Clin. Cardiol. 23, 254–258 (2000)

Long-Term Prognosis of Patients with Angina Treated with Enhanced External Counterpulsation: Five-Year Follow-Up Study

WILLIAM E. LAWSON, M.D., JOHN C.K. HUI, PH.D., PETER F. COHN, M.D.

Division of Cardiology and Department of Surgery, SUNY at Stony Brook, Stony Brook, New York, USA

Summary

Background: Enhanced external counterpulsation (EECP) is a noninvasive treatment for coronary artery disease (CAD) that has been used successfully in patients not responding to medical and/or surgical therapy.

Hypothesis: The study was undertaken to evaluate the effect of EECP on long-term prognosis in such patients.

Methods: Major adverse cardiovascular events (MACE) were tracked in 33 patients with CAD treated with EECP. Patients were subgrouped based on whether or not they demonstrated an early improvement in radionuclide stress perfusion imaging (Responders vs. Nonresponders) and followed for MACE over a mean follow-up of 5 years. Patient population characteristics included 73% with multivessel disease; 45% with prior myocardial infarction(s); and 61% who had undergone either coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), or both.

Results: There were 26 of 33 (79%) Responders, and 7 of 33 (21%) Nonresponders. Subsequent MACE over the 5-year follow-up included four deaths and eight patients with cardiovascular events [acute myocardial infarct (4), new CABG or PTCA (6), valve replacement (1), unstable angina (1)]. Nonresponders had significantly ($p < 0.01$) more MACE (6/7 or 86%) than Responders (6/26 or 23%). Overall, 21 of the 33 (64%) patients remained alive and without MACE and the need for revascularization 5 years post EECP treatment

Conclusion: This study suggests that, particularly for the majority of patients demonstrating improvement in radionuclide stress perfusion post treatment, EECP may be an effective long-term therapy.

Key words: coronary artery disease, external counterpulsation, prognosis

Introduction

The concept that coronary blood flow could be increased by 20–40% by raising diastolic perfusion pressure was proposed by Kantrowitz and Kantrowitz in 1953.[1] Enhanced external counterpulsation (EECP) applies external pressure to the lower extremities in a timed, sequential manner, using three pairs of pneumatic cuffs, to produce effective diastolic augmentation (Fig. 1). The sequential inflation of pressure cuffs "milks" blood from the vasculature of the legs and is more effective in producing diastolic augmentation and increasing venous return than the earlier one-chamber hydraulic counterpulsation system. The mechanism of action is similar to that of the intraaortic balloon pump (IABP) in producing timed diastolic augmentation. By also augmenting venous return, EECP may further increase cardiac output.

Studies using radionuclide stress testing have documented improved myocardial perfusion, exercise tolerance, and decreased angina following EECP treatment in about 80% of subjects.[3,4] Improvement based on stress myocardial perfusion imaging has been shown to be related to the extent of coronary artery disease (CAD) and prior revascularization.[5,6] The presence of a patent conduit (native coronary or bypass graft) increases the likelihood of a favorable response and has been termed "the patent vessel hypothesis." This is in concert with the demonstration by Kern *et al.* that augmented diastolic pressures and flow generated by the IABP are only effectively transmitted to the distal coronary vasculature in the absence of a significant intervening coronary stenosis.[7,8] Diastolic augmentation increases the diastolic transmyocardial pressure gradient at a time when coronary flow impedance is low, thereby maximizing coronary blood flow and perhaps facilitating development or recruitment of collaterals.

Presented at Biomedicine 1997, Washington, D.C., April 25–27, 1997. This study was supported by grants from Vasomedical, Inc.

Address for reprints:

William E. Lawson, M.D.
SUNY at Stony Brook
HSC T-17-020
Stony Brook, NY 11794, USA

Received: June 11, 1999
Accepted: July 16, 1999

FIG. 1 The enhanced external counterpulsation device used in treating patients with coronary artery disease consists of a control console, a treatment table, three pairs of cuffs wrapped around the lower extremities, and a compressor unit (not shown).

The initial improvement in stress myocardial imaging following EECP has been shown to be maintained in a majority of treated patients over a 3-year follow-up period.[9] The present study was planned to determine whether there was evidence for a sustained clinical benefit from EECP by assessing major adverse cardiovascular events (MACE) over a 5-year post-treatment period. Significant MACE chosen as endpoints included death, myocardial infarction, revascularization [coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)], and cardiac related hospitalization.

Methods

A cohort of consecutive patients with angina treated with EECP from 1989 to 1991 was followed for a mean of 5 years (range 4–7 years). The study protocol and patient informed consent had been approved by the institutional review board of the State University of New York at Stony Brook. When first treated with EECP, the patients had stable but limiting angina pectoris despite medical and/or revascularization therapy (CABG or PTCA). A radionuclide stress test demonstrating reversible perfusion defects consistent with ischemia was also required prior to EECP treatment. The patients received an initial 35–36 h course of EECP administered at 1–2 h daily sessions for 5 days a week and were followed for a mean of 5 years for MACE.

Radionuclide stress tests were performed pre and post initial EECP treatments to the same cardiac work load and double product. The radionuclide stress tests were interpreted in a blinded fashion by two trained readers without knowledge of the patients or of their clinical status. Based on the post-EECP stress radionuclide perfusion imaging, two subgroups were identified: (1) Responders—those patients demonstrating a decrease in the size or number of radionuclide stress perfusion defects post EECP, and (2) Nonresponders—those patients without evidence of radionuclide perfusion defect improvement. Differences pre and post treatment and between these groups were analyzed using the chi-square test, with significance assumed at the $p < 0.05$ level. Multifactorial analysis of patient baseline characteristics predicting a favorable response to EECP treatment was also performed, with significance assumed at the $p < 0.05$ level.

No risk factor modification was attempted post EECP treatment other than that which may have been initiated by the patient or the patient's physician. Follow-up treatment decisions were made by the patient and physician and included additional EECP treatments for some patients.

Exclusions for treatment included decompensated heart failure, aortic valve insufficiency, myocardial infarction within the prior 3 months or unstable angina, severe peripheral vascular disease (occlusive arterial disease or thrombophlebitis), arrhythmias interfering with timing (atrial fibrillation, frequent ectopy, pacemakers), uncontrolled hypertension (blood pressure > 180/110 mmHg), significant bleeding diathesis.

Initial Results

There were 33 patients enrolled in this study. The mean age of the patients was 61.4 years (range 45–74 years); 31 patients were men and 2 were women. Cardiac angiography prior to entry had been performed in 30 of the 33 patients, with 73% patients having multivessel disease; 45% of patients had prior myocardial infarction(s), and 61% of patients had prior revascularization procedures (50 total revascularization procedures: 17 prior CABG in 12 patients, 33 prior PTCA in 15 patients; 7 patients with prior PTCA and CABG) (Table I).

TABLE I Patient characteristics: All treated patients, Responder and Nonresponder subgroups (by initial improvement in radionuclide stress test)

	All patients	Responders	Non-responders	Significance
Age	61.4 ± 9.5	69.8 ± 9.4	67.3 ± 8.2	p = NS
Male sex (%)	31/33 (94)	25/26 (96)	6/7 (86)	p = NS
Diabetes (%)	6/33 (18)	3/26 (12)	3/7 (43)	p = < 0.20
Single-VD (%)	8/30 (27)	8/25 (32)	0/5 (0)	p = < 0.30
Multi-VD (%)	22/30 (73)	17/25 (68)	5/5 (100)	p = < 0.30
Prior MI (%)	15/33 (45)	11/26 (42)	4/7 (57)	p = NS
Prior revasc (%)	20/33 (61)	16/26 (62)	4/7 (57)	p = NS

Abbreviations: Single-VD = single-vessel disease, multi-VD = multivessel disease, MI = myocardial infarction, revasc = revascularization (CABG or PTCA), NS = not significant.

TABLE II Early enhanced external counterpulsation (EECP) effect on antianginal therapy: All treated patients, Responder and Non-Responder subgroups (by initial improvement in post EECP radionuclide stress test)

Antianginal treatment	All patients (n = 33)		Responders (n = 26)		Nonresponders (n = 7)	
	Pre EECP	Post EECP	Pre EECP	Post EECP	Pre EECP	Post EECP
LA nitrates	15	12	10	9	5	3
Beta blockers	15	13	12	10	3	3
Calcium CB	28	26	23	21	5	5
> 1 Less antianginal post Rx	11		8		3	
> 1 More antianginal post Rx	2		1		1	

Abbreviations: Rx = EECP treatment, LA nitrates = Long-acting nitrates, Calcium-CB = calcium-channel blockers.

Enhanced external counterpulsation was well tolerated, with all patients completing the course of therapy. As reported by patients, anginal symptoms (frequency, severity, ease of precipitation, and duration of episodes) decreased in all patients. Antianginal medications at baseline and the effect of EECP treatment are shown in Table II. Post therapy, long acting nitrate use decreased by 20%, beta-blocker use decreased by 13%, calcium-channel blocker use decreased by 7%. Eleven patients (33%) were able to take one or more less antianginal medications post EECP treatment; only two patients (6%) took an additional antianginal medication post treatment.

Radionuclide stress tests performed to the same cardiac work load and double product pre and post initial EECP treatment demonstrated a significant ($p < 0.01$) improvement in perfusion defects in 26 of 33 (79%) patients (Responders). Stress perfusion defects in the remaining seven patients were unchanged post treatment (Nonresponders). It is interesting to note that the improvement in early post EECP stress perfusion did not correlate with change in daily medication use. A decrease in antianginal medication use was seen in 31% of the Responders and in 43% of the Nonresponders (p = NS).

All of the EECP Nonresponders with known angiographic anatomy had multivessel coronary disease and all of the patients with single-vessel coronary disease with known angiographic anatomy (8/8) were Responders to EECP treatment. This was not, however, a statistically significant difference (p = NS). Prior revascularization with PTCA or CABG was also not predictive of response to EECP therapy (p= NS). Baseline characteristics of the Nonresponder group showed them to be older, more likely to be female, and with a higher prevalence of diabetes; none of these differences from the Responder group reached statistical significance (Table I).

Late Results

Over the course of the mean follow-up of 5 years, 13 of 33 (39%) patients underwent additional treatment with EECP (causing the cumulative mean hours of EECP administered for the entire group to rise to 55.7 h over the follow-up period (49.75 h in the Responders and 77.8 h in the Nonresponders). The reasons for additional EECP treatment included worsening or recurrent angina, persistent ischemic defects on radionuclide stress perfusion imaging, "tune ups" (with no objective or subjective evidence of worsening of the patient's condition).

During the follow-up period four patients died and nine patients experienced interim events (Fig. 2). The causes and the timing of the deaths were diverse: one patient died of cardiac arrest 1 year after EECP treatment, a second patient died at 3 years as a complication of angioplasty, a third patient died of congestive heart failure at 3 years, and the fourth death occurred during sleep 6 years after EECP therapy. Interim events requiring hospitalization occurred in eight additional patients and included acute myocardial infarction in three, revascularization procedures in five, aortic valve replacement in one, and unstable angina in one patient.

Mortality or MACE occurred in 6 of 7 patients (86%) of the Nonresponder group. In comparison, significantly fewer, 6 of 26 patients (23%) in the Responder group, reached endpoints ($p < 0.01$). Overall, 21 of the 33 (64%) EECP-treated patients remained alive 5 years after therapy without cardiovascular morbidity or need for repeat revascularization.

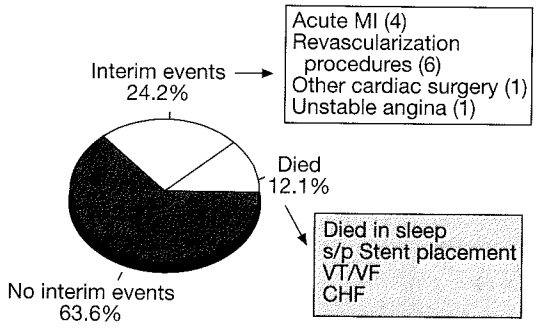

FIG. 2 Graphic representation of the proportion and cause(s) of mortality and cardiovascular morbidity post enhanced external counterpulsation in 33 patients with angina at 5-year follow-up. MI = myocardial infarction, VT = ventricular tachycardia, VF = ventricular fibrillation, CHF = congestive heart failure.

Discussion

Enhanced external counterpulsation has been useful in treating angina, improving exercise tolerance, and decreasing radionuclide stress perfusion defects in about 80% of patients.[3–5] In the recently reported Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial, a prospective, randomized, blinded study of EECP, treatment demonstrated a significant increase in time to ST-segment depression on treadmill exercise testing, a decrease in antianginal medication usage, and sustained quality of life benefits by psychometric testing.[10, 11]

The studied cohort is a population of consecutively treated patients with angina and with predominant multivessel CAD and persistent provokable ischemia despite medications and/or prior revascularization. The patients were followed for a mean of 5 years, with the objective of providing information on the effect of EECP treatment on subsequent major adverse cardiovascular events, including the need for hospitalization and repeat revascularization. The sample size is small, predominately male, and from a single center. While not a primary objective of the study, the size of the sample may have particularly influenced the ability to detect pretreatment patient characteristics predicting a response to therapy. This is probably true of the effect of multivessel disease on response to therapy, where a larger study cohort showed a significant relation between scintigraphic improvement after EECP and extent of disease.[5] While a single center favorably influences procedural consistency, it also introduces bias and is less robust than a multicenter study, which has a broad cross section of providers and patient populations to draw on. The findings of this pilot study warrant confirmation in a larger, blinded, randomized multicenter trial.

The marked difference in MACE noted between the patients demonstrating improvement in their stress radionuclide imaging (79%) and those patients who failed to demonstrate objective improvement with treatment supports a true treatment effect of EECP (Fig. 3). Mortality and cardiovascular morbidity were significantly increased in the group of 7 patients in whom objective improvement was not demonstrable (Nonresponders) in comparison with the group of 26 patients demonstrating improvement in radionuclide stress perfusion imaging (Responders). If the primary effect of EECP was that of a placebo, neither an improvement in radionuclide perfusion nor differences in the frequency of MACE between Responding and Nonresponding patient groups would be expected. By contrast, the immediate effect on use of long-acting antianginals after treatment is similar in both Responder and Nonresponder groups and is probably a placebo effect.

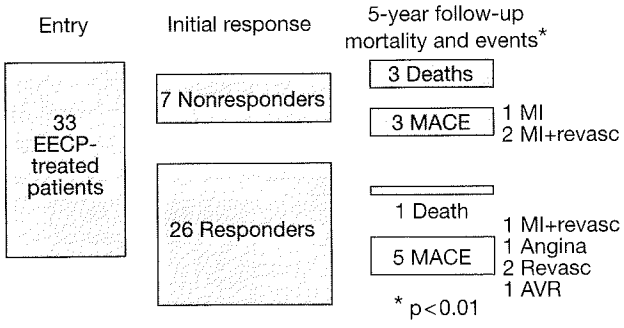

FIG. 3 Effect of initial response to enhanced external counterpulsation (EECP) on subsequent mortality and major adverse cardiovascular events (MACE). MI = myocardial infarction, revasc = revascularization, MACE = major adverse cardiovascular event, AVR = aortic valve replacement.

The 5-year survival of EECP-treated patients was 88%, which is similar to mortality rates reported in contemporary medical and revascularization (CABG or PTCA) trials such as the Coronary Artery Surgery Study (CASS),[12] the CABG meta-analysis,[13] and the Bypass Angioplasty Revascularization Investigation (BARI) (Table III).[14] The patient characteristics of our cohort were similar to those in patients in these trials who had multivessel disease, mean left ventricular ejection fraction of about 50%, and previous myocardial infarction rates of 30–50%. Unlike patients in these groups, most of the patients treated with EECP had had prior PTCA and/or CABG. As this is a historical comparison, it is unclear whether this result could be expected from a randomized trial.

When mortality is considered together with the interim rate of nonfatal events in 8 of the 33 (24%) treated patients, 21 of the 33 (64%) EECP-treated patients remained alive and free of MACE, including the need for revascularization, over a follow-up period of 5 years.

Conclusion

Previous studies have demonstrated that EECP improves myocardial stress perfusion in about 80% of patients, with the

TABLE III Comparison of 5-year survival rates for enhanced external counterpulsation (EECP) versus reported medical and surgical trials

Ref. No.	Study	5-Year survival
	EECP	88%
12	CASS—medical treatment	78%
13	CABG meta-analysis (medical)	84%
	(CABG)	90%
14	BARI—PTCA	86%
	—CABG	89%

EECP patient characteristics were similar to most of those patients having multivessel disease, mean LVEF about 50%, and previous MI rate 30–50%. However, many of the EECP patients also had prior PTCA and/or CABG.

Abbreviations: CASS = Coronary Artery Surgery Study, CABG meta-analysis = Coronary Artery Bypass Graft Surgery Trialists Collaboration, BARI = Bypass Angioplasty Revascularization Investigation, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting.

benefit sustained in a majority of treated patients over a 3-year follow-up.

The present study focuses on outcomes of mortality and major adverse cardiovascular events in an expanded cohort with a 5-year follow-up. Overall, 64% of patients were alive and without interim cardiovascular events or need for revascularization at a mean follow-up of 5 years. Most patients (79%) demonstrated improved early stress perfusion scintigraphy. The frequency of death and major adverse cardiovascular events was significantly lower in this group of patients than in the remaining Nonresponder group (23 vs. 86%; $p<0.01$). The low frequency of patients with post-treatment events suggests that EECP may be a long-term, cost-effective, noninvasive treatment for chronic angina pectoris in responding patients.

Acknowledgment

The authors appreciate the expert and enthusiastic assistance of Lynn Burger, R.N.

References

1. Kantrowitz A, Kantrowitz A: Experimental augmentation of coronary flow by retardation of arterial pulse pressure. *Surgery* 1953;34: 678–687
2. Soroff HS, Hui J, Giron F: Current status of counterpulsation. *Crit Care Clin* 1986;2:277–295
3. Lawson WE, Hui JCK, Soroff HS, Zheng ZS, Kayden DS, Sasvary D, Atkins H, Cohn PF: Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *Am J Cardiol* 1992;70: 859–862
4. Lawson WE, Hui JCK, Zheng ZS, Burger L, Jiang L, Lillis O, Oster Z, Soroff H, Cohn PF: Improved exercise tolerance following enhanced external counterpulsation: Cardiac or peripheral effect? *Cardiology* 1996;87:1–5
5. Lawson, WE, Hui JCK, Guo T, Burger L, Cohn PF: Prior revascularization increases the effectiveness of enhanced external counterpulsation. *Clin Cardiol* 1998;21:841–844
6. Lawson WE, Hui JCK, Oster ZH, Zheng ZS, Cabahug C, Katz JP, Dervan JP, Burger L, Jiang L, Soroff HS, Cohn PF: Enhanced external counterpulsation as an adjunct to revascularization in unstable angina. *Clin Cardiol* 1997;20:178–180
7. Kern MJ, Aguirre FV, Tatineni S, Penick D, Serota H, Donohue T, Salter K: Enhanced coronary blood flow velocity during intra-aortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol* 1993;21:359–368
8. Kern MJ, Aguirre F, Bach R, Conohue T, Siegel R, Segal J: Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. *Circulation* 1993;87: 500–511
9. Lawson WE, Hui JCK, Zheng ZS, Oster Z, Katz JP, Diggs P, Burger L, Cohn CD, Soroff HS, Cohn PF: Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995;75:840–841
10. Arora RR, Chou TM, Jain D, Nesto RW, Fleischman B, Crawford L, McKiernan T: Results of the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): EECP reduces anginal episodes and exercise-induced myocardial ischemia. *Circulation* 1997;96(8):I-466 (2602)
11. Arora RR, Chou TM, Jain D, Nesto RW, Fleischman B, Crawford L, McKiernan T: Results of the Multicenter Enhanced External Counterpulsation (MUST-EECP) outcomes study: Quality of life benefits sustained six months after treatment. *Circulation* 1998; 98(suppl I):I-350 (1838)
12. Emond M, Mock MB, Davis KJ, Fisher LD, Holmes DR Jr, Chaitman BR, Kaiser GC, Alderman E, Killip T III, and Participants in the Coronary Artery Surgery Study (CASS): Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1994; 90:2645–2657
13. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, Morris C, Mathur V, Varnauskas E, Chalmers TC: Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563–570
14. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996; 335:217–225