Clinical Guide

Introduction

Enhanced External Counterpulsation (EECP®) is a FDA cleared noninvasive medical device for the treatment of patients suffering from coronary artery disease (CAD). It is a device that improves cardiac output, increases circulation and pressure gradient across stenosis to recruit collaterals. It also increases shear stress on the endothelium, improving endothelial function, reduces circulating inflammatory markers and arterial stiffness, inhibits smooth muscle cells proliferation and migration. It has been demonstrated to be safe and effective in the treatment of angina pectoris as well as chronic heart failure. 1,2

EECP® Therapy Operations

EECP® system consists of three sets of inflatable pressure cuffs wrapped around the calves, the lower and upper thighs, including the buttocks. The cuffs are rapidly and sequentially inflated, starting from the calves and proceeding upward to the buttocks during the relaxation (diastolic) phase of each heartbeat, creating a strong arterial retrograde flow towards the heart and significantly increasing blood flow to the coronary arteries at a time when resistance to coronary blood flow is at its lowest level. The inflation of the cuffs also simultaneously increases the volume of venous blood returned to the right side of the heart, providing greater filling of the ventricle for ejection. Just before the beginning of the next cardiac cycle when the heart begins to contract, all three cuffs simultaneously deflate, leaving an empty vascular space in the lower extremities to receive blood ejecting from the heart, thereby significantly reducing the workload of the heart. The inflation/deflation activity is monitored constantly and coordinated by a microprocessor that interprets electrocardiogram signals, monitors heart rhythm and rate information, and actuates the inflation and deflation in synchronization with each cardiac cycle (see Figure 1). The inflation/deflation cycle is repeated every heartbeat, increasing energy supply to the heart, improving cardiac output, while at the same time reducing the workload of the heart.

Figure 1: The QRS complex of the electrocardiogram is used to provide a triggering signal for the calf inflation valve to open around the peak of T-wave, the lower thigh valve will open 50 ms later, to be followed by the upper thigh valve another 50 ms later. The pressure in the cuffs will hold as long as possible to allow maximization of diastolic augmentation. Then all three-deflation valves will open at the same time around the peak of P-wave to let the emptied peripheral vasculature to receive the blood ejected by the heart, leading to systolic unloading.
**EECP® Treatment System**

The EECP® therapy systems are Food and Drug Administration (FDA) cleared for marketing in the treatment of stable and unstable angina, congestive heart failure, acute myocardial infarction, and cardiogenic shock.

![Figure 2: EECP® Lumenair system.](image)

Figure 2: EECP® Lumenair system. Patient selection and contraindications as well as precautions should be followed carefully to avoid risk of adverse clinical events. Blood pressure, respiration rate, oxygen saturation and weight should be monitored during EECP® treatment to avoid exacerbation of heart failure, especially in patients with low ejection fraction. Physical assessment, especially peripheral skin condition, should be examined after every treatment session.

The treatment is administered to patients on an outpatient basis, usually in daily one-hour sessions, five days per week over seven weeks for a total of 35 treatments. EECP® is equally effective if it is given twice daily, each with one-hour session separated by a minimum of 30-minutes break for a total of three and a half week. The procedure is well tolerated and most patients begin to experience relief of chest pain due to their coronary artery disease after 15 to 20 hours of therapy.

**Patient Selection**

EECP® is primary used as a non-pharmacologic outpatient therapy for patients with chronic stable angina pectoris as well as symptoms of heart failure. Effective July 1, 1999, The Centers for Medicare and Medicaid (CMS) and other third-party insurance payers reimburse for the treatment of angina symptoms in patients who have been diagnosed with disabling angina (Class III or Class IV, Canadian Cardiovascular Society Classification or equivalent classification) who are not readily amenable to surgical intervention, such as PTCA or cardiac bypass.

Patients with severe, diffuse coronary atherosclerosis and persistent angina, or significant silent ischemia burden, in whom coronary revascularization has been unsuccessful or incomplete, and symptomatic patients at high risk of adverse events related to invasive revascularization, such as elderly patients and those with diabetes, challenging coronary
anatomies, or debilitating heart failure, renal failure, or pulmonary disease, have also been shown to derive benefit from EECP® therapy. 1, 2, 23 EECP® therapy has also been shown to be effective in relieving angina symptoms in patients with cardiac syndrome X. 22 Benefits of EECP® have also been determined in the management of angina in the elderly, 24 angina patients with left main disease, 27 and in patients with mild refractory angina (CCS Class II). 8 EECP® therapy is equally effective in reducing angina symptoms in patients with or without diabetes, 25 and in patients with all ranges of body mass index. 26

EECP® therapy has also been shown to improve exercise capacity in heart failure patients with NYHA Class II/III, 12-14 and in exercise peak oxygen consumption in older patients with heart failure. 15 EECP® therapy has also been demonstrated to be equally effective in providing symptomatic benefits in angina patients with either systolic or diastolic heart failure. 16 For patients with left ventricular dysfunction, the beneficial effects of EECP® therapy has been shown to sustain up to 2-year at follow-up. 17-18

Contraindications

According to the current FDA labeling, EECP® Therapy System should not be used for the treatment of patients with:

- Arrhythmias that interfere with machine triggering,
- Bleeding diathesis,
- Active thrombophlebitis,
- Severe lower extremity vaso-occlusive disease,
- Presence of a documented aortic aneurysm requiring surgical repair,
- Pregnancy.

Precautions

- Patients with blood pressure higher than 180/110 mmHg should be controlled prior to treatment with enhanced external counterpulsation.
- Patients with a heart rate more than 120 bpm should be controlled prior to treatment with enhanced external counterpulsation.
- Patients at high risk of complications from increased venous return should be carefully chosen and monitored during treatment with enhanced external counterpulsation. Decreasing cardiac afterload by optimizing diastolic augmentation may help minimize increased cardiac filling pressures due to venous return.
- Patients with clinically significant valvular disease should be carefully chosen and monitored during treatment with enhanced external counterpulsation. Certain valve conditions, such as significant aortic insufficiency, or severe mitral or aortic stenosis, may prevent the patient from obtaining benefit from diastolic augmentation and reduced cardiac afterload in the presence of increased venous return.
Special clinical issues

- Elderly patients with age 80 years or older can be treated with EECP with angina classification reduced by at least 1 class and quality of life improved in 76%. At 1 year, 81% reported maintenance of angina improvement.24
- Diabetes: CAD patients with diabetes can safely and effectively be treated with comparable results to non-diabetic CAD patients.25
- Obesity: EECP® treatment is equally safe and effective across patients with diverse range of body mass index, including obese patients (BMI > 30 kg.m²) and morbidly obese (BMI > 40 kg.m²). 26
- Peripheral vascular disease: listed as precaution due to inadequate diastolic augmentation can gain benefits from EECP® treatment similar to all other CAD patients.1
- Abdominal aortic aneurysm (AAA) with increased risk of rupture or retrograde thromboembolic events has not been reported with EECP® treatment. AAA larger than 4.0 cm should be referred to vascular surgeon for evaluation.1
- Atrial fibrillation can be treated with EECP® with rate control between 40-100 bpm
- Pacemakers and defibrillators could undergo EECP® safely and derive clinical benefits with appropriate monitoring. Rate-adaptive pacemaker may lead to trigger a paced tachycardia due to patient’s body motion and can be turned off during EECP®.
- Treatment protocol: the 35 hours daily treatment is associated with angina reduction and improved exercise tolerance in at least 75% of patients. Extension of therapy by 10-12 hours is associated with further improvement.1
- Repeat therapy: within 2 years after initial EECP® treatment, 18% of patients undergo another course of re-treatment due to recurrent angina, persistent angina with benefit similar to patients who respond to their first course.34,35

Evidence-Based Clinical Results

There are more then 150 papers published in peer reviewed medical journals documenting EECP® therapy is a noninvasive, safe, low-cost and highly effective treatment for patients with coronary artery disease. For a list of all published paper, visit: www.Vasomedical.com. Major results of a few selected papers are summarized below:

1. There are two randomized controlled trials, one for patients with chronic angina pectoris and one for patients with chronic heart failure.

1.1 The Multicenter Study of Enhanced External Counterpulsation (MUST-ECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes

A multicenter (7 university hospitals), prospective, randomized, blinded, control trial in 139 angina patients
with documented coronary artery disease and positive exercise treadmill test were treated with either active counterpulsation (applied cuff pressure up to 350 mm Hg), and inactive counterpulsation (<75 mm Hg). Exercise duration increased in both groups, with time to ≥ 1-mm ST-segment depression increased significantly from baseline in the active group compared with the inactive group (p=0.01), as well as a significant reduction in the number of angina episodes (p<0.05).

1.2a Prospective Evaluation of EECP in Heart Failure (PEECH): 13,14

187 subjects with mild-to-moderate symptoms of heart failure were randomized to either EECP® treatment with protocol-defined pharmacologic therapy (PT) or PT alone. 35% in the EECP® therapy group and 25% in control group increased their exercise time by at least 60 sec (p=0.016) at 6 months. However, there was no between group difference in the percentage of subjects with at least 1.25 ml/kg/min increase in peak volume of oxygen uptake. New York Heart Association (NYHA) functional class improved in the active treatment group at 1-week (p<0.01), 3 months (p<0.02), and 6 months (p<0.01). The Minnesota Living with Heart Failure score also improved significantly in the treated group at 1 week (p<0.002) and 3 months (p=0.01) after treatment, versus no significant changes in the control group.

1.2b A Subgroup Analysis of the PEECH Trial: EECP Improves Exercise Duration and Peak Oxygen Consumption in Older Patients With Heart Failure 15

This paper reports the results of a pre-specified subgroup analysis of 85 elderly patients (65 years or older) enrolled in the PEECH trial. At 6-months post treatment, the percentage of subjects with >60-second increase in exercise duration was significantly higher in EECP® patients compared with the control group (p=0.08). Moreover, in contrast to the overall PEECH study (see above), the older
patient group demonstrated a significantly higher percentage of responders with >1.25 ml/kg/min increase in peak volume of oxygen consumption (p=0.017). In addition, the mean changes in exercise duration and peak oxygen consumption from baseline were significantly increased compared with the control group at 1 week, 3 months and 6 months following completion of treatment.

2. Two International EECP® Patient Registries (IEPR I with 5,000 patients and IEPR II with 2,500 patients) have been completed in July 2001 and Oct 2004 respectively by the Epidemiology Data Center of the University of Pittsburgh to determine the patterns of use, safety and efficacy of EECP for a period of 2–3 years post treatment. Data collected were patients’ demographics, medical history, CAD status, quality of life, CCS Classification, medication, angina frequency and adverse clinical events before EECP, post EECP, and during follow-up periods.28-36

At Baseline, patients treated with EECP® therapy have an average age of 67 years old, with significant risk factors (43% diabetes, 84% hyperlipidemia and 75% hypertension) and suffered from severe CAD (87% with prior PCI/CABG, 69% with prior MI, 31% heart failure). 86% of patients were Canadian Cardiovascular Society (CCS) angina class III and IV patients.29 Post-EECP® therapy, 81% of the patients improved with reduction of at least one CCS class.30 The benefits were sustained at 1-year (75%), 30 2-year (73%),32 and 3-year (74%)33 follow-up (see figures for the Distribution of the percent of patients according to their CCS angina class). The percent of patients in CCS class III and IV reduced from 86% at baseline to 25% at 1-year, 24% at 2-year and 21% at 3-year follow-up, with 27%, 30% and 35% of patients had no angina during the 1, 2 and 3-year follow-up period.

Mechanisms of Action

There are many pathophysiologically pathways by which EECP® therapy achieves its long-term beneficial effects. There is evidence of improved endothelial function via the hemodynamic effects of increased shear stress on the arterial wall, reducing arterial stiffness and providing
protective effects against inflammation, thereby inhibits intima hyperplasia. There is also evidence to suggest that EECP therapy triggers a neurohormonal response that induces the production of growth and vasodilatation factors, which together with the hemodynamic effects of increasing pressure gradient across the occlusive site during EECP® therapy, promotes recruitment of new arteries, while dilates and normalizes the function of existing blood vessels. The recruitment of new arteries, known as “collateral blood vessels”, bypass blocked or narrowed vessels and increase blood flow to ischemic areas of the heart muscle that are receiving an inadequate supply of blood.

**EECP® Mechanisms of Action**

- **Improve Neurohormonal Factors**
  - Systolic Unloading
  - Diastolic Augmentation
  - Increase Cardiac Output

- **Reduce Proinflammatory Cytokines and Adhesion Molecules**
  - Tumor necrosis factor - α ↓
  - Monocyte chemotactic protein – 1 ↓

- **Improve Endothelial Function**
  - Vasodilation ↑
  - Intimal Hyperplasia ↓
  - Release of Endothelial Progenitor Cell ↑

- **Collaters Development**
  - Blood flow to ischemic region ↑
  - Vascular growth factors ↑
  - Capillary density ↑

- **Improve blood flow to ischemic regions**

**Hemodynamic Effects**

During EECP® treatment has been documented in the descending aorta with increased stroke volume and presence of retrograde flow, as well as significant increase of blood flow in the coronary arteries using intracoronary Doppler. The increase in flow velocity increases shear stress on the endothelium and improves endothelial functions with significant increase of plasma nitric oxide level and improvement in flow-mediated vasodilatation.

In addition, significant decrease (29%) of inflammatory cytokines
tumor necrosis factor-\(\alpha\) in patients with angina, and increase of circulating plasma endothelial progenitor cell after EECP\(\textregistered\) therapy have been reported.\(^{41,40}\)

The long-term benefits of EECP\(\textregistered\) therapy from improvement in endothelial functions lead to inhibition of vascular smooth muscle cells migration and proliferation, attenuation of oxidative stress and inflammation and inhibits intimal hyperplasia as demonstrated by the experimental work on hypercholesterolemic pigs in which the coronary arteries and aortas of 35 male pigs randomly assigned to control, high-cholesterol diet (HCD) and HCD+EECP. The EECP group enjoyed a reduction of intima-to-media area ratio by 42% compared with HCD group. EECP treated group also increased the protein expression of endothelial nitric oxide synthase and suppressed the phosphorylation of extracellular signal-regulated kinases \(\frac{1}{2}\).\(^{46}\)

In patients suffering from angina pectoris, 34 1-hour EECP\(\textregistered\) treatments in 20 patients caused a significant decline in the augmentation index and an increase in reflected wave travel time, demonstrating a reduction of arterial stiffness, resulting in a decrease in left ventricular afterload, myocardial oxygen demand and angina episodes and improved Canadian Cardiovascular Society functional class.\(^{42}\)

In summary, the acute hemodynamic effects during EECP\(\textregistered\) Therapy of systolic unloading and diastolic augmentation not only provide a chance for myocardial muscle to rest and accumulate energy reserve, the higher pressure gradient across stenosis generated during diastolic when resistance to coronary flow is at its minimum would help to enhance collateral generation, while the increased cardiac output and promotion of retrograded flow induce higher shear stress on the endothelium, improve endothelial functions and increase release of neurohomonal and vascular growth factors that induce vasodilatation, inhibit intima hyperplasia and develop collateral circulation to achieve long-term clinical benefits. There are several review papers on EECP\(\textregistered\) therapy expanding these concepts.\(^{47,48}\)
Cost Effectiveness

1. Reimbursement for refractory angina
   
   There are approximately 6.8 million people in the United States suffering from angina, with 400,000 new cases diagnosed annually, and 80-100,000 patients suffered from refractory angina. Effective July 1, 1999, the Centers for Medicare and Medicaid Services (CMS) and many other third-party insurance payers provide coverage for patients who have been diagnosed with disabling angina (Class III or Class IV, Canadian Cardiovascular Society Classification or equivalent classification) who, in the opinion of a cardiologist or cardiothoracic surgeon, are not readily amenable to surgical intervention, such as PTCA or cardiac bypass because:
   (1) Their condition is inoperable, or at high risk of operative complications or post-operative failure,
   (2) Their coronary anatomy is not readily amenable to such procedures; or
   (3) They have co-morbid states, which create excessive risk.

2. Heart Failure patients with ischemic etiology
   
   In addition, there are 5 million patients in the United States and approximately 22 million worldwide suffering from heart failure. It is the leading cause of hospitalization in patients over age 65, and is one of the largest burdens on the U.S. healthcare system, costing in excess of $20 billion annually. EECP® therapy offers an opportunity to redefine the standard of care in how this group of patients is treated and has been demonstrated to reduce both emergency room (ER) visits and hospitalizations in heart failure patients with left ventricular dysfunction by 86% and 83% respectively, from 1.4 to 0.2 ER visits and 2.4 to 0.4 hospitalizations per patient per year. 

Reference

Clinical Practice

1. Primer: Practical Approach to the Selection of Patients for and Application of EECP

**Angina Pectoris**


**Quality of Life**


**Heart Failure**


**Acute Coronary Syndrome**


**Co-Morbidities**


**International EECP Patient Registry/Consortium**


36. Impact of External Counterpulsation Treatment on Emergency Department Visits and Hospitalizations in Refractory Angina Patients with Left Ventricular Dysfunction. Soran O, Kennard ED, Bart BA, Kelsey SF. *Congestive Heart Failure*. 2007 Jan-Feb;13(1):36-40

**Hemodynamics**


Mechanisms of Action


Experimental


Review Papers
