Two-Year Clinical Outcomes After Enhanced External Counterpulsation (EECP) Therapy in Patients With Refractory Angina Pectoris and Left Ventricular Dysfunction (Report from the International EECP Patient Registry)

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Enhanced external counterpulsation (EECP) is a noninvasive circulatory assist device that has recently emerged as a treatment option for refractory angina in left ventricular (LV) dysfunction. This 2-year cohort study describes the long-term follow-up of patients who had severe LV dysfunction that was treated with EECP for angina pectoris and reports clinical outcomes, event-free survival rates, and the incidence of repeat EECP. This study included 363 patients who had refractory angina and LV ejection fraction ≤35%. Most patients reported quality of life as poor. After completion of treatment, there was a significant decrease in severity of angina class ($p < 0.001$), and 72% improved from severe angina to no angina or mild angina. Fifty-two percent of patients discontinued nitroglycerin use. Quality of life improved substantially. At 2 years this decrease in angina was maintained in 55% of patients. The 2-year survival rate was 83%, and the major adverse cardiovascular event-free survival rate was 70%. Forty-three percent had no reported cardiac hospitalization; 81% had no reported congestive heart failure events. Repeat EECP was performed in 20% of these patients. The only significant independent predictor of repeat EECP in a proportional hazard model was failure to complete the first EECP treatment course (hazard ratio 2.9, 95% confidence interval 1.7 to 4.9). Improvements in angina symptoms and quality of life were maintained at 2 years. In conclusion, for patients who have high-risk LV dysfunction, EECP offers an effective, durable therapeutic approach for refractory angina. Decreased angina and improvement in quality of life were maintained at 2 years, with modest repeat EECP and low major cardiovascular event rates. **(Am J Cardiol 2006;97:17–20)**

The United States Food and Drug Administration cleared enhanced external counterpulsation (EECP) for the treatment of stable angina, unstable angina, cardiogenic shock, and acute myocardial infarction in 1995. Since then, the procedure has been widely used for the treatment of angina. Because EECP increases right ventricular filling pressure by augmenting venous return during diastole, clinicians conjectured that its use in patients who had left ventricular (LV) dysfunction and heart failure might be contraindicated. However, the arterial hemodynamic effects of EECP are similar to those of intra-aortic balloon counterpulsation, with similar diastolic augmentation and decreased afterload.[1,2] Pilot data have shown that a LV ejection fraction ≤35% is not associated with an increase in adverse events during EECP.[3] Further, EECP has proved to be safe and effective in patients who have congestive heart failure with LV dysfunction.[4] However, the long-term efficacy of EECP in patients who have refractory angina and LV dysfunction has not been evaluated. The purpose of this project was to describe the 2-year follow-up of patients who had severe LV dysfunction that was treated with EECP for refractory angina pectoris and to report the clinical outcomes, event-free survival rates, and incidence of repeat EECP.

Methods

Patient population and study: The International EECP Patient Registry (IEPR) phase I study began in January 1998 and enrolled consecutive patients who underwent EECP for chronic angina. More than 5,000 patients were enrolled from >100 international centers. The IEPR methods has been previously described.[5] Patients in the IEPR

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Table 1
Characteristics of patients (n = 363) with left ventricular ejection fraction ≤35% before starting enhanced external counterpulsation therapy

Age (yrs)	67 ± 11
Men	78%
Previous myocardial infarction	85%
Previous coronary bypass	72%
Previous percutaneous coronary intervention	70%
Hypertension*	68%
Hyperlipidemia†	78%
Current smoker	10%
Diabetes mellitus	45%
Noncardiac vascular disease	35%
History of congestive heart failure	61%
LV ejection fraction (%)	28 ± 7

Values are means ± SD or percentages.
* Diagnosed by a physician and treated with medication and/or diet.
† Documented serum cholesterol level >240 mg/100 ml or treatment for high cholesterol level by a physician with medication and/or diet.

Table 2
Adverse events for patients (n = 363) with left ventricular ejection fraction ≤35% during enhanced external counterpulsation therapy

Death	0.8%
Myocardial infarction	0.3%
Coronary bypass	0.3%
Percutaneous coronary intervention	0.8%
Death/myocardial infarction/coronary bypass/ percutaneous coronary intervention	1.9%
Unstable angina pectoris	4.1%
Congestive heart failure	3.3%
Skin breakdown	2.5%
Musculoskeletal	2.2%

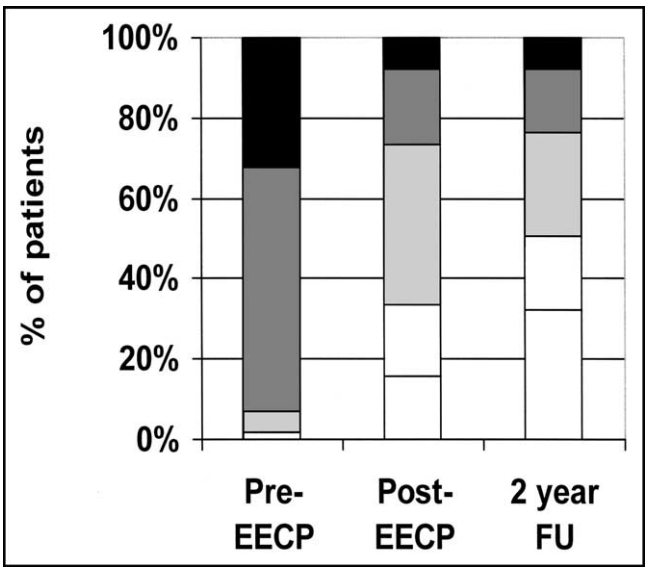

Figure 1. Angina classes 0 *(white bars)*, I *(pale gray bars)*, II *(medium gray bars)*, III *(dark gray bars)*, and IV *(black bars)* before EECP (n = 363), after EECP (n = 358), and at 2-year follow-up (FU; n = 265).

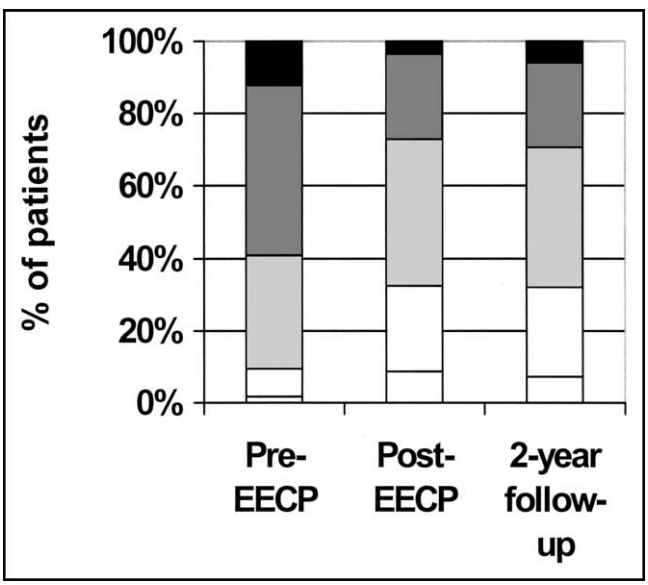

Figure 2. Quality of life rated as poor *(black bars)*, fair *(dark gray bars)*, good *(medium gray bars)*, very good *(pale gray bars)*, and excellent *(white bars)* before and after EECP and at 2-year follow-up.

were required to give informed consent, and the IEPR tracks the demographics, entry characteristics, clinical events, and outcomes of consecutive patients who undergo EECP treatment for angina, with no exclusion due to demographics, clinical status, or outcome. Canadian Cardiovascular Society classification was used to assess angina status. Quality of life was assessed by patients who used 5-point scales for health status, quality of life, and satisfaction with quality of life. At 6-month, 1-year, and 2-year follow-ups, patients were interviewed by telephone or at a clinic visit, and data concerning interim clinical events, hospitalizations, and current symptomatology were recorded. Major adverse cardiac events were specified as the composite of death, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. Patient data were included only from sites with ≥85% complete follow-up.

The IEPR-generated database was queried to select the cohort of patients who underwent EECP for LV dysfunction. LV dysfunction was defined as a LV ejection fraction ≤35% as assessed by echocardiography (30%), ventriculography (58%), or gated blood pool scan (12%).

EECP therapy (Vasomedical, Inc., Westbury, New York) was administered to all patients. EECP equipment is comprised of an air compressor, a computer module, 3 sets of cuffs, and a treatment table. Systolic and diastolic pressure waves are monitored throughout treatment by noninvasive finger plethysmography. Cuffs are wrapped around a patient's calves, thighs, and lower buttocks and a computer-controlled pneumatic system acts to inflate and deflate the cuffs. Inflation and deflation are triggered by events in the cardiac cycle through microprocessor-interpreted electrocardiographic signals. A full course of therapy typically consists of 35 1-hour sessions offered once daily.

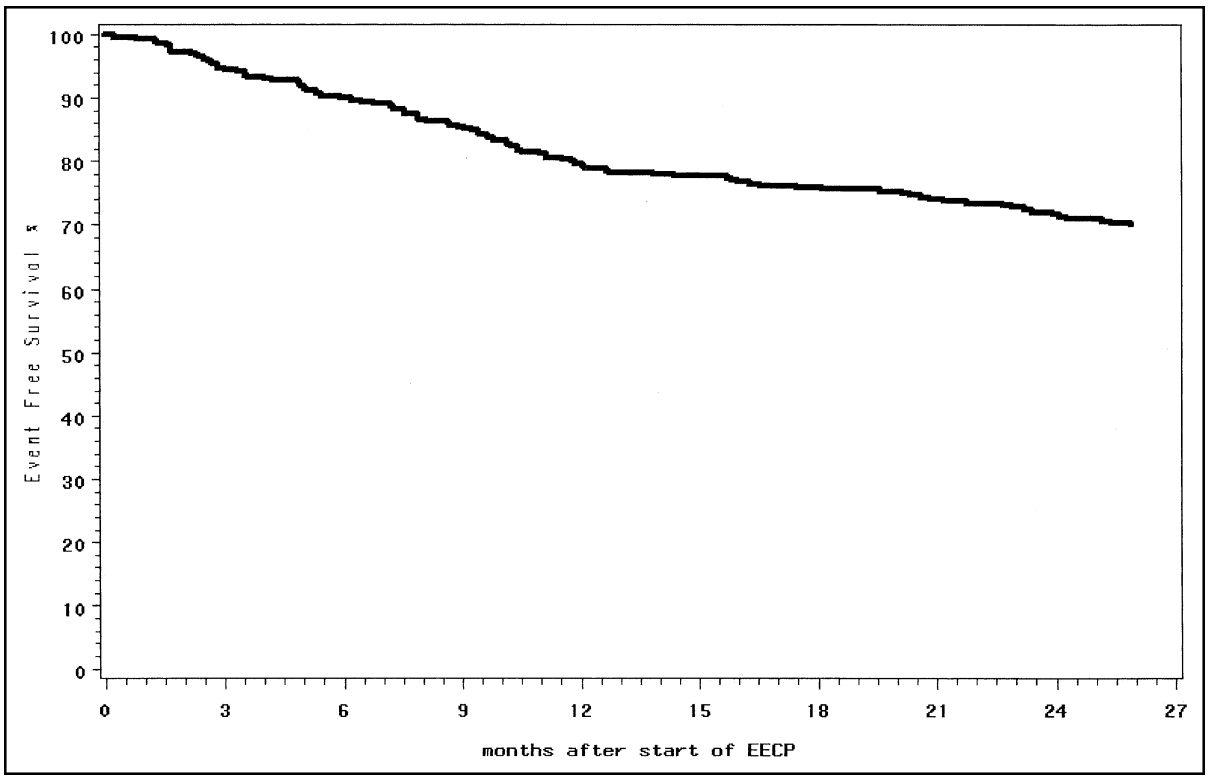

Figure 3. Event-free survival rate. Events were death, coronary artery bypass grafting, myocardial infarction, and percutaneous coronary intervention.

Statistical analysis: Baseline characteristics are presented for categorical variables as the proportion of patients who reported and as mean ± SD for continuous variables. Kaplan-Meier survival analysis was used to model follow-up events. Predictors of repeat EECP were determined with Cox's proportional hazards model. Two-tailed p values <0.05 were considered statistically significant.

Results

The IEPR included 363 patients who had angina with LV dysfunction. Patients' average duration of clinical coronary artery disease was nearly 13 years; 84% had multivessel disease and 93% were not candidates for further revascularization due to the extent and severity of disease, LV dysfunction, co-morbid conditions, previous interventions, or risk/benefit ratio. Angina was severe (class III/IV) in 93% of patients. There was a high prevalence of cardiac risk factors (i.e., 77% had a history of smoking and 82% had a family history of premature atherosclerotic cardiovascular disease) (Table 1). More than 50% reported quality of life as 4 or 5 (i.e., poor, on the 5-point scale, where 5 is worst).

On average, patients underwent an EECP treatment course of 32 hours, with 81% completing the course. Twelve percent discontinued due to a clinical event, and 7% stopped due to patient preference. Women and those who had a history of congestive heart failure were less likely to complete the treatment course (75% of women vs 82% of men, $p = 0.15$; therapy completed by 78% of those who had congestive heart failure vs 85% of those who did not, $p = 0.08$). There was a significant difference in the rate of exacerbation of heart failure between those who did not complete treatment and had previous heart failure and those who had no heart failure (16% of those who stopped treatment vs 0%, $p = 0.05$). Major adverse cardiovascular events that occurred over the course of EECP therapy were low (Table 2).

After completion of treatment, there was a significant decrease in severity of angina ($p < 0.001$). Of the total cohort, 77% of patients decreased by ≥1 angina class, 18% had no angina, and 2% had an increase in angina class (Figure 1). The mean number of weekly angina episodes decreased by 8.2 ± 12.9 episodes ($p < 0.001$). Of those who used nitroglycerin as needed, 52% of patients discontinued nitroglycerin use after EECP. Quality of life showed a significant increase ($p < 0.001$; Figure 2).

At 2 years, 83% survived and the event-free survival rate was 70% (Figure 3). Forty-three percent had no cardiac hospitalizations, and 81% had no congestive heart failure events. Comparison of patients who showed no decrease in angina with those who showed decreased angina showed no difference in major adverse cardiovascular events at 2 years; however, those who showed no initial response reported significantly unstable angina in the 2-year period (28% vs 16%, $p = 0.02$). There was a significant difference in

Table 3
Medication use before and after enhanced external counterpulsation and at two-year follow-up

Medication	Before EECP	After EECP	Follow-up
β Blocker	71.2%	75.6%	72.6%
Calcium channel blocker	30.7%	30.4%	30.7%
Angiotension-converting enzyme	60.5%	61.1%	52.8%
Angiotensin receptor blocker	15.5%	14.6%	11.3%
Antiplatelet	76.4%	75.2%	73.5%
Lipid lowering	75.8%	76.6%	77.7%

survival rate between those who did not complete and those who completed treatment (71% vs 85%, $p < 0.001$). There was a sustained decrease in angina class in 55% of survivors compared with after EECP (Figure 1). Improvement in quality of life was also maintained (Figure 2).

Use of β blockers, calcium blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiplatelets, and hypolipidemic medication was similar at baseline, immediately after EECP, and at 2 years (Table 3).

Repeat EECP was performed in 20% of patients. Failure to complete the original treatment course was the only significant independent predictor of repeat EECP (hazard ratio 2.9, 95% confidence interval 1.7 to 4.9).

Discussion

EECP has been shown to decrease angina and stress myocardial perfusion in patients who have coronary artery disease.[6–8] Previously, however, a primary concern was that the increased venous return that resulted from EECP would precipitate an exacerbation of heart failure in patients who developed angina pectoris and had a history of heart failure with LV dysfunction. Recent reports have demonstrated that, despite depressed LV function, patients respond acutely to treatment with EECP.[4] The present results represent the largest reported long-term follow-up series of consecutive patients who had LV dysfunction that was treated with EECP for refractory angina pectoris. These patients are characterized by chronic multivessel coronary artery disease, with a high prevalence of coronary disease risk factors, severe angina refractory to medical therapy or conventional invasive revascularization, and a poor quality of life. Most patients were not candidates for further coronary revascularization. Despite this clinical profile with frequent anginal symptoms and markedly depressed LV systolic function, most patients demonstrated a significant decrease in angina and improvement in quality of life after EECP and this decrease was maintained in most patients at 2-year follow-up. Selection bias, which was minimized by reporting on patients from sites with ≥85% follow-up compliance, and survival bias may account for differences among patients who were or were not available for 2-year follow-up.

A primary limitation of this study is the lack of a control group to assess outcomes. We previously compared demographics and clinical outcomes from patients who were enrolled in the IEPR and those from patients who were in the National Health Lung Blood Institute Dynamic Registry and underwent elective percutaneous coronary intervention for refractory angina.[9] Despite an unfavorable baseline profile and risk factors in the IEPR, comparison of EECP with percutaneous coronary intervention showed an increased event-free survival rate, with a similar incidence of severe angina pectoris in patients who received EECP. EECP may offer a safe treatment option for patients who have LV dysfunction and angina pectoris. However, identifying a proper comparison group and interpreting differences in outcomes from different registries are challenges. Although difficult to perform in patients who have exhausted nearly all treatment options, a more rigorous evaluation of the effect of EECP on these outcomes will require a randomized clinical trial.

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