General Cardiology

CARDIOLOGY

Cardiology 2005;103:201–206
DOI: 10.1159/000085170

Received: October 5, 2004
Accepted: October 7, 2004
Published online: April 13, 2005

Predictors of Benefit in Angina Patients One Year after Completing Enhanced External Counterpulsation: Initial Responders to Treatment versus Nonresponders

William E. Lawson[a] John C.K. Hui[a] Elizabeth D. Kennard[b]
Gregory Barsness[c] Sheryl F. Kelsey[b] for the IEPR Investigators

[a]State University of New York at Stony Brook, New York, N.Y., [b]University of Pittsburgh, Pittsburgh, Pa., and [c]Mayo Clinic, Rochester, Minn., USA

Key Words
Angina · Enhanced external counterpulsation · Outcomes · Canadian Cardiovascular Society angina classification

Abstract
Enhanced external counterpulsation (EECP) has been shown to reduce Canadian Cardiovascular Society angina class. This study examines the factors that affect the reduction at 1 year, especially in patients who do not demonstrate an initial response. The data of 2,007 consecutive patients enrolled in the International EECP Patient Registry were analyzed. After 36.6 ± 4.9 h of EECP, angina was reduced by at least one class in 82.7%. At 1 year, 35.4% of initial nonresponders and 70.6% of responders remained improved by at least one angina class and free of major adverse cardiovascular events. Multivariate predictors of 1-year benefit are initial response to treatment (odds ratio 4.5, 95% CI 3.5–5.8), baseline angina class compared with class IV (odds ratios: class I 2.1, CI 0.93–4.81; class II 0.62, CI 0.43–0.87; class III 0.80, CI 0.62–1.01) and no history of congestive heart failure (odds ratio 1.41, CI 1.14–1.74).

Introduction

Enhanced external counterpulsation (EECP) is a noninvasive treatment used for patients with angina refractory to medical therapy who are not revascularization candidates. The system consists of three sets of cuffs wrapped around the calves, lower and upper thighs of the patients. The pneumatic cuffs are sequentially inflated at the onset of diastole, causing diastolic augmentation and increasing venous return, cardiac output and coronary blood flow. Cuff deflation is timed to end diastole, to reduce vascular resistance, and provides systolic unloading, which further increases the cardiac output [1, 2].

EECP has been shown to be effective in reducing both angina and myocardial ischemia in patients not responding to medical therapy and without revascularization alternatives [3–12]. Many of these patients are high risk because of age, extensive coronary disease, extensive previous revascularization, severity of left ventricular dysfunction or comorbidity. In small patient cohorts, EECP has been shown to have extended benefit, with continued reduction in angina, improvement in quality of life and persistent reduction in major adverse cardiovascular events (MACE) for up to 5 years after treatment [18, 19].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0008–6312/05/1034–0201$22.00/0

Accessible online at:
www.karger.com/crd

William E. Lawson, MD
SUNY Stony Brook, HSC T-17-020
Stony Brook, NY 11740 (USA)
Tel. +1 631 444 1066, Fax +1 631 444 1054
E-Mail william.lawson@stonybrook.edu

Table 1. Patient characteristics and medical history before EECP of patients in cohort (n = 2,007)

Age, years (range 32.9–100)	66.4 ± 10.6
Gender (male), %	75.4
Race (white), %	95.1
Duration of coronary artery disease, years	11.1 ± 8.2
Prior MI, %	70.4
History of congestive heart failure, %	31.9
Unstable angina, %	2.6
Prior PCI, %	67.2
Prior CABG, %	71.6
Prior revascularization (PCI or CABG), %	88.8
Multivessel coronary artery disease, %	77.0
Left ventricular ejection fraction, % (18.3% of patients had an ejection fraction <35%)	47.3 ± 14.3
Family history of coronary artery disease, %	79.1
History of diabetes mellitus, %	43.1
History of hypertension, %	70.8
History of hyperlipidemia, %	81.9
Non-cardiac vascular disease, %	30.1
Past or present smoking, %	73.2

Table 2. Medications at baseline

Medication	Patients, %
Beta-blockers	71.7
Calcium channel blockers	45.8
Angiotensin-converting enzyme inhibitors	40.6
Angiotensin receptor blockers	8.7
Nitrates (long acting)	79.4
Lipid lowering	73.6
Aspirin	75.6

The objective of the current analysis was to compare 6-month and 1-year outcomes and to determine predictors of 1-year angina status in patients who demonstrated initial clinical improvement (responders) versus those who did not show immediate benefit (nonresponders) after completing a course of EECP for chronic angina. Data were obtained from the International EECP Patient Registry (IEPR). The IEPR is a prospective study that tracks consecutive patients enrolled from a diverse group of providers and centers to evaluate patterns of use and efficacy of EECP treatment. All participating patients gave informed consent. The registry is voluntary, with no payments made to either patients or treatment centers.

Methods

The IEPR is coordinated at the Epidemiology Data Center of the University of Pittsburgh Graduate School of Public Health. It collects and analyzes data on consecutive patients treated with EECP at participating centers. Information collected includes patient demographics, clinical characteristics and both immediate and long-term outcomes.

Enhanced external counterpulsation was typically prescribed as a course of 1-hour daily sessions, 5 days a week for 7 weeks, for a total treatment of 35 h. EECP was performed under continuous medical supervision with monitoring of the electrocardiogram, pulse oximeter and finger plethysmogram. Demographics, medical history and angina status were obtained at baseline. Telephone follow-up was performed at 6 and 12 months after treatment. Information collected included an evaluation of Canadian Cardiovascular Society (CCS) angina functional class, angina frequency and nitroglycerin use, changes in medications, quality of life and interim events – MACE: death, myocardial infarction (MI), angioplasty (percutaneous coronary intervention; PCI), coronary bypass surgery (coronary artery bypass grafting; CABG). The present study included consecutive patients receiving at least 30 h of treatment. Patients were divided into two groups: those patients with a reduction of at least one CCS angina class after EECP (responders) and those not showing reduction in angina (nonresponders).

Statistical Analysis

Discrete variables were analyzed by χ^2 testing and continuous variables by the unpaired t test. Significance was defined as $p < 0.05$. Kaplan-Meier survival analysis was used to estimate rates of MACE. Logistic regression analysis was used to determine independent predictors of acute angina reduction and 1-year benefit (continued or new angina reduction with no invasive revascularization), and the Cox proportional hazards model was used to determine predictors of MACE at 1 year.

Results

A cohort of 2,007 consecutive EECP patients completing at least 30 h of EECP with information available on acute angina reduction and 1-year follow-up was analyzed. The mean number of hours of treatment was 36.6 ± 4.9. The patient demographic characteristics, cardiac history and angina status at entry are shown in table 1. Medications at baseline are listed in table 2.

Clinical Outcome

CCS angina class was reduced by at least one class in 1,665 patients (83.0%) immediately after completion of the course of EECP (responders); 342 patients (17.0%) had no initial reduction in angina (nonresponders). In the cohort responding to EECP with reduction in angina class, weekly angina episodes decreased from 10.4 ± 13.1 to 1.7 ± 3.9 ($p < 0.001$). The nonresponding cohort also

demonstrated a smaller but still significant decrease in weekly angina episodes from 11.5 ± 13.1 at baseline to 5.8 ± 9.2 after treatment ($p < 0.05$). The frequency of nitroglycerin usage/week decreased significantly in the responders from 9.3 ± 12.3 to 1.6 ± 4.5 ($p < 0.001$), but not significantly in the nonresponders from 10.5 ± 12.9 to 5.2 ± 8.0. Improvement in quality of life was reported in 63% of responders versus 37% of nonresponders ($p < 0.001$).

The only significant, independent predictor of lack of initial response to EECP was baseline angina class (I, II, III versus IV with odds ratios 5.0, 4.8, 1.4 and CI 2.4–10.4, 3.2–7.0 and 1.0–2.0, respectively).

At 1 year after the completion of EECP, 15% of nonresponders had undergone invasive revascularization (CABG or PCI) versus 8% of responders ($p = 0.0001$). In addition, 6% of nonresponders versus 5% of responders had died (p = not significant) (table 3). For the remaining patients free of MACE, there was a persistent reduction in CCS angina class over baseline at 1-year follow-up, as shown in figure 1. Interestingly, the initial group of nonresponders to EECP demonstrated increasing reduction in CCS angina class over time. In both initial responders and nonresponders there was a sustained reduction in angina episodes per week at 6 months: 2.8 ± 6.1 and 5.8 ± 8.9 for responders and nonresponders, respectively. At 12 months, the number of angina episodes per week was 3.1 ± 6.4 and 5.4 ± 8.6. Frequency of nitroglycerin usage per week remained decreased at 6 and 12 months in the responders group (6.1 ± 8.4 and 6.0 ± 7.8, respectively). For nonresponders, the frequency of nitroglycerin usage per week tended to drift back to baseline (8.3 ± 11.9 at 6 months and 8.7 ± 11.9 at 1 year). However, there was a parallel reduction in both responders and nonresponders alike in the use of nitroglycerin from baseline to 6 and 12 months (responders: from 71.7 to 41.4 to 45.2%; nonresponders: from 72.5 to 63.6 to 61.2%).

The patient-rated quality of life measures as shown in figure 2 demonstrated a large improvement immediately after EECP in the responders, which remained improved at 6-month and 12-month follow-up. However, for the nonresponders, even though there was some improvement in quality of life measures immediately after EECP, there was a gradual drift back to levels before EECP at 6 and 12 months.

Overall, 72% of the responders and 37% of the nonresponders survived to 1 year without MACE and with angina less than that reported before EECP therapy. Logistic regression analysis showed independent factors predicting this benefit to be: initial response to treatment

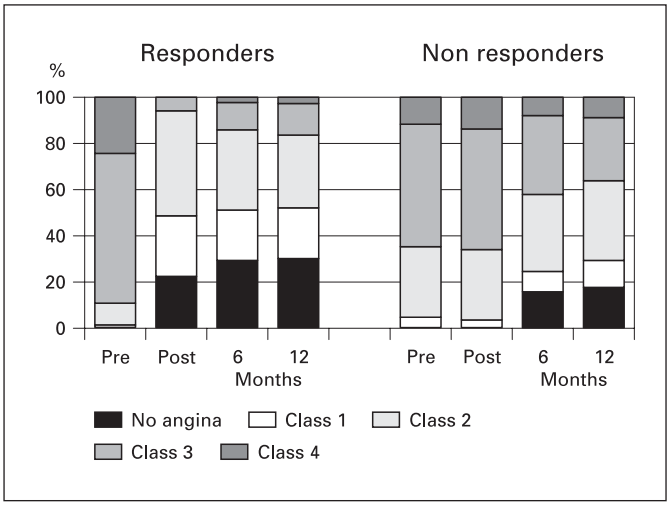

Fig. 1. CCS angina class in responders and nonresponders: before EECP, immediately after EECP, 6 and 12 months after EECP (patients alive with no CABG or PCI who reported angina status at 1 year; n = 1,597).

Table 3. MACE rates for initial nonresponder and responder groups at 6 and 12 months after EECP follow-up

Cohort	6 months, %	12 months, %	p value
Death			
nonresponders	4.2	6.0	0.42
responders	2.0	5.0	
Myocardial infarction			
nonresponders	3.3	5.6	0.81
responders	2.7	5.3	
CABG			
nonresponders	3.0	4.3	0.13
responders	1.0	2.8	
PCI			
nonresponders	6.4	11.2	0.0002
responders	2.8	5.8	
CABG or PCI			
nonresponders	9.1	14.6	0.0001
responders	3.8	8.2	
MACE[1]			
nonresponders	14.0	22.8	0.0001
responders	7.6	16.1	

Rates are Kaplan-Meier estimates; p values are log-rank tests to 12 months. Responder was defined as a reduction of at least one angina class immediately after EECP.

[1] Death/MI/CABG/PCI.

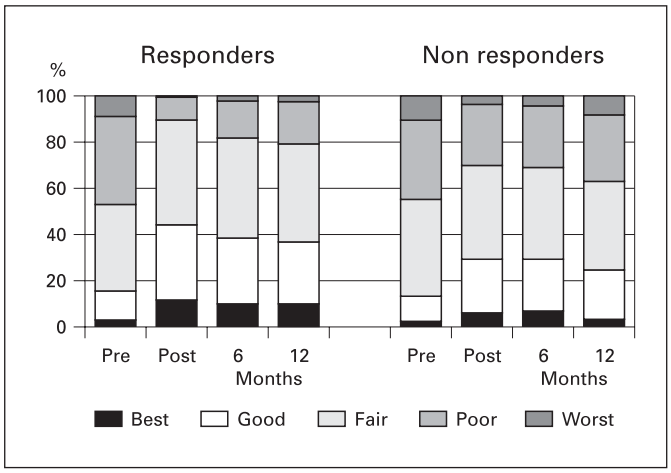

Fig. 2. Quality of life score in responders and nonresponders: before EECP, immediately after EECP, 6 and 12 months after EECP (patients alive with no CABG or PCI who reported angina status at 1 year; n = 1,597).

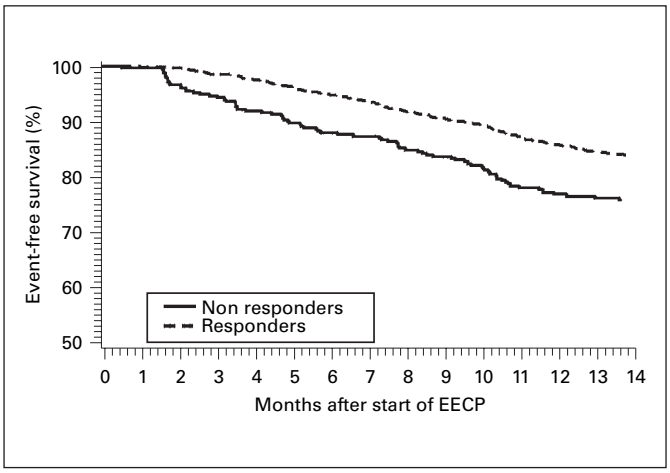

Fig. 3. Survival free from MACE (death/MI/CABG/PCI) for responders and nonresponders (Kaplan-Meier).

(odds ratio 4.5; 95% CI 3.5–5.8), baseline angina class of CCS class I (odds ratio 2.1; 95% CI 0.93–4.81), class II (odds ratio 0.62; 95% CI 0.43–0.87) and class III (odds ratio 0.80; 95% CI 0.62–1.01) compared with CCS class IV, and no history of congestive heart failure (odds ratio 1.41; 95% CI 1.14–1.74).

Major Adverse Cardiovascular Events

Patients received an average of 36.6 ± 4.9 h of treatment, with 95.6% completing the prescribed course of treatment. During the course of treatment (or in the 5 days immediately following the last treatment), MACE were uncommon, occurring in 0.7% of patients (MI 0.3%, PCI 0.3%, CABG 0%, death 0.1%). The most frequent cardiovascular events during treatment included unstable angina in 1.7% and decompensated heart failure in 0.9%.

There were significant differences in the frequency of MACE differentiating the EECP responders and nonresponders (table 3). At 12 months, the frequency of PCI (11.2 vs. 5.8%; p = 0.0001) and cumulative MACE (22.8 vs. 16.1%; p = 0.0001) were significantly increased in nonresponders. The rates of death (6.0 vs. 5.0%; p = 0.42), CABG (4.3 vs. 2.8%; p = 0.13) and MI (5.6 vs. 5.0%; p = 0.81) were similar in both groups.

Independent predictors of MACE at 1 year included left ventricular ejection fraction (hazard ratio 0.92; CI 0.85–0.99 for 10% increase), diabetes mellitus (hazard ratio 1.40; CI 1.12–1.75) and baseline angina class versus patients in CCS class IV (hazard ratio 0.47, CI 0.15–1.47 for class I; hazard ratio 0.60, CI 0.39–0.94 for class II; hazard ratio 0.88, CI 0.69–1.14 for class III). As demonstrated by the Kaplan-Meier plot (fig. 3), separation of the curves occurred early after treatment and progressively increased over time after treatment.

Discussion

Initial and follow-up reduction in angina was higher than previously reported because the current cohort included only patients completing 30 or more hours of treatment, whereas previous reported data included patients with fewer than 30 h of EECP [1, 3, 4]. Patients failing to substantially complete the course of EECP demonstrate much less reduction in angina. It is unclear whether patients fail to improve because they do not complete the course of therapy or do not complete the course of therapy because they are not benefiting from EECP. The current study compares two groups of patients completing 30 h of treatment, one group responding to EECP (as defined by a reduction of at least one CCS class) and the other group demonstrating no initial benefit (nonresponders). It is of interest, despite the lack of initial response, that the nonresponders still demonstrated benefit over their baseline status at 1-year follow-up. While this may reflect the unpredictable clinical course of patients with angina, a course characterized by exacerbations and

spontaneous improvements, it is also consistent with recent findings demonstrating continued improvement in endothelial function after EECP [16] and prior studies demonstrating continued improvement in quality of life after treatment [22]. However, while symptoms improved in a substantial portion of initial nonresponders at 1 year, MACE at 1 year was overall significantly higher in the nonresponding group.

It is probable that there is a significantly positive benefit to the 30 or more hours of contact patients experienced. It has been well demonstrated that recurrent patient visits may improve health and quality of life measures as an independent variable. The substantial contact with health care providers during EECP probably has the benefit of reinforcing hygienic measures and improving compliance with health care measures. Prior studies have also suggested that EECP has a positive impact on psychosocial functioning [22], related in part to the improvement in cardiovascular health.

Patients with the most disabling angina have the most potential for benefit from EECP, as measured by reduction in angina class. However, factors such as durability of benefit and reduction of adverse cardiovascular events are as important as the initial improvement in this cohort of patients. The current study examines benefit in terms of angina class and freedom from MACE. When examined in this fashion, CCS class IV patients continue to demonstrate a substantial benefit. The relative risk:benefit ratio would support the current treatment paradigm as cost-effective.

Conclusions

One-year angina reduction without MACE was achieved in 72% of initial responders to EECP treatment. However, a surprising 37% of initial nonresponders demonstrated similar benefit at 1 year. Predictably, patients not responding to EECP demonstrated a higher frequency of MACE at 1 year, including significant increase in the rate of PCI. Factors predicting 1-year benefit included the absence of a history of congestive heart failure and baseline angina status.

Acknowledgement

The IEPR is sponsored by Vasomedical Inc., Westbury, N.Y., USA.

References

1 Suresh K, Simandl S, Lawson WE: Maximizing the hemodynamic benefit of enhanced external counterpulsation. Clin Cardiol 1998;21:649–653.

2 Taguchi I, Ogawa K, Oida A, Abe S, Kaneko N, Sakio H: Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. Am J Cardiol 2000;86:1139–1141.

3 Lawson WE, Hui JCK, Lang G: Treatment benefit in the enhanced external counterpulsation consortium. Cardiology 2000;94:31–35.

4 Lawson WE, Hui JCK: Enhanced external counterpulsation for chronic myocardial ischemia. J Crit Illness 2000;15:629–636.

5 Soran OZ, Crawford LE, Schneider VM, et al: Enhanced external counterpulsation in the management of patients with cardiovascular disease. Clin Cardiol 1999;22:173–178.

6 Lawson WE, Cohn PF, Hui JCK, et al: Enhanced external counterpulsation: US clinical research. Cardiovasc Rev Rep 1997;18:25–29.

7 Cohn P, Arora RR, Chou TM, et al: Comparison of prognostic surveys used in the multicentre study of enhanced external counterpulsation (MUST-EECP) (abstract). J Eur Soc Cardiol 1999;20(suppl):479.

8 Lawson WE, Hui JCK, Soroff HS, et al: Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am J Cardiol 1992;70:859–862.

9 Masuda D, Nohara R, Inada H, et al: Improvement of regional myocardial and coronary blood flow reserve in a patient treated with enhanced external counterpulsation – Evaluation by nitrogen-13 ammonia PET. Jpn Circ J 1999;63:407–411.

10 Urano H, Ikeda H, Ueno T, Matsumoto T, Murohara T, Imaizumi T: Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. J Am Coll Cardiol 2001;37:93–99.

11 Michaels AD, Accad M, Ports TA, Grossman W: Left ventricular unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. Circulation 2002;106:1237–1242.

12 Lawson WE, Hui JCK, Zheng ZS, et al: Improved exercise tolerance following enhanced external counterpulsation: Cardiac or peripheral effect. Cardiology 1996;87:271–275.

13 Lawson W, Hui J, Guo T, et al: Prior revascularization increases the effectiveness of enhanced external counterpulsation. Clin Cardiol 1998;21:841–844.

14 Stys TP, Lawson WE, Hui JCK, Fleischman B, Manzo K, Strobeck JE, Tartaglia J, Ramasamt S, Suwita R, Zheng ZS, Liang H, Werner D: Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol 2002;89:822–824.

15 Arora RR, Chou TM, Jain D, et al: The multicenter study of enhanced external counterpulsation (MUST-EECP): Effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;33:1833–1840.

16 Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, Nesto R, Ferrans CE, Keller S: Effects of enhanced external counterpulsation on health-related quality of life continue 12 months after treatment: A substudy of the multicenter study of enhanced external counterpulsation. J Investig Med 2002; 50:25–32.
17 Wu GF, Qiang SZ, Zheng ZS, et al: A neurohormonal mechanism for the effectiveness of enhanced external counterpulsation. Circulation 1999;100:I–832.
18 Qian X, Wu W, Zheng ZS, et al: Effect of enhanced external counterpulsation on nitric oxide production in coronary disease. J Heart Dis 1999;1:193.
19 Urano H, Lida S, Fukami K, Sugano R, Satoh A, Kanaya S, Otsuka Y, Matsuoka H: Intermittent shear stimuli by enhanced external counterpulsation (EECP) restores endothelial function in patients with coronary artery disease. Circulation 2000;102:II–57.
20 Lawson WE, Hui JCK, Zheng ZS, et al: Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am J Cardiol 1995;75:840–841.
21 Lawson WE, Hui JC, Cohn PF: Long-term prognosis of patients with angina treated with enhanced external counterpulsation: Five-year follow-up study. Clin Cardiol 2000;23:254–258.
22 Springer S, Fife A, Lawson W, Hui JCK, Jandorf L, Cohn PF, Fricchione G: Psychosocial effects of enhanced external counterpulsation in the angina patient: A second study. Psychosomatics 2001;42:124–132.
23 Fricchione GL, Springer S, Lawson W, Hui JCK: Potential intervention for depression associated with increased mortality risk in patients after myocardial infarction. Am J Cardiol 2001;89:112–113.
24 Fitzgerald CP, Lawson WE, Hui JCK, Kennard ED, IEPR investigators: Enhanced external counterpulsation as initial revascularization treatment for angina refractory to medical therapy. Cardiology 2003;100:129–135.
25 Lawson WE, Kennard ED, Hui JCK, Holubkov R, Kelsey SF, IEPR investigators: Analysis of baseline factors associated with reduction in chest pain in patients with angina pectoris treated by enhanced external counterpulsation. Am J Cardiol 2003;92:439–443.