Primer: practical approach to the selection of patients for and application of EECP

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SUMMARY

Over the past decade, the frequency of use of enhanced external counterpulsation (EECP®) has increased in patients with angina, irrespective of medical therapy and coronary revascularization status. Many patients referred for EECP® have one or more comorbidities that could affect this treatment's efficacy, safety, or both. By use of data from more than 8,000 patients enrolled in the International EECP® Patient Registry, we provide practical guidelines for the selection and treatment of patients. We have focused on considerations for patients who have one or more of the following characteristics: age older than 75 years, diabetes, obesity, heart failure, and peripheral vascular disease. We have also reviewed outcomes and treatment recommendations for individuals with poor diastolic augmentation during treatment, for those with atrial fibrillation or pacemakers, and for those receiving anticoagulation therapy. Lastly, we examined relevant data regarding extended courses of EECP®, repeat therapy, or both. While clinical studies have demonstrated the usefulness of EECP® in selected patients, these guidelines permit recommendations for the extended application of this important treatment to subsets of patients excluded from clinical trials.

KEYWORDS angina, diabetes, external counterpulsation, heart failure, registry

REVIEW CRITERIA

A search for original articles published between 1980 and 2006 and focusing on external counterpulsation was performed in MEDLINE and PubMed. The search terms used were "enhanced external counterpulsation" and "external counterpulsation". All papers identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

Symptomatic ischemic heart disease continues to have a major impact on morbidity and mortality in men and women in industrialized countries. More than 6 million people in the US suffer from angina pectoris.[1] While most patients can be treated with lifestyle modifications, pharmacologic antianginal therapy, percutaneous coronary intervention (PCI), or CABG surgery, many patients have residual myocardial ischemia and angina. Enhanced external counterpulsation (EECP®) is a noninvasive treatment that involves the sequential inflation of three sets of lower-extremity cuffs during diastole, leading to increased venous return and cardiac output, systolic unloading, and augmentation of the coronary artery perfusion pressure. EECP® can reduce the severity and frequency of angina pectoris and extend time to exercise-induced ischemia in patients with symptoms of stable angina.[2] After a standard 35 h course of EECP® (administered in 1 h daily treatments, 5 days per week over 7 weeks), approximately three-quarters of patients experience an improvement in angina symptoms, functional class, and quality of life (Figure 1).[3] In most patients, these results are sustained at 2 years' follow-up.[4]

The purpose of this paper is to serve as a practical guide to the selection of patients and the application of EECP®. We reviewed data from the International EECP® Patient Registry (IEPR) to evaluate the therapy's safety and efficacy and its use in individuals with the following characteristics: age older than 75 years, diabetes, obesity, heart failure, and peripheral vascular disease. We also reviewed outcomes and treatment recommendations for individuals with suboptimum diastolic augmentation during treatment, those with atrial fibrillation or pacemakers, and those receiving anticoagulation therapy. Lastly, we examined relevant registry data regarding extended EECP® regimens, repeat therapy, or both. While clinical studies have demonstrated

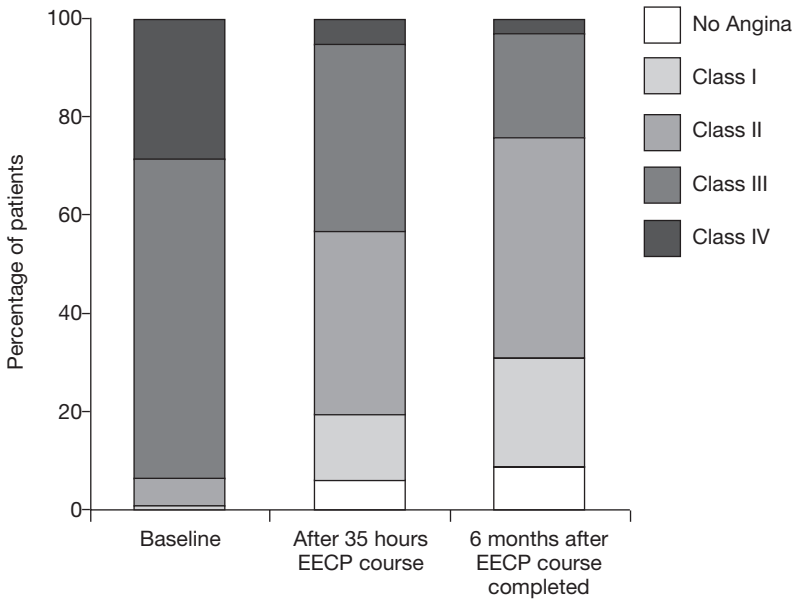

Figure 1 Mean Canadian Cardiovascular Society angina class among patients undergoing a course of EECP® therapy. The severity and frequency of angina pectoris in the study population was reduced following a standard 35 h course of EECP®, the effects of which were even greater at 6 months. Data from a prospective substudy of the International EECP® Patient Registry 2 that evaluated the indications, potential benefits, and safety associated with prolongation of a standard course of EECP® in patients with chronic angina. Abbreviation: EECP®, enhanced external counterpulsation.

Table 1 Demographic characteristics of patients in the International EECP® Patient Registry ($n = 7,973$).

Characteristic	Value
Mean (SD) age (years)	67.0 (10.8)
Male (%)	75
Hypertension (%)	75
Hyperlipidemia (%)	84
Diabetes mellitus (%)	43
Family history of CAD (%)	78
Noncardiovascular disease (%)	34
Previous smoker (%)	61
Current smoker (%)	8

Abbreviations: CAD, coronary artery disease; EECP®, enhanced external counterpulsation.

the usefulness of EECP® in selected individuals, these practical guidelines permit a discussion of the extended application of this important treatment to subsets of patients who have been excluded from clinical trials.

THE INTERNATIONAL EECP® PATIENT REGISTRY

The first phase of the IEPR (IEPR-1) enrolled 5,056 consecutive patients from 119 US and 21 international sites who were undergoing EECP® for chronic angina between January 1998 and July 2001 (Tables 1–3; see Supplementary Information 1 online for a list of the study centers, site investigators and coordinators involved). The second phase of the IEPR (IEPR-2) enrolled 2,917 consecutive patients from 95 US sites who were undergoing EECP® for chronic angina between January 2002 and October 2004. Since these registries aimed to collect data on as broad a range of patients as possible, the only criteria for entry were that the patients gave informed consent and underwent at least 1 h of EECP® treatment for chronic angina.

The IEPR methods have been previously described.[5] Briefly, patients' demographics, medical history and coronary disease status were recorded, and quality of life was assessed, before EECP® treatment (a standard regimen of 35 h over 7–8 weeks). At the end of therapy, data were collected on Canadian Cardiovascular Society classification of angina, antianginal medication use, quality of life, and adverse clinical events. IEPR-2 recorded more-detailed heart failure information, including NYHA class, number of hospitalizations for heart failure, Duke Activity Status Index (DASI) scores, and responses to the Kansas City Cardiomyopathy Questionnaire. Data were collected in telephone interviews 6 months and 12 months after the last EECP® treatment session, and yearly thereafter for 3 years in IEPR-1 and for 2 years in IEPR-2.

PATIENT SELECTION

General features of selection of patients

Definitive, evidence-based indications for EECP® use have not been established in all groups of patients, but in some groups the benefits of this therapy have been determined. Patients with class II–IV angina resulting from obstructive epicardial coronary artery disease, who are not candidates for revascularization, derive benefit from EECP®,[2] provided that aggressive medical therapy is used (i.e. β-blockers, nitrates, and calcium-channel blockers for angina, and angiotensin-converting-enzyme inhibitors, β-blockers, hypolipidemic agents, and antiplatelet agents to prevent cardiovascular events).[6] 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 (e.g. the elderly 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.[2] Benefits of EECP® have also been determined in patients without decompensated heart failure but severe mitral insufficiency, in those with frequent premature beats and occasional irregular rhythm (although these patients can experience some discomfort from cuff inflation and deflation), and in those with NYHA class II–III heart failure.[7] The Prospective Evaluation of EECP® in Congestive Heart Failure (PEECH) trial[7] showed that EECP® therapy improved exercise tolerance and quality of life in patients with chronic angina, although the improvement in oxygen consumption was not significant. For patients with compensated left ventricular systolic dysfunction owing to ischemic or nonischemic cardiomyopathy, EECP® can be administered safely; however, EECP® use should be limited among patients with class III–IV angina and those with symptomatic ischemic heart disease. Use should be avoided altogether among those with decompensated heart failure, severe pulmonary or systemic hypertension, severe aortic insufficiency, severe lower extremity peripheral vascular disease, or uncontrolled arrhythmia (Box 1).

No absolute requirements exist for the evaluation of patients before and after EECP®; however, we suggest that most patients undergo a cardiovascular evaluation to determine their optimum medical management, risk factor modification, and revascularization options. In addition, stress imaging tests to assess the extent of ischemia are often useful before and 1 month after EECP®, but whether they can be performed will depend on the patient's clinical indications. Access might be available to a recent echocardiogram done to investigate for valvular disease in patients with heart murmur in whom stress imaging cannot be performed. Of note, before EECP® therapy commences, patients with heart failure should be assessed to decide the optimum medical regimen and for patients with atrial fibrillation, rate control and anticoagulation should be optimized.

Table 2 Baseline coronary disease factors and revascularization status for patients in the International EECP® Patient Registry ($n = 7,973$).

Characteristic	Value
Mean (SD) years since CAD diagnosis	11 (9)
Prior MI (%)	69
Multivessel disease (%)	80
Heart failure (%)	31
Mean (SD) LVEF (%)	47 (14)
Prior PCI or CABG (%)	87
Mean (SD) number of angina episodes per week	10 (14)
CCS angina class (%)	
I	3
II	11
III	60
IV	26

Abbreviations: CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; EECP®, enhanced external counterpulsation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3 The 1-year cumulative clinical outcomes after enhanced external counterpulsation ($n = 4,565$).

Clinical events	Value
Death (%)	5.0
MI (%)	4.8
Heart failure exacerbation (%)	6.5
Hospitalization for a cardiac cause (%)	26.7
PCI (%)	7.5
CABG (%)	3.1
CCS angina class (%)	
No angina	27.0
I	19.0
II	30.0
III	19.0
IV	6.0
Angina class ≤1 lower after EECP® (%)	76.0
Mean (SD) number of angina episodes per week	4 (7)
Quality of life[a]	
Health improved (%)	51.0
Quality of life improved (%)	47.0
Health satisfaction improved (%)	55.0

[a]From International EECP® Patient Registry-1; patients' self-assessment. Abbreviations: CCS, Canadian Cardiovascular Society; EECP®, enhanced external counterpulsation; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Special issues in the selection of patients

Elderly patients

The prevalence of diffuse coronary artery disease, chronic total coronary artery occlusions, left ventricular dysfunction, and comorbid conditions that limit the efficacy of coronary revascularization is raised in elderly patients.[8] While some studies

Box 1 Criteria for patient selection for enhanced external counterpulsation.

Clinical Indications

CCS class II–IV angina pectoris refractory to medical therapy and revascularization

CCS class II–III heart failure

Contraindications

Arrhythmias that interfere with machine triggering

Decompensated heart failure (i.e. central venous pressure >7 mmHg, and pulmonary edema)

Severe pulmonary hypertension (pulmonary artery mean >50 mmHg)

Uncontrolled systemic hypertension (>180/110 mmHg)

Severe aortic insufficiency

Severe lower extremity peripheral vascular disease with rest claudication or non-healing ischemic ulcers

Aortic aneurysm requiring surgical repair

Current or recent (within 2 months) lower extremity thrombophlebitis

Lower extremity deep venous thrombosis

Bleeding diathesis, or warfarin therapy with INR ≥3.0

Pregnancy

Abbreviations: CCS, Canadian Cardiovascular Society; INR, international normalized ratio.

suggest that coronary revascularization in elderly patients with angina improves quality of life,[9] whether long-term survival is also improved is unclear. Therapies and interventions must be tailored to individual elderly patients with symptomatic heart disease.[10,11]

In IEPR-1, 8% of patients were aged 80 years or older.[12] A comparison of this elderly group with younger groups showed no difference in angina severity or mean ejection fraction. A greater proportion of older patients were female and fewer had previous coronary revascularization or diabetes mellitus. Eighty percent of the elderly patients were able to complete a course of EECP® of at least 35 h duration. Of these patients, angina classification was reduced by at least one class and quality of life improved in 76%. At 1 year, 81% of these elderly patients reported maintenance of angina improvement. Rates of congestive heart failure exacerbation and skin problems related to EECP® during therapy rose with increasing age. Overall, however, EECP® provides a low-risk, noninvasive, adjunctive therapy for elderly patients with symptomatic coronary artery disease.

Diabetes

Diabetes mellitus is an important public health problem and its worldwide prevalence is increasing dramatically.[13] At the time coronary artery disease is diagnosed in patients with diabetes it is more extensive, morbidity and mortality related to coronary revascularization are higher, and success rates with this procedure are lower than in patients without diabetes.[14] Small vessel disease, distal disease, and endothelial dysfunction are common features in individuals with both diabetes and ischemic heart disease.[15]

EECP® can safely and effectively treat angina in patients with diabetes.[16] Across the whole IEPR, 40% of the cohort had diabetes. Upon completion of EECP®, 72% of patients with diabetes and 75% of those without diabetes had a reduction in angina by at least one class, which was maintained at 1-year follow-up.[16] The rates of adverse cardiac events were similar in the two groups for the composite endpoint of death, myocardial infarction, CABG surgery, and PCI. The composite endpoint of death occurred in 17% of patients with diabetes versus 15% without diabetes. Patients with diabetes are more likely to have skin abrasions during treatment than patients without diabetes.[16] To lessen this adverse effect, stockings can be worn under the treatment pants. If a skin abrasion occurs, the cuff over the affected area can be left open during subsequent sessions.

Obesity and underweight

Studies have shown that the degree of diastolic augmentation during EECP® can impact the short-term and long-term antianginal benefits of this therapy.[17] Since EECP® involves placement of cuffs over the calf, thigh, and hip/buttock areas, the size of these areas and the degree of subcutaneous fat could impact upon the degree of augmentation and ultimately the clinical effect of EECP®. In IEPR-2, 41% of patients with severe coronary artery disease were obese (BMI >30 kg/m^2), of whom 5% were morbidly obese (BMI >40 kg/m^2). The peak diastolic augmentation ratio, cumulative hours of treatment, change in angina class, and DASI scores were similar across BMI groups. The highest rate of discontinuation for clinical events (14%) was

seen among the underweight (3% of patients in IEPR-2 were underweight [BMI ≤20 kg/m^2]), with skin breakdown being the most frequent cause (10%). A large amount of adipose tissue might provide a cushioning effect that helps to reduce rates of skin breakdown. Proper cuff sizing, secure wrapping, and padding over bony prominences reduce this likelihood; the EECP® systems used in the IEPR-2 (Vasomedical Inc., Westbury, NY) have cuffs in five sizes. Multivariate analysis revealed that older age, history of stroke, history of heart failure, and diabetes were predictors of clinical events, but that BMI was not.[18]

Heart failure

EECP® seems to be a promising therapy for the treatment of heart failure.[7,19,20] A pilot study reported that EECP® increased exercise capacity, peak oxygen uptake and exercise duration, and improved functional status and quality of life in patients with heart failure.[21] In a multicenter, prospective, randomized, controlled clinical trial, the safety and efficacy of EECP® as an adjunctive therapy was assessed in patients with class II–III heart failure receiving optimum pharmacologic therapy for left ventricular systolic dysfunction.[7] EECP® improved exercise tolerance, heart failure symptoms and quality of life, but did not increase peak oxygen consumption. Of all patients enrolled, 70% had ischemic cardiomyopathy, among whom subgroup analysis seemed to show that the benefits of EECP® were limited.

In the IEPR, 15% of patients undergoing EECP® for angina also had a left ventricular ejection fraction of 35% or less. After completion of treatment, 72% of patients improved from severe angina to no or mild angina. In addition, patient quality of life improved substantially and the exacerbation of heart failure was noted in 3% of patients. The reduction in angina and improvement in quality of life was maintained at 2 years.[22] On the basis of these findings, EECP® should be considered for patients with stable class II–III heart failure symptoms owing to ischemic cardiomyopathy who are taking optimum medical therapy. Those with evidence of volume overload decompensation should not undergo EECP® until they are stabilized with medical therapy. Box 2 lists recommendations for monitoring patients with heart failure during EECP® treatment.

Box 2 Practical recommendations for the treatment of patients with heart failure by enhanced external counterpulsation.

- Use a patient's history and physical examination to assess central venous pressure, left ventricular third heart sound, pulmonary edema, and peripheral edema to ensure a stable condition
- Obtain vital signs, including pulse oximetry saturation measurements
- Initiate EECP® treatment and raise the applied cuff inflation pressure to the therapeutic level within 5 min
- Record a finger plethysmographic tracing and oxygen saturation measurement
- Oxygen saturation might decrease during EECP® resulting from shallow respirations and, therefore, patients should be encouraged to take several deep breaths if the oxygen saturation decreases by ≥3% from the initial measurement; if the oxygen saturation continues to be low or if the patient develops dyspnea or arrhythmia, discontinue treatment

Abbreviation: EECP®, enhanced external counterpulsation.

Peripheral and aortic vascular disease

Severe peripheral arterial disease is listed as a contraindication to EECP® therapy; however, some data support the safety and efficacy of EECP® in these patients (Box 1). Theoretical concerns in patients with peripheral arterial disease include inadequate augmentation of coronary blood flow owing to vascular arterial obstruction, increased risk of vascular rupture or retrograde thromboembolic events in patients with abdominal aortic aneurysms, and pain or skin breakdown in patients with severe peripheral ischemia. On the other hand, patients could derive clinical benefits regarding claudication similar to those derived from exercise training.

In IEPR-2, peripheral arterial disease was defined as a documented history of aneurysm, with or without occlusive peripheral arterial disease, including claudication, arterial insufficiency, aortoiliac or femoral arterial disease, or abdominal aortic aneurysm. According to this definition, 23% of patients had a history of peripheral arterial disease. This subgroup of patients were older, and had more extensive coronary artery disease, lower ejection

fractions, and worse angina at baseline. In addition, the prevalence of prior revascularization, heart failure, carotid arterial disease, chronic renal insufficiency, diabetes, hypertension, and previous smoking was higher in this subgroup. Not surprisingly, a higher percentage of patients with peripheral arterial disease suffered adverse events over the year following enrollment than those without, including hospitalization (15.4% versus 11.2%; $P<0.05$), unstable angina (6.3% versus 3.4%; $P<0.01$), myocardial infarction (2.3% versus 1.0%; $P<0.05$), and heart failure exacerbation (3.4% versus 1.4%; $P<0.01$). The frequencies of stroke, revascularization, and death did not differ between the two groups of patients, but the combination of death, myocardial infarction, CABG surgery, and PCI was more common in those with than in those without peripheral arterial disease (4.8% versus 2.6%; $P<0.01$). Improvements in angina class and nitroglycerin use were similar in all patients after EECP®. Quality of life, as measured by the DASI questionnaire, was significantly lower at baseline for patients with peripheral arterial disease (12.0 versus 9.4; $P<0.001$), and the magnitude of improvement was slightly lower (4.7 versus 5.9; $P=0.02$). Thus, overall, patients with peripheral arterial disease gained benefit from EECP® in IEPR-2, although the severity of disease and whether patients had undergone previous revascularizations was unknown.

Abdominal aortic aneurysm is frequently cited as an exclusion criterion for EECP® therapy, and abdominal ultrasonography is used as a screening test in some therapy programs (AD Michaels *et al.*, unpublished data). In theory, aneurysms could rupture or expand in response to hemodynamic changes during EECP®; however, the actual clinical risk is unknown. Abdominal aortic aneurysm rupture has not been reported in association with EECP®, which suggests an exceedingly low rate of this complication even in patients with unrecognized aneurysms. Current guidelines from the American College of Cardiology and American Heart Association recommend one-time screening ultrasonography as standard clinical care for men aged 65–75 years who have ever smoked.[23] Patients in whom peripheral vascular disease is suspected should also have screening ultrasonography to detect any abdominal aortic aneurysm before EECP® therapy; any aneurysm that is large enough to warrant repair by current clinical criteria would preclude EECP® therapy.

Anticoagulation

The therapeutic pressures applied to the lower extremities during EECP® therapy range from 220 mmHg to 300 mmHg as measured by the EECP® system, although actual applied pressure is lower. EECP® therapy is frequently withheld from anticoagulated outpatients because of safety concerns. Although the risk of hemorrhagic or other procedural events during EECP® is not raised in patients receiving antiplatelet therapy, some concern has been expressed about patients taking warfarin.

In IEPR-2, 411 (13%) patients were taking warfarin (mean baseline international normalized ratio [INR] was 2.1 ± 0.7). Among the patients receiving warfarin, 9% had an INR higher than 3.0. In addition, patients receiving warfarin were generally older and had a significantly (all $P<0.001$) higher prevalence of heart failure (51% versus 27%), left ventricular ejection fraction of 35% or less (35% versus 16%), prior stroke (19% versus 9%), and defibrillator use (15% versus 5%) than patients not taking warfarin. Patients in the warfarin subgroup were also significantly less likely to be in sinus rhythm (71% versus 92%; $P<0.001$) or to complete an EECP® treatment course (74% versus 84%; $P<0.001$) than the rest of the IEPR-2 population.

Angina reduction by at least one angina class was slightly less common in patients anticoagulated with warfarin than in those not receiving this drug (71% versus 77%; $P<0.05$). In addition, the rates of heart failure exacerbation and death during the 7-week treatment course were higher in the warfarin subgroup than in the rest of the study population (4.6% versus 1.8%, $P<0.01$ for heart failure exacerbation; 1.9% versus 0.4%, $P<0.05$ for death). Skin breakdown and musculoskeletal complaints in patients taking warfarin were similar to those reported by patients not receiving warfarin. A baseline INR of 3.0 or higher was associated with early termination of EECP® in relation to a clinical event, including skin breakdown, heart failure exacerbation, and musculoskeletal complaints. Among anticoagulated patients, angina reduction was similar regardless of the baseline INR. Particular vigilance is warranted in patients taking warfarin before and during EECP® therapy.

ISSUES IN EECP® THERAPY

Poor hemodynamic augmentation

The degree of diastolic augmentation during EECP® is noninvasively monitored by finger plethysmography. Cuff inflation and deflation is adjusted based in part on this feature. Studies have shown that the hemodynamic effects of EECP® are maximized when the ratio of diastolic to systolic flow is 1.5 or more.[24] From IEPR-1, finger plethysmographic waveforms on the final day of EECP® therapy showed that 37% of the patients had a diastolic augmentation ratio in the optimum range.[17] The factors associated with low diastolic augmentation ratios were: age 65 years or older, female sex, hypertension, noncardiac vascular disease, being a current smoker, multivessel coronary disease, heart failure, depressed left ventricular systolic function, previous CABG surgery or EECP® therapy, severe angina class, and having a coronary anatomy unsuitable for revascularization. At 6-month follow-up, the incidence of heart failure exacerbation and unstable angina, and angina class were lower, and mean quality of life score was higher among patients with a diastolic augmentation ratio of 1.5 or more than in patients with lower values.[17] Patients with suboptimum diastolic augmentation ratios do, however, achieve symptomatic benefits with EECP® therapy; therefore, EECP® should not be withheld in these patients.

High diastolic augmentation was associated with improved response to EECP® in the IEPR and, therefore, we recommend that efforts are made during therapy to achieve maximum augmentation ratios. Correct cuff size, wrapping, and timing by the EECP® therapist are essential factors in yielding hemodynamic success. The use of excessive padding could attenuate the transmission of the cuff pressure to the arterial vasculature, resulting in suboptimal augmentation.

Atrial fibrillation

In 2004, the FDA revised its recommendations about EECP® therapy in patients with heart rhythm disturbances after reviewing the clinical data from IEPR-2. Of the 2,304 patients for whom clinical follow-up data were available at 9 months, atrial fibrillation had been documented during EECP® in only 74 (3.2%) patients. Patients with atrial fibrillation were older (73 ± 8 years versus 66 ± 11 years) than those without atrial fibrillation in the general IEPR-2 study population and a greater number of this subgroup had a history of congestive heart failure (57% versus 23%), left ventricular ejection fraction lower than 35% (46% versus 14%), and chronic renal insufficiency (32% versus 10%; all $P<0.001$). Despite these differences, however, similar rates of EECP® therapy completion, nitroglycerin discontinuation, and reduction in angina by at least one class were reported in the two groups. After treatment, mean diastolic augmentation area ratios for patients with and without atrial fibrillation were improved to a similar degree. In addition, an equal distribution of adverse events across the two groups during the 6-month follow-up period was reported, except for all-cause mortality and hospitalization for congestive heart failure, which were significantly higher in patients with atrial fibrillation (10.7% versus 2.6%, $P<0.001$ for death; 12.2% versus 2.9%, $P<0.001$ for hospitalization). This difference was, however, probably related to the higher incidence of mortality and congestive heart failure risk predictors among patients with atrial fibrillation at baseline.

Most patients with atrial fibrillation tolerate EECP® therapy very well when average heart rate is kept within the range 50–90 beats/min, independent of rhythm. The EECP® cuff inflation is timed to the patient's electrocardiographic rhythm and is, therefore, irregular in patients in atrial fibrillation, except in those with 100% ventricular pacing. Irregularity in inflation could lead some patients to become anxious, but it might not alter the effectiveness of therapy. If frequent ectopy or tachycardia (heart rate >100 beats/min) are present, however, the cuff inflations occur too rapidly to provide effective counterpulsation. Conversely, if marked bradycardia is present (<50 beats/min) the cuff inflations might be sustained and cause discomfort. Should any of these circumstances occur, it is advisable to delay further EECP® treatments until appropriate heart rate control has been achieved.

Pacemakers and defibrillators

Implantable cardiac devices (pacemakers and implantable cardioverter-defibrillators) were removed from the FDA's contraindications to EECP® treatment in 2004. Prudent concern for the compatibility of these devices with other technologies is, however, still warranted. In IEPR-2, 127 (10%) patients with a pacemaker or an implantable cardioverter-defibrillator

underwent EECP® for angina. These patients were older (71 years versus 66 years), had a lower left ventricular ejection fraction (35% versus 48%), and had a higher prevalence of heart failure (62% versus 33%; $P<0.01$ for all) than those without implantable devices. The two groups exhibited similar rates of EECP® therapy completion, nitroglycerin discontinuation, decrease by at least one angina class, and adverse events during therapy. A practical issue to bear in mind to ensure the safe delivery of EECP® to patients fitted with a cardiac pacemaker is that the patient's body motion during cuff inflation and deflation might lead rate-adaptive pacemakers to trigger a paced tachycardia during EECP®. The rate-adaptation mode can be turned off if this situation arises. Implantable cardioverter-defibrillator devices do not require reprogramming.

The number of patients with symptomatic coronary disease, heart failure, and cardiac arrhythmia is growing and, therefore, the number with rhythm disturbances and implanted electronic cardiac devices will continue to rise. With appropriate monitoring, these patients could undergo EECP® safely and derive clinical benefit.

TREATMENT TIMING AND DURATION

EECP® therapy generally involves daily treatments administered over the course of several weeks. The standard duration of counterpulsation treatment is based on empiric data derived from studies performed in China. The findings suggested that a total of 36 treatments (6 days per week for 6 weeks) resulted in a favorable clinical response in the majority of patients. For practical reasons related to the modern 5-day working week, current practice involves administration of 5 daily 1 h treatments per week over a 7-week period, providing a total of 35 treatments. Some patients have undergone two 1 h EECP® treatment sessions daily in an attempt to shorten the total EECP® treatment duration to less than 4 weeks; however, no data show clearly whether this regimen results in more or less favorable clinical outcomes.

The standard course of EECP® is associated with angina reduction and improved exercise tolerance in at least 75% of patients,[5] but some individuals have been prescribed extended courses of therapy in the hope of further symptomatic improvement. A prospective substudy of IEPR-2 evaluated the indications, potential benefits, and safety associated with prolongation of a standard course of EECP® in patients with chronic angina. Of 1,126 patients enrolled in IEPR-2 between January 2002 and December 2003 from sites providing 6-month follow-up, 75 (7%) patients completed more than 35 1 h treatments. Among these patients, treatment was extended for a mean of 10.3 ± 9.8 h. The indications for treatment extension, alone or in combination included persistent angina (67%), patient's preference (41%), and physician's preference (40%). Patients with a high frequency of angina, high baseline nitroglycerin use, and prior revascularization or current suitability for further revascularization at baseline were more likely to complete additional sessions than other patients (all $P<0.05$). Skin breakdown, musculoskeletal complaints and adverse cardiac events did not increase significantly during the extended period. In patients prescribed more than 35 h of EECP®, angina class improved even further at the completion of the extended treatment course than after standard therapy. At 6-month follow-up, angina severity and functional class (measured by the DASI) continued to improve. A mean of 10 h additional EECP® seems safe and has been associated with a significant incremental improvement in symptoms and functional class; however, data on the benefits of extended EECP® therapy come from only a very small population of patients.

REPEAT THERAPY

Available data on the indications, frequency, and efficacy of re-treatment are derived largely from the IEPR-1 and IEPR-2. Within 2 years of EECP® treatment around 18% of patients completing the initial course of EECP® undergo re-treatment.[25] The most common reasons for re-treatment are recurrent angina, persistent angina, and failure to complete the initial course of therapy. Reimbursement coverage issues largely determine whether re-treatment is available to patients. Coverage is generally provided for an initial 35 h treatment for disabling (Canadian Cardiovascular Society class III or IV) angina pectoris refractory to maximum medical therapy and not amenable to revascularization. Other issues that physicians must take into account are the patient's angina severity, comorbidities, and response to the initial course of therapy, and antianginal treatment alternatives.

About 13% of patients do not complete the initial course of EECP® treatment, mainly because of the patient's preference and adverse events. Patients failing to complete the initial course of treatment are generally eligible for reimbursements to cover a 35 h course at a later date, and around 30% of patients return within 1 year for re-treatment.[25] The reasons for not completing the first course of therapy must be considered carefully and adequately addressed before re-treatment is started.

The characteristics most associated with repeat treatment after a full course of EECP® is completed are prior PCI, prior CABG surgery, and hypertension. Extensions of the initial course of treatment, generally by up to 10–12 h, are typically approved by reimbursers; in some cases a further 35 h of treatment has been approved, although the extension might be contingent on a favorable, but incomplete, response to the initial therapy, indicated by alleviation of angina, decrease in anti-anginal medication use, or improvements on radionuclide stress test perfusion imaging or exercise tolerance. In the IEPR, re-treatment occurred after a median interval of 378 days from the end of the initial therapy. At re-treatment, patients realize a benefit similar to that among patients who respond to a first course, with 70% improving by at least one angina class and nitroglycerin use decreasing accordingly.[25] Interestingly, among re-treated patients, response rates to the initial course of EECP® therapy are high, with 89% improving by at least one angina class. The return for treatment of such a highly responsive group of patients probably reflects, to some degree, selection bias by the patient, the health-care provider, or the insurer.

CONCLUSIONS

EECP® is a safe, noninvasive adjunctive treatment for a wide range of patients with ischemic heart disease if careful screening is done before therapy is started and close attention is paid during EECP®. The practical guidelines provided in this Review permit recommendations for the extended application of this important treatment to subsets of patients who have been excluded from clinical trials.

Supplementary information is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

KEY POINTS

- An extended course of enhanced external counterpulsation (EECP®) yields a sustained reduction in angina severity and improved quality of life in most patients treated for refractory angina
- EECP® is safe and effective in elderly patients and those with diabetes, compensated heart failure, atrial fibrillation, and pacemakers if precautions are taken before and during therapy
- For patients with inadequate angina reduction after 35 h of treatment, an extension of therapy by 10–12 h is associated with further reductions
- Repeated courses of EECP® for patients with recurrent symptoms are effective

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AD Michaels, OZ Soran, WE Lawson and SF Kelsey have declared associations with Vasomedical Inc. See the article online for full details of the relationship. The other authors declared they have no competing interests.

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