Mechanisms and Evidence for the Role of Enhanced External Counterpulsation in Heart Failure Management

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Balloon counterpulsation has gained widespread acceptance as a therapy for cardiogenic shock. However, over the past four decades a parallel method of noninvasive counterpulsation, enhanced external counterpulsation (EECP), has been defined and developed. Mechanisms of benefit for this technology continue to emerge and include enhanced coronary and other key target organ perfusion beds. Other mechanisms include angiogenesis and enhanced cellular metabolism. Beyond putative mechanisms there is ample evidence for improved and sustained outcomes in patients with and without left ventricular dysfunction. This evidence comes from long-term registry reports and randomized clinical trials. With respect to heart failure (HF), there is registry, pilot trial, and randomized clinical trial evidence of safety and efficacy. This paper summarizes some of the mechanisms and outcomes of EECP in HF patients and helps to elucidate the role of EECP in the management of patients with chronic HF.

Introduction

The benefits of counterpulsation are well known in the context of intra-aortic balloon pumping for circulatory assistance. The technique was invented in the 1950s, was commercially introduced in the 1970s, and has gained popularity ever since. Less well known is the development of a noninvasive (external) method producing the same hemodynamic benefits that progressed in parallel over the same period. Early efforts focused on acute conditions, especially cardiogenic shock, and the first publication comparing both methods appeared in 1973 [1]. In 1980, Amsterdam et al. [2] published a collaborative trial in which the benefits of external counterpulsation in acute myocardial infarction with circulatory shock were demonstrated. Early devices produced counterpulsation using electrocardiogram-gated inflation and deflation of cuffs wrapped around the lower extremities, but they were crude, bulky, and less hemodynamically efficient compared with intra-aortic counterpulsation, hindering their adoption.

In time, major progress was made. First, air replaced water to fill the cuffs, allowing for lighter, faster equipment and more responsiveness to pressure changes. Second, sequential cuff inflation was introduced, significantly increasing the hemodynamic effect. Altogether, the hemodynamic effect of current devices are greater than those of intra-aortic counterpulsation [3•].

Concurrently, assessment of the technique in the treatment of chronic stable angina was initiated [4], but with disappointing results due to the brief treatment regimen (four 2-hour sessions) applied at the time. Gradually, US developers of this promising therapeutic method lost interest, but Chinese researchers engaged in continuing development of the device. Years later, enhanced external counterpulsation (EECP) (ie, rapid electrocardiogram-gated sequential inflation and simultaneous deflation of cuffs wrapped around the calves, thighs, and buttocks at suprasystolic pressures during diastole) was reintroduced into the United States in the late 1980s. In a series of small studies, researchers at Stony Brook University (New York), verified results Chinese researchers had achieved in the treatment of chronic stable angina using 35 or 36 1-hour treatments over 4 to 7 weeks. Based on these results, a prospective sham-controlled trial, multicenter study of enhanced external counterpulsation was performed (MUST-EECP) [5]. Results demonstrated an increase in time to exercise-induced ST-segment depression and a reduction in anginal episodes, clearly establishing the benefits of EECP in the treatment of chronic stable angina pectoris. Subsequent reports have validated these trial results and documented the long-term symptom relief [6] and quality-of-life benefits [7] achieved. Medicare initiated reimbursement coverage in 1999, and today EECP therapy is used to treat stable angina pectoris in more than 20,000 US patients annually [8].

Mechanisms of Action

Numerous studies have been performed to elucidate the mode of action of EECP (Table 1). Evidence to date suggests that a complex ensemble of actions underpins the overall effect of the therapy.

Michaels et al. [3•], in particular, clearly demonstrated the acute increases in coronary artery pressures and flow rates with EECP in a well-designed set of experiments using in situ coronary pressure and flow wires. Similar observations were made by Taguchi et al. [9•], who demonstrated that EECP increases venous return and in turn cardiac output significantly more than intraaortic balloon counterpulsation (IABP) does. The acute increase in venous return was matched by an increase in atrial natriuretic peptide, a good indicator of left ventricular (LV) filling [10]. This ability to provide acute circulatory support is further confirmed by other studies that show improved perfusion to various organs, such as the heart [3•], the eye [11], the brain [12], the skin [13], and the kidney [14]. In studies of the effect of EECP on flow velocity in the eye, increases were seen only in areas of decreased perfusion or when atherosclerosis was present, suggesting that this effect depends on abnormal vascular function [11]. A key hypothesis follows from the acute hemodynamic effects of EECP, the enhanced diastolic flow, and the related increase in shear stress. Increased shear stress is known to trigger angiogenesis and to improve vascular function through the modulation of vasoactive factors. Wu et al. [15] recently found evidence of angiogenesis after EECP in a dog model, confirming findings noted in a much earlier study [16]. In this model, EECP triggered an impressive growth of coronary collaterals, though this model may not directly apply to humans, because dogs aggressively develop coronary collaterals with stimulation. However, recent evidence from human studies supports this hypothesis, albeit indirectly. EECP dramatically increased levels of serum vascular endothelial growth factor [17] and other similarly active factors in patients [18]. More direct evidence is provided in an elegant study by Werner et al. [19] using assessments of changes in ocular blood flow after a short course of EECP.

In parallel, accumulating evidence shows that EECP has positive effects on vascular function, affecting all vessels, whether coronary or peripheral. Improved endothelial function [20•] and arterial compliance [21] after EECP therapy have been documented in separate, well-controlled investigations. Additionally, improved myocardial perfusion has been observed by several investigators [22–25]. Though data from one study failed to provide supporting evidence of increased perfusion, it did confirm the clinical benefits of EECP [26]. The effects of EECP on coronary vascular function are illustrated by the resolution of a coronary syndrome associated with coronary vascular dysfunction, as described in a case report from the Mayo Clinic [27]. Notably, the patient remained symptom free for at least 3 months after the end of the treatment, further illustrating that EECP can improve coronary vascular function while providing sustained benefits.

EECP produces a marked decrease in the level of plasma endothelin, which gradually returns to normal after treatment discontinuation [28]. Nitric oxide increased during treatment with EECP, and blood levels remained elevated for at least 3 months after treatment, although they eventually decreased [29]. Consistent with this evidence, a recent trial by Levenson et al. [30] demonstrated that after a single hour of EECP, the cyclic guanosine monophosphate level was increased in plasma and platelets, further suggesting an activation of the nitric oxide pathway. Others found that atrial natriuretic peptide tends to decrease following the application of EECP [13,23]. Additionally, it has been shown that B-type natriuretic peptide, which was significantly elevated prior to treatment, was markedly lowered upon treatment initiation and continued to decrease thereafter.

In summary, data suggest that EECP favorably affects perfusion by favoring angiogenesis and improving vascular function. These effects seem to benefit all organs and appear to be dose dependent, as changes occur immediately upon treatment initiation, increase with the number of treatment sessions, and are most often maintained well beyond the end of therapy.

The effects of EECP at the cellular level have also been explored but are less understood. Data from Masuda et al. [31] suggest that cellular metabolism is favorably affected by EECP. In their study, k mono, the index of regional myocardial oxygen metabolism, remained unchanged in nonischemic regions but was improved when ischemia was present, again suggesting that EECP primarily affects areas where vascular or metabolic abnormalities are present. In studies of EECP in patients with heart failure (HF), results indicated that the etiology of HF does not significantly affect the effectiveness of the device, while other data suggest that EECP may directly affect contractility [32]. During the application of EECP to coronary artery disease patients and healthy volunteers, oxygen uptake increased [33]. Likewise, no difference in benefit was observed in large cohorts of patients with stable angina pectoris who also had a diagnosis of congestive heart failure (CHF), regardless of the presence or absence of LV systolic dysfunction [34]. Taken together, these data suggest that EECP may affect the myocardium in ways other than vascular, ie, at the level of cellular metabolism.

Understanding the acute effects of EECP appears straightforward, but it is more difficult to understand how EECP provides long-term benefits. Several hypotheses have been formulated. We believe that the end results of EECP treatment are explained by the cumulative effects of changes occurring at the vascular and possibly cellular levels.

Table 1. Studies investigating mechanism of action of EECP

Study	N	Population	Design	Effects
Jacobey et al. [16]	21	Dogs	2 groups: acute coronary occlusion with and without EECP (additional testing of EECP on normal dogs and dogs with chronic ischemia)	After acute coronary occlusion, mortality of 54% in control group vs 11% in EECP group; EECP (x2h) opened dormant coronary collaterals in dogs with conditions of ischemia (acute or chronic) but not in normal dogs
Applebaum et al. [12]	35, 18	CAD	Single group: 2 subgroups (carotid and renal blood flow)	Significantly increased carotid and renal blood flow in all subjects studied (35 and 18, respectively)
Taguchi et al. [9•]	23, 12	AMI	2 groups: EECP (1h) vs IABP	Similar diastolic augmentation in both groups; increased right atrial pressure, pulmonary capillary wedge pressure, and cardiac index in the EECP group only
Masuda et al. [18]	11	Chronic stable angina	Single group: EECP 35 (1h) sessions	Promoted release of angiogenesis factors, especially HGF, through increased shear stress and resulted in increased functional collateral vessels
Werner et al. [19]	12, 12	Healthy; CAD	2 groups: healthy vs CAD (blood flow velocity measured during 1st min of EECP application)	Significantly increased blood flow velocity in the ophthalmic artery of CAD subjects by 11.4% but not in healthy subjects
Urano et al. [22]	12	Stable angina	Single group: EECP 35 (1h) sessions	Improved LV diastolic filling and reduced myocardial ischemia as measured by thallium scintigraphy
Masuda et al. [23]	11	Stable angina	Single group: EECP 18–35 (1h) sessions	Improved myocardial perfusion measured at stress by N-ammonia PET scan, at the same cardiac workload, follow-up vs baseline
Michaels et al.[3•]	10	Diagnostic catheter	Single group: EECP (300 mm Hg)	Acutely increased coronary artery pressure and flow velocity following significant increase in diastolic pressure in the central aorta
Stys et al. [25]	175	Stable angina	Single group: EECP 35 (1h) sessions	Improved myocardial perfusion measured at stress by radionuclide scan, at the same cardiac workload, follow-up vs baseline
Bonetti et al. [20•]	23	CAD	Single group: EECP 35 (1h) sessions	Improved endothelial function as shown by increased reactive hyperemia index
Tartaglia et al. [24]	25	Stable angina	Single group: EECP 35 (1h) sessions	Improved myocardial perfusion measured at stress by SPECT and maximal exercise (different workloads at baseline follow-up)
Levenson et al. [30]	55	30 subjects with chronic, stable CAD, 25 with high CV risk factors	Randomized, sham controlled (EECP vs sham EECP, single [1h] session)	Significantly increased plasma cGMP concentration and platelet content; inhibition reduced and stimulation increased cGMP, suggesting activation of nitric oxide pathway
Taguchi et al. [10]	24	AMI	Single group: EECP single (1h) session	Increased CI and ANP, but not BNP (increase in BNP being associated with worsening of cardiac function)
Werner et al. [11]	20	Central or branch retinal artery occlusion	2 groups: hemodilution and EECP (2h) vs hemodilution alone	Immediately increased perfusion in ischemic retinal areas in EECP group; increase in perfusion in both groups with no difference between groups 48 h later
Michaels et al. [26]	34	Stable angina	Single group: EECP 35 (1h) sessions	No change in myocardial perfusion measured at stress by radionuclide, at same cardiac workload at baseline and follow-up; clinical and exercise capacity improvements following EECP attributed to peripheral training effect
Wu et al. [15]	12	Dogs	Randomized controlled; acute coronary occlusion with and without EECP	Significantly increased density of micro vessels in infarcted regions of EECP group compared with controls; improved myocardial perfusion as assessed by SPECT
Grayson et al. [33]	20	Chronic, stable CAD and healthy, sedentary volunteers	2 groups: CAD (10) and healthy, sedentary volunteers (10); single (1h) EECP session	Increased oxygen uptake (VO2) during active EECP in both groups
Levenson et al. [30]	30	Chronic, stable CAD	Randomized, sham controlled (EECP vs sham EECP, 35 [1h] sessions)	Significantly decreased carotid artery wall stiffness and vascular resistance, EECP vs sham EECP

AMI—acute myocardial infarction; ANP—atrial natriuretic peptide; BNP—brain natriuretic peptide; CAD—coronary artery disease; cGMP—cyclic guanosine monophosphate; CV—cardiovascular; EECP—enhanced external counterpulsation; HGF—hepatocyte growth factor; IABP—intra-aortic balloon pump; LV—left ventricular; PET—positron emission tomography; SPECT—single-photon emission.

EECP in HF: Evidence

Initial evidence regarding benefits in patients with left ventricular dysfunction (LVD) and HF emanated from a large prospective registry, International EECP Patient Registry (IEPR), coordinated by the University of Pittsburgh. The IEPR tracks immediate and long-term outcomes in sequentially enrolled patients from numerous centers, allowing real-life experience to be collected formally and published. As expected, a large proportion (about 22%) of the patients treated for stable angina pectoris also had systolic dysfunction or symptoms of HF (Table 2).

Soran et al. [35] initially published results in this subgroup, reporting that this cohort of patients with systolic dysfunction has more severe background disease compared with patients with normal ventricular function. However, both populations showed significant benefits in terms of symptom relief (67.8% vs 76.2% improved Canadian Cardiovascular Society Class, $P < 0.01$) and quality of life immediately after treatment with EECP as well as 6 months thereafter. Major adverse clinical events (MACE) (death, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention) were similar during treatment, but exacerbation of HF (5.4% vs 1.0%, $P < 0.001$) and unstable angina (4.2% vs 2.0%, $P < 0.05$) were higher in patients with LVD. These authors reported that such benefits were sustained at 2 years in the majority of patients, with a 2-year survival of 83% and a major cardiovascular event–free survival rate of 70% [36•]. This considerable experience with EECP therapy in patients with systolic dysfunction led to the obvious question: What is the safety and efficacy of the device in patients with HF?

The hemodynamic effects of EECP are twofold. In addition to diastolic arterial augmentation with cuff inflation, venous return is also significantly augmented. However, systemic vascular resistance and cardiac afterload are drastically reduced when the cuffs are deflated. Only when both effects are combined properly will the increase in venous return be compensated and not result in pulmonary congestion or even pulmonary edema. Because of these important hemodynamic effects, several potential safety concerns remained that required testing in a safety pilot trial [37•].

The population was carefully defined to include only patients in stable clinical condition and without any fluid overload. This single-group feasibility study provided evidence that EECP (35 1-hour sessions) could be administered safely to this population. Additionally, there were encouraging indications of effectiveness. Peak oxygen uptake (+27.1%) and exercise duration (+15.6%) were increased at 6 months, as were symptoms and quality-of-life measures. Furthermore, results were similar regardless of whether the cause of HF was idiopathic or ischemic. Interestingly, echocardiography suggested an improvement in ventricular function that was sustained over the follow-up period [32].

These promising pilot results, including putative mechanisms of action and a reasonable safety profile, led investigators to the initiation of a controlled prospective trial, the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) Trial, the design of which has been described elsewhere [38•]. In summary, this was a randomized controlled trial of patients with a diagnosis of HF (ischemic or idiopathic; left ventricular ejection fraction ≤ 35%, New York Heart Association [NYHA] Class II/III) receiving optimal medical therapy. After a 2-week baseline period, subjects were randomized to either optimal care alone or optimal care plus EECP. Treatment with EECP entailed 35 1-hour sessions over a 7-week period. All subjects were then followed for an additional 6 months, and blinded evaluators (core laboratory and site investigators) performed all subject assessments at 1 week, 3 months, and 6 months after completion of EECP. Two coprimary endpoints were defined, the percentage of subjects who increased exercise duration by 60 seconds or more and the percentage of subjects who increased peak oxygen uptake by 1.5 mL/kg/minute or more. Both thresholds were selected to be above any effect observed in the placebo groups or inactive drug groups of prior trials in similar populations.

Results at 6 months showed that exercise duration increased by 60 seconds or more in a larger number of subjects receiving EECP than in the control group. Exercise duration increased 1 week, 3 months, and 6 months post-treatment, and peak oxygen uptake increased at 1 week but not at later time points. NYHA stage was significantly improved at all time points, and quality of life increased significantly 1 week and 3 months post-treatment. PEECH was unique in that all patients had to be optimally treated at baseline in order for investigators to assess whether additional functional improvements could be achieved. Results showed that in optimally treated patients with mild-to-moderate HF, EECP provided functional benefits beyond what optimal medical therapy alone can provide. The final PEECH results are currently in press.

These results are supported by smaller prospective or retrospective single-group studies. EECP was shown to increase LV ejection fraction in groups of patients with normal or mildly depressed LV function, while no changes in diastolic function were found [39]. In the IEPR, EECP was shown to improve functional capacity in patients with LVD as assessed by the Duke Activity Status Index, a questionnaire that correlates well with peak oxygen uptake [40]. Other data from the same registry showed that the effects of EECP were similar when systolic function was preserved (diastolic HF) or depressed in patients with angina pectoris and a history of CHF [41•]. Symptoms, functional status, frequency of anginal episodes, and use of on-demand nitroglycerin improved to a similar degree, while MACE were also similar in both groups. A single-group study showed that in patients with class II/III angina pectoris, severe coronary artery disease,

Table 2. Evidence in heart failure

Study	*N*	Population	Design	Results
Soran et al. [35]	1402	Chronic stable angina	Observational (EECP registry), 2 groups: LVEF > 35% (1090), LVEF ≤ 35% (312)	Patients with LVD had improved anginal status similar to patients without LVD immediately after and 6 mo after EECP, despite more history of MI and CHF, longer duration of CAD, and more severe CCS class at baseline; patients with LVD experienced more AEs during EECP treatment and at 6-mo follow-up, a significantly higher proportion of patients in the LVD group had CV outcomes (15.4% vs 8.3%)
Soran et al. [37•]	32 enrolled, 26 treated, 23 with follow-up, 19 completed study	Chronic stable HF, LVEF ≤ 35%, NYHA II-III	Open, single group: EECP 35 (1h) sessions, 6-mo follow-up	6-mo follow-up: NYHA (n=23)—12 maintained improvement, 5 remained unchanged, and 4 worsened; exercise duration—15.6% increase (n=19); peak VO_2—27% increase (n=19); quality of life—improvement maintained (n=19); echocardiography substudy—significant increase in PAMP was observed after EECP therapy from 4.2 ± 2.0 to 5.4 ± 2.0* mW/cm^4
Feldman et al. [38•]	187 randomized, 178 treated, 164 with follow-up	Chronic stable HF, LVEF ≤ 35%, NYHA II-III, optimal care	Controlled, single-blind: EECP 35 (1h) sessions, 6-mo follow-up	6-mo follow-up (164 subjects): exercise duration—increase ≥ 60 sec in 35% (EECP) vs 25% (control), P = 0.016; peak VO_2—no difference between groups in percentage of subjects who improved by 1.5 mL/kg/min or more, peak VO_2 increased at 1 wk post-treatment overall (strong trend) and in ischemic heart disease subgroup (P < 0.05), EECP group on average tended to maintain improvement, whereas control group showed a progressive deterioration of peak VO_2 over time; NYHA—shift in NYHA class significantly better in the EECP group; quality of life—significantly greater improvement from baseline as measured by MLHQ physical and emotional scores, a significantly higher proportion of subjects in EECP group reported improvement in their health as compared with 1 y ago (SF-36)
Arora et al. [39]	14	Chronic stable refractory angina, CCS I-III	Single group: EECP 35 (1h) sessions	Improved systolic function as measured by increase of LVEF at rest and at stress using echocardiography in subjects with normal and mild systolic dysfunction
Lawson et al. [41•]	746	Chronic stable angina with CCS III (90%), IV (10%), history of HF	Observational (EECP registry), 2 groups: LVEF > 35% (391 S), LVEF ≤ 35% (355 D)	Post EECP (32h): angina reduced by ≥ 1 class in 72% in both groups at 1-y follow-up; angina—less than pre EECP in 78% (D) vs 76% (S); MACE—24.3% (D) vs 23.8% (S)

AEs—adverse events; CAD—coronary artery disease; CCS—Canadian Cardiovascular Society; CHF—congestive heart failure; CV—cardiovascular; D—diastolic; EECP—enhanced external counterpulsation; HF—Heart Failure; LVD—left ventricular dysfunction; LVEF—left ventricular ejection fraction; MACE—major adverse clinical events (death, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention; MI—myocardial infarction; MLHQ—Minnesota Living with Heart Failure Questionnaire; NYHA—New York Heart Association; PAMP—plasma proadrenomedullin *N*-terminal 20 peptide; S—systolic; SF—short form; VO_2—volume of oxygen consumption.
*P < 0.05 vs baseline in 8 subjects participating in the substudy.

and prolonged QRS (mean 105 ± 19 msec), EECP did not promote electrophysiologic remodeling [42]. However, in a group of patients with angina pectoris, Bart et al. (unpublished data) showed that while EECP did not induce any significant changes in the time-domain measures of heart rate variability, the low to high frequency ratio was increased, a change that has been associated with decreased mortality [43]. The application of EECP to patients with pacemakers does not appear to raise concerns at this time.

When to Recommend EECP for Patients with HF

Indications for use of EECP therapy approved by the US Food and Drug Administration include stable and unstable angina, CHF, acute myocardial infarction, and cardiogenic shock. Considerable experience has been accumulated in stable angina and HF in recent years, although use in acute conditions has been scarce to date. In fact, use of EECP in patients with symptoms of coronary artery disease (chronic stable angina pectoris or angina equivalent) has become well established. As illustrated by large registry studies, EECP provides consistent benefits in patients regardless of age, ventricular function, prior diagnosis of HF, or gender [44–47]. Furthermore, EECP is effective in the presence of diabetes mellitus [48]. This experience is important because about 25% of patients treated for symptoms of stable angina pectoris have a concomitant diagnosis of HF and experience similar benefits, though, as expected, they incur a slightly higher rate of clinical events. Because the recently completed PEECH Trial demonstrated functional benefits in patients with HF and LVD, it is timely to consider data from the trial and from the larger scale registries in recommending a role for EECP in HF. Subjects in the PEECH Trial differ in many ways from the populations enrolled in other trials of HF. Although a LV ejection fraction of 35% or less and mild to moderate HF (NYHA class II/III) are usual inclusion criteria, other requirements set the PEECH Trial population apart. Three key requirements characterized subjects in the trial, namely they had to be clinically stable, essentially free of edema (trace ankle edema only), and treated with guideline-recommended medications (angiotensin-converting enzyme inhibitors I or angiotensin receptor blocker and β-blocker) titrated to appropriate doses at baseline. Compared with recent positive randomized trials in mild-to-moderate HF, the control group in PEECH is similar to the subgroup that is actively treated and free of fluid overload. This is illustrated by the very low rate of clinical events observed over the course of the study. Despite optimal medical management and a stable condition, these patients sought additional functional improvement. From this standpoint, PEECH has defined a new treatment target in HF, and EECP has been shown to enable physicians and patients to improve functional status and quality of life.

The population observed in the registries is quite different from the PEECH Trial population in that when present, HF is not the primary indication for EECP. Furthermore, as inclusion consists of consecutive patients presenting for EECP due to angina undergoing at least 1 hour of therapy, the array of treatment is much wider and reflects real-life conditions more accurately. It is notable, therefore, that the registries show EECP to be well tolerated and able to provide benefits equally in patients with or without HF.

While the safety of EECP in patients without significant fluid overload has been demonstrated, few data exist to guide the use of EECP in patients with more severe fluid overload or acute decompensated HF. Further experience and investigation are clearly needed in this area. Experience from spontaneous adverse event reports and studies show that when applied at lower pressure to patients with unsatisfactory fluid balance, EECP can precipitate pulmonary edema. This is consistent with data discussed earlier showing that EECP increases venous return and transiently increases pulmonary capillary wedge pressure. Additionally, experience gathered from various studies, in particular PEECH and the IEPR, shows that there is little or no reason for concern about treating patients with pacemakers, including biventricular devices.

Conclusions

EECP can benefit patients with HF who already receive optimal medical care without having achieved the degree of functional benefit they desire. The available data are consistent across several studies, and the results of the PEECH Trial provide the best available basis to date for assessing the efficacy of this unique therapy. It can be argued that EECP may well be the intervention of choice in patients with coronary artery disease and CHF, provided that medical therapy is optimal and edema is very limited or absent. Certainly its impact on residual ischemic burden will play a role in patient outcomes. When one considers its noninvasive approach and the wealth of data supporting its safety and improved outcomes, it is likely that EECP therapy will gain an important role in the armamentarium of emerging HF therapies.

More research will help to confirm the effectiveness of EECP and establish the cost-effectiveness of this therapeutic approach. The functional benefits observed in the PEECH Trial should be confirmed, although an outcome trial in the same population may be of little relevance. Outcomes achieved in real-life practice settings, as reflected in a large, diverse registry, should be evaluated for HF patients, similar to the approach used so successfully for the stable angina population.

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