

Enhanced External Counterpulsation in the Treatment of Chronic Refractory Angina: A Long-term Follow-up Outcome from the International Enhanced External Counterpulsation Patient Registry

Poay Huan Loh, MB, BCh, BmedSc (Hon),* John G.F. Cleland, MD,*[†] Amal A. Louis, MD,[‡] Elizabeth D. Kennard, PhD,[§] Jocelyn F. Cook, RGN,* John L. Caplin, MD,[†] Gregory W. Barsness, MD,^{||} William E. Lawson, MD,[¶] Ozlem Z. Soran, MD,** Andrew D. Michaels, MD, MAS^{††}

*Department of Academic Cardiology, University of Hull, Hull Royal Infirmary; [†]Department of Cardiology, Hull and East Yorkshire Hospitals NHS Trust, Hull; [‡]Department of Cardiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [§]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; ^{||}Cardiovascular Division, Mayo Clinic, St. Mary's Hospital, Rochester; [¶]Stony Brook University Medical Center, SUNY Health Sciences Center, Stony Brook, New York; **Cardiovascular Institute University of Pittsburgh, Pittsburgh, Pennsylvania; ^{††}Division of Cardiology, University of Utah, Salt Lake City, Utah, USA

ABSTRACT

Background: The management of patients who suffer from medically refractory angina and are unsuitable for conventional revascularization therapy is often unsatisfactory. Enhanced external counterpulsation (EECP) is a noninvasive treatment that is safe and effective immediately after a course of treatment. However, the duration of benefit is less certain.

Hypothesis: To evaluate the 3-year outcome of EECP treatment.

Methods: One thousand four hundred and twenty seven patients from 36 centers registered in the International EECP Patient Registry (IEPR) – Phase 1 was prospectively followed for a median of 37 months. Two hundred and twenty patients (15.4%) died, while 1,061 patients (74.4%) completed their follow-up.

Results: The mean age was 66 ± 11 years and 72% were men. Seventy-six percent had multivessel coronary disease for 11 ± 8 years. Eighty-eight percent had a prior percutaneous or surgical revascularization and 82% were unsuitable for further coronary intervention.

Immediately post-EECP, the proportion of patients with severe angina (Canadian Cardiovascular Angina Classification [CCS] III/IV) were reduced from 89% to 25%, $p < 0.001$. The CCS class was improved by at least 1 class in 78% of the patients and by at least 2 classes in 38%. This was sustained in 74% of the patients during follow-up.

Thirty-six percent of the patients had CCS II or less angina, which was better than pre-EECP state without a major adverse cardiovascular event during follow-up. More severe baseline angina and a history of heart failure or diabetes were independent predictors of unfavorable outcome.

Conclusion: An EECP improves angina and quality of life immediately after a course of treatment. For most of the patients, these beneficial effects are sustained for 3 years.

Key words: external counterpulsation, angina pectoris, refractory pain, coronary artery disease, ischemic heart disease

Introduction

The treatment of chronic angina pectoris is difficult when standard medical therapy and conventional revascularization fail to provide satisfactory symptomatic control.¹ Enhanced external counterpulsation (EECP) is a potential treatment that is safe, noninvasive, and technically simple. It involves application of pneumatic cuffs to the lower

extremities, which are sequentially inflated during diastole and simultaneously deflated prior to the onset of systole. This augments systemic and coronary perfusion pressure while reducing left ventricular afterload.² The action also increases venous return and cardiac output.³ The EECP can improve angina, quality of life (QOL), exercise tolerance, time to ST-segment depression during exercise stress

testing, myocardial perfusion at rest and during stress, and dobutamine stress-induced regional wall motion abnormality in patients with refractory angina.^{4–8}

The beneficial effects of EECP can be achieved immediately after a course of treatment with long-term sustained improvement in anginal control and QOL.⁵ However, the duration of these long-term benefits is less certain.

Phase 1 of International EECP Patient Registry (IEPR-1) enrolled consecutive patients treated with EECP in more than 100 centers with a follow-up duration of 3 years.⁹ One of the objectives was to monitor the long-term benefits of EECP in a broad range of patients in a clinical setting. This study aimed to assess the 3-year outcomes of EECP in these patients and the factors associated with a favorable outcome.

Methods

International Enhanced External Counterpulsation Patient Registry – Phase 1

The setup of IEPR-1 has been described previously.⁹ All participating centers received approval from their Institutional Review Boards and/or Local Ethics Committees, and all patients gave their written informed consent. Consecutive patients from each center who had at least 1 h of EECP treatment were enrolled. Patients were treated using EECP equipment (Vasomedical Inc., Westbury, NY, USA). A standard course of 35 one-hour treatment sessions was recommended.^{4,9} The data collected included demographics, medical history, disease characteristics, symptoms, and QOL at baseline. Treatment information, clinical events, and symptoms were documented during and at the end of treatment. The follow-up was conducted by telephone interview or clinic visits at 6 months and 1, 2, and 3 years to collect data on anginal status, QOL, clinical events, and hospitalizations.

Patients

Five thousand patients from 99 American and 9 international centers were enrolled between January 1998 and July 2001. The 3-year follow-up was completed in October 2004. To avoid selection bias and potential bias introduced by poorly compliant centers, only patients from centers with at least 80% compliance in follow-up data submission were included.

Outcome Measures

The primary outcome is anginal status measured by Canadian Cardiovascular Angina Classification (CCS). Other measures include weekly angina episodes and nitroglycerin (GTN) use. The patients graded their QOL using a simplified 5-point scale where 1 represents the worst and 5 represents the best QOL. The data at baseline, immediately

post-EECP (last treatment hour), and 3-year follow-up were compared.

Clinical Events

The clinical events included skin breakdown (e.g., abrasions, blisters, and ecchymoses), musculoskeletal problem (e.g., severe back, leg, or muscle pain), unstable angina (UA), new onset or exacerbation of heart failure (HF), percutaneous coronary intervention (PCI), coronary bypass operation (CABG), myocardial infarction (MI), death and major adverse cardiovascular event (MACE) and composite of death/MI/CABG/PCI. Clinical events occurring during the treatment period and within 1 week after the last treatment were considered as treatment events.

Statistical Analysis

Continuous data are presented as mean \pm SD if normally distributed, and as median (interquartile range) otherwise. Categorical data are presented as percentages. Barker's test was used to compare the changes in CCS class. The differences in weekly angina episodes and GTN use were compared using Wilcoxon's t-test approximation. The Cochran Armitage test for trend was performed to assess the changes in medication use. The event rates were estimated using Kaplan-Meier survival analysis. Logistic regression analysis was performed to identify baseline factor(s) that were associated with unfavorable immediate and long-term outcome and data are presented as (odds ratio [OR], 95% confidence interval [CI]). A 2-tailed test with $p < 0.05$ was considered significant.

Results

One thousand four hundred and twenty seven patients from 36 centers were included. The overall data compliance rate was 89.8%. These patients were followed for a median of 37.4 (33.7–38.5) months. One thousand and sixty one (74.4%) patients completed their 3-year follow-up, while 220 (15.4%) died. However, 146 (10.2%) patients did not complete their 3-year follow-up. They were followed for a median of 15.8 (8.1–26.1) months and were included in analyses for post-treatment outcome and follow-up clinical events.

The patients received a mean of 33.3 ± 9.6 h of treatment over a mean period of 48 days. Eight-two point seven percent of the patients completed their prescribed course of treatment. Seven point one percent of the patients discontinued their treatment, while 8.8% were terminated because of clinical events. The mean diastolic augmentation increased from 0.8 ± 0.5 at the first treatment hour to 1.0 ± 0.6 at the last hour.

Baseline Patient Characteristics

The mean age was 66.3 ± 10.8 years. Most of the patients were men and had preserved left ventricular ejection fraction (LVEF). They had a long history of significant coronary artery disease (CAD) and most suffered from frequent and severe angina (CCS III/IV). The majority had had at least one previous revascularization and were not candidates for further conventional intervention (Table 1).

Compared with other patients, the 146 patients who did not complete their 3-year follow-up were younger (64.3 ± 11.7 versus 66.4 ± 10.7 years, $p < 0.05$), their angina was more severe (CCS III/IV 91.7% versus 88.8%, $p < 0.01$) and frequent (10 [4–20] versus 6 [3–14] episodes/week, $p < 0.01$), and history of HF was more prevalent (44.8% versus 33.8%, $p < 0.01$). However, the workload they achieved on exercise stress test at baseline; their LVEF, the duration, distribution, and extent of their CAD; history of prior MI, previous revascularization, other cardiovascular risk factors, and medication use were similar to other patients.

Angina, Quality of Life, and Medication Use

Immediately post-EECP, the proportion of patients who suffered from CCS III/IV angina reduced from 89.2% to 24.9%, $p < 0.001$. The CCS class improved by at least 1 class in 77.9% of the patients and by 2 classes in 38.0%. Sixteen point three percent of patients had no angina. These were sustained in those 1,033 patients whose anginal status was documented at 3-year follow-up (Figure 1A). Of the patients who responded to the QOL questionnaires there was sustained improvement in their QOL after 3 years, $p < 0.001$ (Figure 1B).

The frequency of angina reduced by 4 (2–11) episodes/week immediately post-EECP. Seventy-six percent of the patients experienced at least 50% reduction in the frequency of angina. This was sustained at 3-year follow-up (Table I).

The frequency of GTN use and the proportion of patients who required GTN for symptom control reduced immediately post-EECP and at 3 years. There was a small but significant reduction in calcium channel blocker and long-acting nitrate use at follow-up (Table 2).

As any MACE may affect anginal status, subgroup analysis was performed on 743 patients who did not suffer from any MACE. Similar pattern of sustained improvement was observed in these patients and 67% of them reported the same or decreased angina at 3 years (Figure 1A).

Clinical Events

Clinical events that occurred during the treatment period were mainly due to musculoskeletal discomfort (1.5%), skin breakdown (2.5%), HF (2.2%), and UA (4.5%). A MACE was rare and included MI (0.8%), PCI (0.8%), CABG (0.6%), and death (0.5%).

TABLE 1: Baseline patient characteristics (n = 1427)

Age (years)	66.3 ± 10.8
Age > 65 years	57.3
Men	72.2
LVEF (%)	46.6 ± 14.8
LVEF < 35%	19.8
Cardiovascular history	
Duration of CAD (years)	10.8 ± 8.2
Prior myocardial infarction	70.0
Prior PCI	67.1
Prior CABG	69.0
Prior PCI or CABG	87.1
Multivessel CAD	78.0
Unsuitable for revascularization	88.0
Heart failure	34.8
Noncardiac vascular disease	30.2
Prior EECP	3.8
Cardiovascular risk factors	
Diabetes mellitus	44.0
Hypertension	70.5
Hypercholesterolemia	81.3
Smoker	
Previous	64.4
Current	8.5
Anginal status	
CCS Class	
I	2.2
II	8.6
III	62.8
IV	26.4
Angina frequency (episodes/week)	6 (3–14)
Nitroglycerin use (times/week)	3 (0–8)

All data are percentages unless otherwise stated as means ± SD or median (interquartile range). Abbreviations: CAD = coronary artery disease; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society anginal classification; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

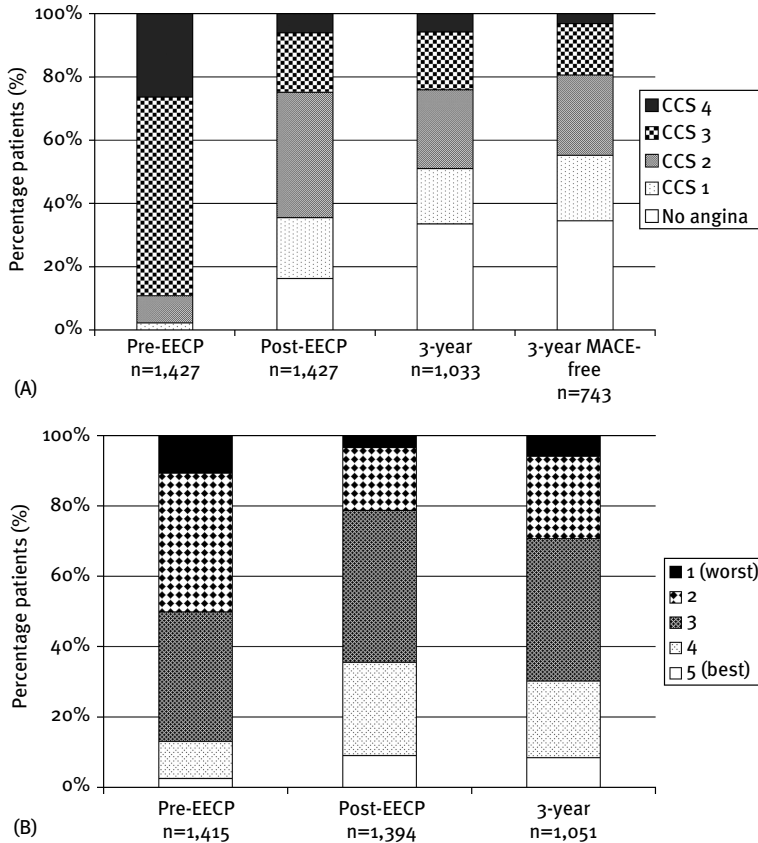


Figure 1: (A) CCS and (B) Simplified 5-point QOL scores.

Table 3 shows the cumulative repeat EECp and clinical event rates during follow-up. Other events included UA (25.4%) and new onset or exacerbation of HF (12.9%).

Predictors of Outcome

Seventy-six percent of the patients had immediate improvement in CCS class without any cardiovascular events. Univariate logistic regression analysis showed that men, severe pre-treatment angina (CCS III/IV), and absence of a history of HF, diabetes, or hypertension were associated with such an outcome. A CCS III/IV class (OR 1.80 [1.25–2.59]) and freedom from HF (OR 1.82 [1.41–2.32]) were independent predictors of favorable immediate response on multivariate analysis.

We defined favorable long-term outcome as being in CCS II or milder angina that was better than in the pretreatment state and without requiring repeat EECp or suffering from any MACE at 3 years. This was achieved in 36.4% of the patients and was associated with duration of CAD,

LVEF, prior revascularization, a history of HF, diabetes or noncardiac vascular disease, angina severity, and suitability for CABG. On multivariate analysis, severe pre-treatment angina (OR 1.54 [1.09–2.17]) and a history of HF (OR 1.43 [1.01–1.82]) and diabetes (OR 1.35 [1.07–1.69]) were independent predictors of unfavorable long-term outcome.

Discussion

This is the longest follow-up report from the IEPR-1 and confirms the safety and immediate benefits of EECp. It shows that sustained symptomatic and QOL benefit can be achieved in most patients for up to 3 years. This is associated with a reduction in anti-anginal medication use.

The immediate benefit of EECp in improving angina control and QOL has been shown in randomized controlled trials and supported by objective evidence using makers of myocardial ischemia.^{4–8} The improvement in exercise tolerance and myocardial perfusion can be sustained for up to 3 years.¹⁰ The proposed mechanisms of sustained long-term benefit are multifactorial and include improvement in endothelial function, collateral recruitment and angiogenesis, exercise training effect, and neuro-hormonal modulation.^{11–14} These may improve myocardial perfusion and metabolism, reduce myocardial oxygen consumption while increasing peripheral oxygen uptake, and improve left ventricular systolic and diastolic function.¹³ However, immediate reduction in angina and increase in exercise tolerance can occur without any improvement in myocardial perfusion, suggesting that early benefits of EECp may be attributed to peripheral effects similar to that of exercise training.¹⁵ The improvement in exercise capacity may then lead to long-term improvement in myocardial perfusion and sustained symptomatic control.

Consistent with previous studies, patients with more severe angina and without a history of HF were more likely to gain immediate symptomatic benefit.¹⁶ Patients with more severe angina, diabetes, and a history of HF are more likely to suffer from unfavorable long-term outcome. Nevertheless, EECp can improve symptom, QOL, and exercise tolerance in patients with left ventricular systolic dysfunction and angina, and/or HF.^{17,18}

The natural history of chronic refractory angina has not been well described, and whether or not EECp can alter its clinical course is unclear. In a preliminary

TABLE 2: Weekly angina frequency, nitroglycerin use, and medications at pre-EECP, post-EECP, and 3-year follow-up

	pre-EECP	post-EECP	3-year
Number of patients	1427	1427	1033
Weekly angina (episodes/week)	6 (3–14)	1 (0–3)*	1 (0–3)*
Weekly nitroglycerin use (times/week)	3 (0–8)	0 (0–2)*	0 (0–2)*
Patients required nitroglycerin	73.7	38.3*	41.4*
Other medications			
Antiplatelets/coumadin	80.4	80.3	78.4
Beta-blockers	73.9	75.2	72.2
Long-acting nitrates	79.0	78.2	73.1*
Calcium channel blockers	45.2	44.0	40.3**
Lipid lowering agents	74.3	75.5	76.0
Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers	47.6	47.2	46.4

All data are percentages unless otherwise stated as median (interquartile range). * p<0.001 and **p<0.05 when compared to pre-EECP. Abbreviations: EECP = enhanced external counterpulsation.

TABLE 3: Cumulative 3-year repeat EECP and major cardiovascular event rates

Clinical events	Cumulative event rates
Repeat EECP	22.5 (20.1–24.9)
Percutaneous coronary intervention	16.4 (14.3–18.5)
Coronary artery bypass grafting	7.5 (6.0–9.0)
Myocardial infarction	11.8 (10.0–13.7)
Death	17.0 (14.9–19.1)
Major adverse cardiovascular events	40.8 (38.8–43.5)

Data are presented as percentage (95% CI). Abbreviations: CI = confidence interval; EECP = enhanced external counterpulsation.

report from a randomized controlled trial, the addition of EECP to optimal medical therapy reduces the mortality and MI rates in patients with CAD.¹⁹ The 3-year mortality rate observed in our study is similar to that of a group of patients suffering from CCS IV angina and treated medically, or high-risk CABG candidates who had nonprognostic coronary lesions and received CABG or spinal cord stimulation.^{20,21} Consistent with previous studies, the rate of revascularization in our study is high.²⁰ This reflects the dynamic nature of atherosclerosis that existing lesions may progress and new lesions

may develop over time. Therefore, careful re-evaluation is required when there is a change in the symptom status.

The differences between patients who were and were not available for 3-year follow-up may be attributed to selection or survival bias. However, this has been minimized by only including patients from centers with at least 80% compliance in the follow-up data submission. Further, there are similarities between these 2 groups of patients. Although this is an observational study without a control group, it represents the experience of a diverse group of patients in an actual clinical setting. An EECP can benefit patients without the associated risk of other more invasive alternatives. Randomized controlled studies comparing different treatment modalities will help in identifying the most appropriate treatment option.

Conclusion

An EECP can improve symptom control and QOL in a diverse group of patients suffering from chronic refractory angina. The immediate benefits can be sustained in the majority of patients for up to 3 years, especially in those with better baseline functional class and without diabetes or HF. This study highlights that patients with refractory angina can have significant long-term MACEs. Further effort is needed to address their unmet needs.

Conflict of Interest

Dr. Michaels received consulting fees and Speakers Bureau honoraria from Vasomedical Inc., Westbury, New York, USA.

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