [3]. 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-

Table 1. *Mechanism of Action of EECP*

Study (Ref.)	Methods	Results	Mechanism of Action of EECP
Stys et al 2002 (9)	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).	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.	EECP leads to expanded myocardial perfusion via increased collateralization and decrease in myocardial oxygen demand.
Zhang et al 2007 (10)	35 pigs in 3 groups (high-cholesterol diet, high-cholesterol diet plus EECP, usual diet); histopathological and immunohistochemical analyses of coronary arteries and aortas.	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.	Chronic exposure of vascular endothelial cells and vascular smooth muscle cells to high physiological shear stress during EECP has antiproliferative and vasoprotective effects.
Akhtar et al 2006 (11)	Plasma nitrate and nitrite (NOx) and endothelin-1 (ET-1) levels measured serially in 13 EECP patients.	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.	Neurohormonal evidence that EECP improves endothelial function.
Bonetti et al 2003 (12)	Reactive hyperemia-peripheral arterial tonometry (RH-PAT) measured in 23 patients before, during, and after a course of EECP.	RH-PAT index increased after each treatment, and at one month follow-up in those patients who experienced clinical benefit from EECP.	EECP enhances peripheral endothelial function.
Nichols et al 2006 (13)	Radial artery pressure waveforms recorded by applanation tonometry and central aortic pressure waveforms generated using a mathematical transfer function in 20 EECP patients.	Reflected wave amplitude decreased from 13±7.1mmHg to 8.7±6.8mmHg ($p<.001$) causing a significant decrease in central aortic augmentation index from 18±9.6mmHg to 12±8.4mmHg ($p<.001$).	EECP improves wave reflection characteristics and reduces arterial stiffness by 30%.
Casey et al 2008 (14)	12 EECP patients vs 9 sham patients; Plasma tumor necrosis factor-$\acute{\alpha}$ (TNF), monocyte chemoattractant protein-1 (MCP), and soluble vascular cell adhesion molecule-1 (VAM) were measured before and after course of EECP.	EECP patients had a 29% reduction in TNF (6.9±2.7 vs. 4.9±2.5 pg/ml, $p < 0.01$) and a 19% reduction in MCP (254.9±55.9 vs. 190.4±47.6 pg/ml, $p<.01$) as compared to control. No change in VAM for either group.	EECP decreased circulating levels of proinflammatory biomarkers.
Barsheshet et al 2008 (15)	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.	EECP increased EPC number by 75% (10.2 to 17.8/10^5 mononuclear cells; $p < .05$), and CFUs by 214% (3.5 to 11.0; $p=.01$).These parameters in the control group did not change.	EECP is associated with increased number and colony-forming capacity of circulating EPCs.

onary collateral circulation. 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

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

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

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.

documented that increased peak diastolic arterial wall shear stress during EECP (107%, $P < .001$) 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, antithrombotic, 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%, $P < .05$) 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

Exercise Tolerance (% of pts)	Time to ST Depression	Cardiac Perfusion (% of pts)	Other Findings
N/A	N/A	N/A	–
↑ (67)	N/A	↑ (78)	Benefits sustained at 3-yr follow-up
↑ (81)	N/A	↑ (78)	Decrease PVR and HR response to exercise (training effect)
N/A	N/A	↑ (80)	The presence of a patent vascular conduit (native coronary or bypass graft) predicts a favorable response to EECP
↑	N/A	↑ (75)	Benefit sustained at 2-yr follow-up
↑	↑	N/A	Double-blind placebo controlled trial
N/A	N/A	↑ (79)	Benefit sustained at 5-yr follow-up
N/A	N/A	N/A	Efficacy independent of provider setting or experience
↑	↑	↑	Improved left ventricular diastolic filling
↑	↑	↑	Coronary perfusion increased at baseline and during dipyridamole provocation
N/A	N/A	N/A	EECP equally effective in men and women, young and elderly (65yrs)
N/A	N/A	N/A	EECP can be used to avoid revascularization
↑	N/A	↑ (83)	Lower double product at same level of exercise showing peripheral vascular conditioning
N/A	N/A	↑	Comparable benefit for both previously revascularized and non-revascularized patients
↑	↑ (80)	↑ (80)	–
N/A	N/A	N/A	Equal benefit in systolic and diastolic heart failure
↑	N/A	N/A	Benefit sustained at 2-yr follow-up; EECP equally beneficial in mild vs. severe angina
N/A	N/A	↑	Maximal benefit seen in pts with worst systolic failure
↑	N/A	N/A	Sustained improvement in 78% at 1-yr follow-up
N/A	N/A	N/A	Benefits sustained at 1-yr follow-up
N/A	N/A	N/A	Refractory angina pts with LV dysfunction had 18% reduction in all-cause ED visits and 33% reduction in hospitalization rates at 6-mos follow-up
N/A	N/A	N/A	Single-blind placebo controlled trial; EECP decreased circulating levels of pro-inflammatory biomarkers
N/A	N/A	N/A	Placebo controlled trial; EECP increases number and colony-forming capacity of circulating EPCs
N/A	N/A	N/A	Benefits sustained at 3-yr follow-up

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-

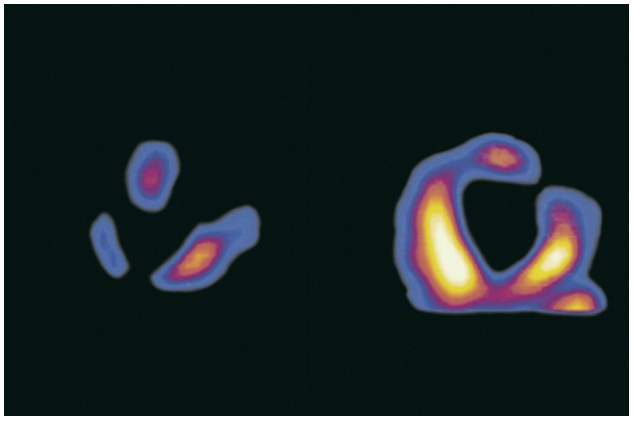

Figure 4. Positron emission tomography scans demonstrating baseline ischemia (left) and improved myocardial perfusion after EECP (right).

blind trial of EECP. A total of 139 patients were randomized to receive EECP or a sham treatment. Only the EECP group had significant (12%, $P = .01$) improvement in time to ST-segment depression on exercise stress tests and decrease in angina episodes (38%, $P < .05$) compared with no change in the sham group. Using the Medical Outcomes Study 36-Item Short-Form Health Survey and the Quality of Life Index-Cardiac Version III to assess the effects of EECP on health-related quality of life, the EECP group reported greater improvements in all 9 quality of life scales, most significantly in bodily pain, social functioning, and quality of life specific to cardiac patients at the end of the treatment and 1 year later [37].

EECP is safe, well-tolerated, and provides sustained favorable results. A recent study illustrating this was done by The International EECP Patient Registry at the Epidemiology Data Center of the University of Pittsburgh. They followed 1427 EECP patients prospectively from 36 centers for a median of 37 months. Multivessel coronary artery disease was present in 76% for 11 ± 8 years. Eighty-eight percent had previous surgical or percutaneous revascularization, 82% were unsuitable for further coronary intervention, and 89% had Canadian Cardiovascular Angina Classification (CCS) III/IV. Adverse events during the treatment period were musculoskeletal discomfort (1.5%), skin breakdown (2.5%), heart failure (2.2%), and unstable angina (4.5%). Major adverse cardiac events (MACEs) were rare and included myocardial infarction (0.8%), percutaneous coronary intervention (0.8%), coronary artery bypass surgery (0.6%), and death (0.5%).

A total of 1061 patients (74.4%) completed follow-up, whereas 220 patients (15.4%) died. Immediately after EECP, the proportion of those with severe angina was reduced from 89% to 25% ($P < .001$.) The CCS class was improved by at least 1 class in 78% of patients and by at least 2 classes in 38%; this functional improvement was maintained 3 years later in 74% of patients. At follow-up, 36% of patients had CCS II or less angina (better than pre-EECP) without a MACE [36]. This is thought-provoking outcome data when one considers that all the patients had advanced symptomatic coronary artery disease.

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 euvolemic 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.

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