Enhanced External Counterpulsation

Description

Enhanced external counterpulsation (EECP) is a noninvasive treatment used to augment diastolic pressure, decrease left ventricular afterload, and increase venous return. It has been studied primarily as a treatment for patients with refractory angina and heart failure.

Background

Enhanced external counterpulsation (EECP) uses timed, sequential inflation of pressure cuffs on the calves, thighs, and buttocks to augment diastolic pressure, decrease left ventricular afterload, and increase venous return. Augmenting diastolic pressure displaces a volume of blood backward into the coronary arteries during diastole when the heart is in a state of relaxation and the resistance in the coronary arteries is at a minimum. The resulting increase in coronary artery perfusion pressure may enhance coronary collateral development or increase flow through existing collaterals. In addition, when the left ventricle contracts, it faces a reduced aortic pressure to work against, since the counterpulsation has somewhat emptied the aorta. EECP has been primarily investigated as a treatment for chronic stable angina.

Intra-aortic balloon counterpulsation is a more familiar, invasive form of counterpulsation that is used as a method of temporary circulatory assistance for the ischemic heart, often after an acute myocardial infarction (MI). In contrast, EECP is thought to provide a permanent effect on the heart by enhancing the development of coronary collateral development. A full course of therapy usually consists of 35 one-hour treatments, which may be offered once or twice daily, usually 5 days per week. The multiple components of the procedure include the use of the device itself, finger plethysmography to follow the blood flow, continuous electrocardiograms (EKGs) to trigger inflation and deflation, and optional use of pulse oximetry to measure oxygen saturation before and after treatment.

Regulatory Status

Varieties of enhanced external counterpulsation (EECP) devices have been cleared for marketing by the Food and Drug Administration (FDA) through the 510(k) process. Examples of EECP devices with FDA clearance are outlined in Table 1.
Enhanced external counterpulsation is considered not medically necessary for all indications, including but not limited to, treatment of chronic stable angina pectoris, heart failure, erectile dysfunction, or ischemic stroke.

Policy Guidelines

This policy only addresses the outpatient uses of EECP, i.e., for the treatment of chronic stable angina or heart failure. This policy does not address its use for unstable angina pectoris, acute myocardial infarction, or cardiogenic shock.

Rationale

Randomized controlled trials (RCTs) that report on relevant clinical outcomes are required to determine whether enhanced external counterpulsation (EECP) is efficacious and whether it is at least as good as alternative treatments. Observational data are of limited utility given the variable natural history of...
disorders such as angina and/or heart failure, the presence of many potential confounders of cardiac outcomes, and the potential for a placebo effect.

The literature base consists of a small number of RCTs, some of which report relevant clinical outcomes and others that report intermediate, or physiologic, outcome measures. In addition to the small number of RCTs, there are a large number of observational studies, including publications from EECP registries and case series, which generally report pre- and post-treatment measures of EECP effectiveness.

**Chronic Stable Angina**

The original literature review for this review was based on a 1999 TEC Assessment on EECP for chronic stable angina, which was updated in 2002 and 2005. These assessments concluded that the evidence was insufficient to determine whether EECP improved the net health outcome or was as beneficial as any established alternatives in patients with chronic stable angina.

Specifically, the 2005 TEC Assessment offered the following observations and conclusions regarding EECP for chronic stable angina (1, 2):

- There is insufficient evidence to draw conclusions about the benefits of EECP.
- The results of the single randomized, controlled trial, the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), discussed further here, must be interpreted with caution, in view of the high subject dropout rate and uncertainty regarding the clinical significance of the reported improvement in physiologic measures, especially when intent-to-treat analysis is applied. (3,4)
- Comparative studies of EECP do not address the hard outcomes of cardiac death or recurrent cardiac events such as myocardial infarction and revascularization procedures. (5,6)
- Several case series and registry-based studies report the outcomes of large numbers of patients treated in a number of different institutions. There are several problems with this kind of evidence. These studies, while contributing to the body of knowledge of EECP, do little to address the efficacy or durability of EECP treatment. The lack of comparison groups makes it impossible to rule out either placebo effect or spontaneous recovery among patients with milder disease.

**Randomized Controlled Trials**

In 1999, Arora et al presented results of the MUST-EECP trial.3 MUST-EECP applied a randomized controlled, double-blinded protocol that compared active treatment to placebo (inactive counterpulsation [CP] sham treatment) among 139 patients with Canadian Cardiovascular Society (CCS) Classification Scales (a functional assessment tool based on the level of exertion that elicits symptoms) class I, II, or III chronic, stable angina. Four outcomes were examined: (1) self-reported frequency of angina, analyzed 2 ways; (2) self-reported use of on-demand nitroglycerin; (3) exercise duration tolerance testing; and (4) time to exercise-induced ischemia (defined as time to depression of ≥1mm in the ST segment on electrocardiogram).
All patients underwent the same 35-hour protocol, followed by an exercise tolerance test within 1 week of completing therapy. Follow-up beyond the treatment period was not conducted. ITT analyses were reported for the angina count and nitroglycerin usage outcomes only. There was a statistically significant difference (p=0.01) between groups in the change in time to 1 mm or greater ST segment depression. Patients in the EECP group had an average difference of 37 seconds longer time to ST segment depression compared with the sham-treated group. There was no significant difference between treatment groups in the change in exercise duration from baseline to the posttreatment period (p<0.31). In addition, there were no statistically significant differences between groups with respect to angina counts (p<0.09) or nitroglycerin use (p>0.1).

In addition to methodologic limitations found in the design, execution, and reporting of this study, the magnitude of the benefit reported is not large. Of the 4 end points of interest, only time to ST segment depression differed statistically in the EECP group compared with the sham group. The clinical significance of a 37-second improvement in time to ST segment depression is unknown, but given that it occurred while the other 3 end points were statistically unchanged with therapy, does not suggest a marked improvement. That both groups showed increased exercise duration suggests a degree of placebo effect; exercise duration possesses a motivational component that time to ST segment depression does not.

In 2002, Arora and colleagues published a 12-month follow-up study to the MUST-EECP trial. (4) However, only 71 (54%) of the original 139 subjects were included in the study. Subjects treated with EECP reported greater improvement in several quality of life scales. However, such findings could not be correlated with treatment response reported in the first study (because of data limitations). The findings are further limited by the small sample size and potentially biased sample of the original subject pool.

A small unblinded RCT published in 2012 (7) addressed one health outcome, change after 7 weeks in CCC angina class, along with multiple intermediate outcomes. Twenty patients with refractory angina (CCS class III) were randomized to EECP or no EECP. Mean CCS class was significantly improved in the EECP group but not in the no EECP group. At 7 week follow-up, soluble Interleukin 2 receptor measurements significantly increased in the EECP and significantly decreased in the no EECP group. There were no differences between groups at 7 weeks in resting cutaneous microvascular blood flow or response to acetylcholine, sodium nitroprusside or local heating.

A small RCT (n=20) was published in 2010 comparing intracoronary blood flows in patients treated with EECP against those treated with a sham procedure. (8) This trial was designed to detect statistically significant differences in collateral flow rates by angiography, not anginal symptoms. After 7 weeks of treatment, collateral flow index increased significantly in the EECP group compared to sham treatment. Conclusions from this study are limited by its small sample size and the unknown significance of short-term collateral blood flow improvements. Similar findings were noted in a comparative study by Buschmann and colleagues of 23 patients published in 2009. (9)

Two publications from a single study reported on blood flow and other measures of arterial function. (10, 11) This study randomized 42 patients with coronary artery disease (CAD) and chronic angina to EECP or sham EECP. EECP improved flow-mediated dilation in the brachial and femoral arteries and
improved numerous serum markers of blood flow and inflammation. The same study also reported that measures of arterial stiffness were improved in the EECP group.

In a 2015 randomized pilot study, Shakouri et al reported on intermediate outcome measures, including plasma nitric oxide, endothelin 1, high-sensitivity C-reactive protein, and QOL, in patients with CAD allocated to 20 sessions of EECP (n=21) or cardiac rehabilitation (n=21).12 There were no statistically significant improvements in physiologic markers and QOL over time in either group and no statistically significant between-group differences in change in any of the parameters evaluation.

**Systematic Reviews**

Systematic reviews of the literature have evaluated EECP for chronic stable angina. In 2010, Amin et al published a Cochrane review of major databases through 2008 on evidence of the effectiveness of EECP for chronic angina pectoris. (13) The solitary RCT identified was the MUST-EECP trial. The reviewers highlighted patient selection for this study. They noted that limiting the study population to patients with CCS class below IV diminished the trial’s generalizability to patients of interest, i.e., patients with the most severe symptoms of chronic angina pectoris.

Also in 2010, Shah et al published a meta-analysis of prospective studies, not limited to RCTs, of EECP in stable angina in which CCS class was adequately reported before and after treatment.(14) The MUST-EECP RCT was not included, because change in CCS class was not a reported outcome. A total of 13 studies met these inclusion criteria (total N=949 patients). Overall, improvement of at least 1 level of angina class occurred in 86% of patients (95% confidence interval [CI], 82% to 90%; p=0.008). No conclusions can be drawn from this analysis given the lack of randomization (comparison group) for most studies analyzed.

In 2009, McKenna and colleagues report on a systematic review and economic analysis of EECP for the treatment of stable angina and heart failure. (15) Four studies (1 RCT and 3 non-randomized comparative studies) comparing EECP treatment with no treatment in adults with chronic stable angina were included in the analysis. (3-6) The systematic review included a study by Barsheshet et al in which 25 patients (15 EECP, 10 controls) were evaluated at the end of treatment. (16) Similar to the Schechter et al study, (6) “CCS classification improved with EECP but not with usual care, however statistical analysis of between group differences was not reported and, for CCS classification, the data were treated as continuous data which is inappropriate for this four-category classification.”

A 2016 systematic review and meta-analysis focused on the effect of EECP on the intermediate measure of myocardial perfusion in patients with CAD. (17) The review included 6 studies reporting on myocardial perfusion or coronary flow outcomes published from 1992 to 2007, including 5 RCTs and 1 prospective, observational, blinded study. In pooled analysis, EECP was associated with increased myocardial perfusion in CAD patients (pooled weighted mean difference, -0.19; 95% CI, -0.38 to 0.00; p=0.049).

**Registry Studies**

Registry-based studies have reported on relatively large numbers of patients. In 1 registry-based study, 450 patients with left ventricular dysfunction (ejection fraction, ≤40%) and refractory angina had 0.7
fewer emergency department visits and 0.8 fewer hospitalizations 6 months after treatment with EECP compared with the 6 months before EECP; 6-month data were available on only 81 patients.18 Drawing conclusions from this study is not possible due to lack of a comparison group.

Another registry-based study (the International Enhanced External Counterpulsation Patient [IECP] Registry) reported long-term (3-year) results on patients with chronic refractory angina for patients in this registry. (19) The registry enrolled 5,000 patients from 99 U.S. and 9 international centers between 1999 and 2001. However, analysis was completed only for those centers that had at least 80% compliance with follow-up data submission; the study reported results on 1,427 patients. In this selective group, 220 patients (15.4%) died, while 1,061 patients (74.4%) completed their follow-up. Immediately post-EECP, the proportion of patients with severe angina (Canadian Cardiovascular Angina Classification [CCS] III/IV) were reduced from 89% to 25%, p<0.001. This was sustained in 74% of the patients during follow-up. More severe baseline angina and a history of heart failure or diabetes were independent predictors of unfavorable outcome. Again, the lack of a control group precludes drawing conclusions about this technology based on this study.

IECP data have also been examined to determine the safety and efficacy of this device in patients with peripheral arterial disease (PAD). PAD, while a common comorbidity of CAD, has been regarded as a contraindication to EECP due to concerns about compression on peripheral blood flow and a potentially greater risk of aortic rupture. Thakkar et al compared registry data in patients with PAD to those without.20 Based on a reduction of 1 or more CCS angina classes, patients with PAD had a similar rate of improvement as did the group without PAD (76.6% vs 79.0%, respectively; p=0.27). Rates of hospitalization for all cardiac causes (6.1% vs 4.4%, respectively; p=0.17) and for unstable angina (5.4% vs 3.5%, respectively; p=0.25) were also similar between groups.

### Other Observational Studies

Numerous individual observational studies have been detailed in previous reviews and are included in systematic reviews previously described. (4-6,9,16,21) For example, 2 prospective cohort studies (N=55 and N=61) with 1-year outcomes have been reported. (22,23) Improved CCS classification was the main reported outcome, which was maintained for 1 year in 79% and 78% of patients in the respective studies. Both studies had higher rates of treatment completion and follow-up than the previously reported (registry) studies of long-term outcomes. These studies address the need for data on treatment durability.

### Section Summary: Chronic Stable Angina

Data on use of EECP in chronic stable angina are insufficient to form conclusions about the efficacy of this treatment. The single randomized trial (MUST-EECP) that included relevant clinical outcomes reported a benefit on 1 of 4 main angina-related outcomes, and the magnitude of this benefit was of uncertain clinical significance. RCTs have reported on intermediate outcomes offer evidence on possible physiologic mechanisms underlying EECP treatment but do not themselves provide evidence of health outcome benefits. Observational studies (e.g., registry data, case series) offer little evidence on the efficacy of this procedure due to the variable natural history of angina, the multiple confounders of cardiac outcomes, and the potential for a placebo effect.
Heart Failure

The 510(k) approval of the Vasomedical devices states that objective measures such as peak oxygen consumption, exercise duration, and pre-load-adjusted maximal left ventricular power are improved following EECP therapy, as well as subjective measures of patient response to therapy, such as quality of life and functional ability measures (24). However, no clinical details of these studies are provided in the FDA summary, and these data are not from controlled trials.

The 2005 TEC Assessment included heart failure in its analysis and concluded the evidence supporting the role of EECP as an effective treatment for heart failure was lacking in both quantity and quality. (11) A single randomized, multicenter study compared EECP to usual care in 187 optimally medically managed patients with New York Heart Association (NYHA) functional class II or III heart failure with an ejection fraction of 35% or less of ischemic or idiopathic etiology. This study, the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH trial), was mostly inconclusive. (25) The design and methods of the PEECH trial were published by Feldman et al. (24) PEECH trial results found statistically improved, but modest, changes in exercise duration and improved functional class but not in QOL or VO2peak. (25)

A subgroup analysis of the PEECH trial showed that subjects ages 65 years and older treated with EECP (n=41) were more likely to meet the exercise duration (35% vs 25% increased by ≥60 seconds) and VO2peak (30% vs 11% increased by ≥1.25 mL/kg/min) improvement thresholds compared with those undergoing sham treatment (n=45); there was no difference at 6 months in NYHA class. (2)

In 2015, Rampengan et al reported on a double-blinded RCT evaluating EECP in patients with CHF treated in Indonesia. (26) Patients with NYHA functional class I or II symptomatic heart failure from various causes were included. Patients were randomized to active EECP (n=56) or sham EECP (n=56), which involved the use of the EECP device at only 77 mm Hg of pressure versus the standard 300 mm Hg. Analysis was per protocol, excluding 6 and 7 patients who dropped out of the active and sham groups, respectively. Post intervention, active EECP group patients were more likely to have a 6-minute walk test (6MWT) distance of 300 meters or greater (98.0% vs 32.7%, p<0.01). The change in 6MWT distance was greater (improved) for the active EECP patients (192.6 meters) than for the sham control patients (-9 meters; p<0.05).

Similar to the registry evidence for EECP for angina, registry studies for heart failure have provided relatively little insight into the comparative efficacy of EECP. (27-30) The single-arm study by Soran et al indicated that patients showed some improvements, but the lack of a comparison arm precludes inferences about the true effects of therapy. (31)

The previously described 2009 review by McKenna et al15 included the single trial of EECP for heart failure available at that time, the PEECH study. (25) The authors concluded that the studies did not provide firm evidence of the clinical effectiveness of EECP in refractory stable angina or in heart failure and that high-quality studies are required to investigate the benefits of EECP and whether they outweigh the common adverse effects.
Section Summary: Heart Failure
The evidence for the use of EECP in heart failure includes 2 RCTs that was reported on clinical outcomes. One study reported modest improvements for some outcomes and no improvement on others. A second study reported improvements in the 6MWT, but has methodologic limitations that limit conclusions that can be drawn. The observational studies added little to the evaluation of efficacy due to the variable natural history of heart failure, the multiple confounding variables for cardiac outcomes, and the potential for a placebo effect. Further high-quality RCTs are needed to determine whether EECP is a useful treatment for heart failure.

Other Indications
The use of EECP for other conditions associated with ischemia or vascular dysfunction has been investigated. In 2009, Fraser and Adams produced a Cochrane review on interventions for central retinal artery occlusion (CRAO). (32) One of the 2 RCTs identified compared hemodilution with EECP against hemodilution without further intervention. In this case, the EECP intervention was a single, 2-hour treatment. According to the reviewers, in this study, 20 patients were randomized but not blinded; no sham treatment was given. Primary outcomes were Doppler flowmetry of retinal perfusion and visual acuity. (33)

Published registry studies have also demonstrated improvements in erectile function. (34) Erectile function was improved in a study of 120 men prospectively enrolled from 16 centers. Three of 5 domains of the International Index of Erectile Function were statistically improved with EECP treatment (erectile function, intercourse satisfaction, overall satisfaction), and the total score improved from 28 to 32, a statistically significant improvement. The noncomparative design of this study makes it difficult to draw conclusions on treatment efficacy. Preliminary studies from Asia are also reporting early results on use of EECP to the lower extremities in the treatment of acute ischemic stroke. (35) A 2012 Cochrane review of 2 RCTs of EECP in acute ischemic stroke concluded that the methodologic quality of the studies was poor and reliable conclusions could not be reached from this evidence. (36)

In 2016, Sardina et al reported on an RCT that randomized 30 patients with type 2 diabetes in a 2:1 ratio to EECP (n=20) or standard care for diabetes (n=10), and reported results out to 337 and 6 months. (38) At 6-month follow-up, patients in the EECP group had significant decreases over time in variety of biomarkers of advanced glycation end products, inflammation, and oxidative stress. At 6-month follow-up, the percent change in advanced glycation end products and receptor of advanced glycation end products differed significantly between groups (p<0.05).

Ongoing and Unpublished Clinical Trials
A search of online ClinicalTrials.gov in July 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements
Guidelines from the American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and 5 other medical societies in 2012 guidelines on the management of patients with stable ischemic heart disease indicated EECP “may be considered for relief of refractory angina.” This
recommendation was based on class IIb, level of evidence: B, which indicates the efficacy of the intervention is not well established and further studies would be helpful. (39)

The 2013 ACCF and AHA guidelines on the management of heart failure do not address EECP. (40)

In 2014, ACC and AHA issued a Focused Update on the 2012 guideline on the diagnosis and management of patients with stable ischemic heart disease in which the associations specifically reviewed their recommendation on EECP. Based on this review, the recommendation on EECP remained unchanged from the 2012 guideline. (41)

U.S. Preventive Services Task Force Recommendations

Not applicable.

Summary of Evidence

For individuals who have chronic stable angina who receive enhanced external counterpulsation (EECP), the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and functional outcomes. There is only 1 blinded RCT that includes clinical outcomes, and it reported benefit on only 1 of 4 main angina outcomes. Additional small RCTs have reported changes in physiologic measures associated with EECP but did not provide relevant evidence on clinical efficacy. Because of the variable natural history of angina, the multiple confounding variables for cardiac outcomes, and the potential for a placebo effect, RCT evidence is needed. Therefore, observational studies, including registry studies with large numbers of patients, add little to determinations of efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart failure who receive EECP, the evidence includes RCTs, observational studies, and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and functional outcomes. One RCT that reported on clinical outcomes found a modest benefit with EECP on some outcomes and no benefit on others. A second RCT reported improvements on the 6-minute walk test with EECP, but had methodologic limitations that limit conclusions that can be drawn. The observational studies on EECP in heart failure have limited ability to inform the evidence on EECP due to the multiple confounding variables for cardiac outcomes and the potential for a placebo effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

Medicare published a national coverage decision regarding EECP that mandates coverage for the following indications (42)

“Coverage is provided for the use of EECP for patients who have been diagnosed with disabling angina who, in the opinion of a cardiologist or cardiothoracic surgeon, are not readily amenable to surgical intervention, such as percutaneous transluminal coronary angioplasty 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 amendable to such procedures; or 3) They have co-morbid states which create excessive risk.”
Medicare’s coverage policy also notes that while the FDA has cleared EECP “for use in treating a variety of cardiac conditions, including stable or unstable angina pectoris, acute myocardial infarction and cardiogenic shock, the use of this device to treat cardiac conditions other than stable angina pectoris is not covered.”

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). External Counterpulsation for Treatment of Chronic Stable Angina Pectoris and Chronic Heart Failure. TEC Assessments. 2005;20;Tab 12.


Enhanced External Counterpulsation


### Policy History

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy statement changed to not medically necessary. References 8,9,10 added. “Congestive” removed from policy title.</td>
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<tr>
<td>June 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature search. Title of policy changed to indicate it applies to more indications than only chronic stable angina and heart failure. References 6, 35 added. Policy statement unchanged.</td>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy was updated with literature search, deleting references 36 and 37, and adding new reference 36. The policy statement is unchanged.</td>
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<tr>
<td>December 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 13, 18, 27, 39, and 41 added. Policy statement unchanged.</td>
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### Keywords

Counterpulsation, Enhanced External ECP EECP Enhanced External Counterpulsation

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective January 15, 2017.

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