Angina Patients With Diastolic Versus Systolic Heart Failure Demonstrate Comparable Immediate and One-Year Benefit From Enhanced External Counterpulsation

WILLIAM E. LAWSON, MD,[1] MARC A. SILVER, MD,[2] JOHN C.K. HUI, PhD,[1] ELIZABETH D. KENNARD, PhD,[3] AND SHERYL F. KELSEY, PhD,[3] FOR THE IEPR INVESTIGATORS

Stony Brook, New York; Oak Lawn, Illinois; Pittsburgh, Pennsylvania

ABSTRACT

Background: Enhanced external counterpulsation (EECP) is effective in treating angina in coronary artery disease patients. Whether EECP produces similar immediate and sustained benefits and freedom from adverse events (MACE) at 1 year in patients with severe systolic dysfunction versus diastolic dysfunction is unknown.

Methods and Results: Data of 746 angina patients with a history of heart failure enrolled in the International EECP Registry were divided into 2 groups: left ventricular ejection fraction (LVEF) ≤35% (S) and LVEF >35% (D). Mean LVEF was 51.0 ± 10.2% in diastolic dysfunction (n = 391) versus 26.3 ± 6.9% in systolic dysfunction (n = 355). At baseline, 92.0% of diastolic dysfunction and 90.9% of systolic had Canadian Cardiovascular Society Class III/IV angina with similar number of anginal episodes and nitroglycerin use. After 32 hours of EECP, angina was reduced by ≥1 class in 71.9% of diastolic versus 72.2% of systolic with similar decreases in anginal episodes and nitroglycerin use. At 1-year 78.1% of diastolic and 75.8% of systolic have less angina than pre-EECP. MACE at 1 year was also comparable (24.4 versus 23.8%).

Conclusions: The benefits of EECP in heart failure patients were similar regardless of diastolic or systolic dysfunction. The improvement was sustained at 1 year with similar MACE.

Key Words: Noninvasive therapy, congestive heart failure, angina.

Congestive heart failure (CHF) patients with angina who are not revascularization candidates are particularly difficult to treat. Effective treatment of chronic myocardial ischemia can stabilize or improve cardiac function, decrease adverse remodeling, and lessen the risk of CHF progression and decompensation. Revascularization can benefit patients with systolic dysfunction by improving contractility and can benefit those with diastolic dysfunction by improving left ventricular compliance. Enhanced external counterpulsation (EECP) is an effective and durable treatment for refractory angina in patients with coronary artery disease (CAD), decreasing exertional myocardial ischemia.[1,2] EECP produces immediate and sustained benefits for the angina patient.[3,4] Whether these benefits are similar in those angina patients with a history of heart failure and severe systolic dysfunction, and those patients with a history of heart failure and preserved systolic function (diastolic dysfunction) is unknown.

EECP is typically used to treat medically refractory angina patients who are poor revascularization candidates resulting from extensive coronary disease, lack of targets or conduits, left ventricular dysfunction, and comorbidity. In the majority of treated patients EECP has been shown to improve objective measures of ischemia, including exercise duration, time to ST segment depression, presence and size of stress radionuclide perfusion defects, and myocardial perfusion by positron emission tomography (PET). There is a parallel subjective improvement in functional class, quality of life, and angina.[5,6]

It has been estimated that half of heart failure patients suffer predominantly from diastolic dysfunction. Whether EECP will have similar benefit and risk in these patients as has been demonstrated in systolic dysfunction is unclear.[7,8] This study

From the [1]SUNY Stony Brook, Stony Brook, New York, [2]Advocate Christ Medical Center, Oak Lawn, Illinois, [3]University of Pittsburgh, Pittsburgh, Pennsylvania.

Manuscript received November 18, 2003; revised manuscript received April 6, 2004; revised manuscript accepted April 26, 2004.

Reprint requests: William E. Lawson, MD, SUNY Stony Brook, HSC T-17-020, Stony Brook, NY 11740.

The IEPR is sponsored by Vasomedical Inc, Westbury, New York.

This article was partially presented at the 7th Scientific Meeting of Heart Failure Society of America, September 2003, Las Vegas, Nevada.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2004.04.006

evaluates the safety, benefit, and durability of effect of EECP in angina patients with a history of heart failure and systolic versus diastolic (preserved systolic) dysfunction.

Methods

Data from consecutive angina patients with a history of heart failure were examined from the International EECP Patient Registry (IEPR) based at the Epidemiology Data Center of the University of Pittsburgh Graduate School of Public Health. The IEPR is a prospective registry formed to determine the patterns of use, safety, and efficacy of EECP. It tracks sequential patients enrolled by a wide range of providers and provider settings, collecting patient demographics, treatment characteristics, and outcomes. All participating patients gave informed consent. The data examined were drawn from patients enrolled between January 1998 and January 2002. Patients with a history of clinical CHF were divided into 2 groups; 1 with severe left ventricular systolic dysfunction (EF ≤35%, S) and a second group with preserved systolic function (EF >35%, D). Measures of left ventricular ejection fraction included measurements by left ventriculography, echocardiography, radionuclide imaging. Patient demographics, immediate- and long-term outcomes, freedom from major adverse cardiac events (MACE: all cause death, all myocardial infarctions [MI], angioplasty [PCI], coronary bypass [CABG]) were compared. The information on MACE was obtained from the IEPR as reported by individual center.

Enhanced external counterpulsation was typically prescribed as a 1-hour daily session, 5 days per week over a period of 7 weeks, for a total of 35 hours. Treatment was performed with a nurse in attendance and a supervising physician immediately available. Patients were monitored during treatment by finger plethysmogram, pulse oximetry, electrocardiography, and resuscitative equipment was readily available. Patients had an intake history and physical exam, and an interval history and focused exam before each treatment. In follow-up, interval histories were obtained at 6 and 12 months after treatment. At each follow-up, performed by telephone interview by nurse coordinators, patients were queried as to changes in angina functional class and quality of life, changes in angina pattern and nitroglycerin use, medication changes, and whether interim events had occurred (including cardiac hospitalizations and MACE). In a small number of cases event times and censoring times that were not known were estimated. If the patient was not available (ie, because of death) information was obtained from family or referring physician.

Statistical Analysis

The cohort of patients with a history of CHF and severe systolic dysfunction were compared to the group with a history of CHF and preserved systolic function using chi-squared or Fishers exact tests for discrete variables and Wilcoxon signed-rank test for continuous variables. Significance was defined as $P < .05$. Kaplan-Meier life table analysis was performed to contrast the timing and occurrence of post-EECP MACE in both cohorts. The log-rank test was used to compare survival times.

Results

There were 2388 consecutive patients enrolled in the IEPR between January 1998 and January 2002. Of these patients, there were 746 patients (36% of patients enrolled in the IEPR) with a history of heart failure; 355 had severe left ventricular systolic dysfunction (LVEF ≤35%) at baseline and 391 had preserved left ventricular systolic function (LVEF >35%) at baseline.

Demographics

The mean age of both cohorts of patients with a history of CHF was similar, 67.7 years in patients with systolic dysfunction versus 66.9 years for patients with preserved systolic function ($P = .34$). The 2 groups were similar in prevalence of white race, multivessel CAD, prior CABG or PCI, and the cardiac risk factors of diabetes mellitus, hyperlipidemia, and smoking history. The duration of CAD and prevalence of prior MI were significantly higher in patients with systolic dysfunction. By contrast those with diastolic dysfunction had a significantly higher prevalence of female gender, hypertension, non–cardiac vascular disease, and were more likely to be candidates for additional revascularization (Table 1).

Both groups were comparably treated with aspirin, β-blockers, lipid-lowering agents, and nitrates. However, significant differences existed in the use of calcium channel blockers (CCBs: 27.8% in the systolic dysfunction group versus 49.1% in the diastolic group, $P < .001$), angiotensin-converting enzyme inhibitors (ACEI: 63.4% in systolic dysfunction group versus 47.0% in diastolic group, $P < .001$) and angiotensin receptor blockers (ARBs: 14.1% in the systolic dysfunction group versus 8.4% in the diastolic group $P < .001$). Reflecting the disparity in left ventricular ejection fraction in the 2 groups, ACEI and ARBs were used much more frequently in the cohort with severe left ventricular

Table 1. EECP Patient Characteristics by LV Systolic Function

	LVEF ≤35%	LVEF >35%	*P* Value
Patients in cohort (n=704)	355	391	
LVEF (%)	26.3 ± 6.9	50.9 ± 10.2	
Age (y)	67.7 ± 10.1	66.9 ± 11.6	.34
Male (%)	79.1	65.8	<.001
Years since CAD diagnosis	13.3 ± 8.6	11.9 ± 8.7	.015
Prior MI (%)	89.3	77.6	<.05
Multivessel CAD (%)	83	78.8	.16
Prior PCI or CABG (%)	90.0	91.9	.37
PCI or CABG candidate (%)	5.7	10.2	.026
Diabetes (%)	50.3	55.7	.14
Hypertension (%)	72.2	80.0	.012
Hyperlipidemia (%)	78.8	82.5	.20
Noncardiac vascular disease (%)	34.3	40.7	.074
Past/present smoking (%)	73.1	75.9	NS

CABG, coronary artery bypass grafting; CAD, coronary artery disease; EECP, enhanced external counterpulsation; EF, ejection fraction; LV, left ventricular; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention.

Data are percentages of patients reporting or mean values ± S.D.

dysfunction and CCBs were used more frequently in the cohort with preserved systolic function (Table 2). That only 70% to 72% of patients were treated with aspirin is in line with current practice, if not guideline recommendations.

Treatment Course

At baseline, 90.9% of patients with severe systolic dysfunction and 92.0% of patients with preserved left ventricular systolic function had Canadian Cardiovascular Society class III/IV angina. Anginal episodes and nitroglycerin use were similar in both groups. After a comparable course of EECP treatment, angina was reduced by ≥1 class in 72.2% of patients with severe systolic dysfunction and in 71.9% of patients with preserved left ventricular systolic function (Fig. 1). There were similar decreases in both cohorts in anginal episodes and nitroglycerin use. MACE occurring over the course of therapy in patients with severe systolic dysfunction included 1.7% death, 0.8% myocardial infarction, 0.6% surgical revascularization, and 0.6% PCI, for an overall MACE rate of 3.1%. Patients with preserved systolic function demonstrated comparable events during therapy: 0.8% death, 1.0% MI, 0.5% surgical revascularization, and 0.5% PCI, for an overall MACE rate of 2.3%. The 2 most frequent adverse events occurring during treatment were unstable angina, noted in 4.2% of S and 4.6% of D, and exacerbation of CHF, noted in 5.4% of S and 3.1% of D—differences that were not statistically significant (Table 3).

Table 2. EECP Patient Medications at Entry, Immediately After EECP therapy, and at 1-year follow-up by LV Systolic Function

Entry medications	LVEF ≤35%	LVEF >35%	*P* Value
β-blockers	64.7	72.6	.019
Calcium channel blockers	27.1	47.8	<.001
Angiotensin-converting enzyme inhibitors	64.4	47.1	<.001
Angiotensin receptor blockers	14.7	9.0	.015
Nitrates	82.2	83.9	.54
Lipid lowering	72.7	70.4	.49
Aspirin	72.4	73.8	.68
Immediate post-EECP			
β-blockers	67.2	71.9	.17
Calcium channel blockers	27,2	45.3	<.001
Angiotensin-converting enzyme inhibitors	65.3	47.3	<.001
Angiotensin receptor blockers	15.0	10.5	<.066
Nitrates	79.7	83.6	.16
Lipid lowering	72.4	70.1	.50
Aspirin	73.5	73.6	.98
1-year follow-up			
β-blockers	65.5	69.2	.33
Calcium channel blockers	28.5	43.1	<.001
Angiotensin-converting enzyme inhibitors	58.1	46.1	.003
Angiotensin receptor blockers	11.6	9.9	.49
Nitrates	75.0	82.6	.02
Lipid lowering	70.4	68.3	.56
Aspirin	53.2	60.9	.035

Abbrevations as in Table 1.
Data are percentages of patients reporting.

Follow-Up

Overall, 87% of patients provided information at 1-year follow-up (349 patients in the diastolic dysfunction group [89%], and 298 of the systolic dysfunction group [84%]). The reduction in angina seen immediately after EECP was maintained in the majority of these patients. A reduction of at least one Canadian Cardiovascular Society angina class was seen at 1 year in 76% of S and 78% of D, and 71% of each group reported either no angina or Canadian Cardiovascular Society class I/II angina. The 1-year (15 months after the first hour of EECP) Kaplan-Meier event rates are summarized in Table 4. Death was significantly more frequent in the S group versus the D group (14.1% for S versus 9.2% for D, $P = .039$; Fig. 2) and percutaneous coronary intervention more frequent in the D group (5.8 for S versus 7.3% for D, $P = .043$); overall, MACE occurred at similar rates (23.8% for S versus 24.4% for D, $P = .98$; Fig. 3). The rate of death remained significantly different between the 2 groups when adjusted for differences in baseline characteristics. Using a Cox proportional hazard model the hazard ratio for systolic versus diastolic dysfunction was 1.89 (95% confidence interval 1.03–3.38) when corrected for age, gender, prior myocardial infarction, hypertension, and non–cardiac vascular disease. A similar model for MACE demonstrated no significant difference between the 2 groups when corrected for the baseline differences.

Discussion

EECP is thought to work through multiple mechanisms. Its acute hemodynamic and circulatory actions stimulate growth factors, cause collateral recruitment and development and produce neurohormonal changes that persist post treatment. Notable EECP effects promoting normalization of endovascular tone and reactivity include a downregulation of renin-angiotensin system activity, an increase in nitric oxide, and decreases in endothelin and malondialdehyde (lipid peroxidation).[9–11] In CHF patients, the usual 7-week course of EECP may be of sufficient duration to have effects on myocardial fibrosis and remodeling, provide a "holiday" to normalize myosin expression, and decrease afterload, improving left ventricular contractility and cardiac output.[12,13] These actions may be independent of its benefits in reducing inducible myocardial ischemia.

Prior reports have demonstrated that angina patients with left ventricular dysfunction or a history of left ventricular systolic dysfunction may be safely treated with EECP. Treated patients demonstrate benefits in decreasing angina functional class, anginal episodes, and use of nitroglycerin. In the majority of treated patients benefits are maintained at follow-up.[7,8] Short-term case series have also demonstrated that patients with coronary artery disease and severe left ventricular systolic dysfunction may demonstrate significant increases in cardiac output and ejection fraction and decreases in systemic resistance following a course of EECP treatment. Confirmation of reversal of heart failure remodeling in ischemic and nonischemic cardiomyopathy with

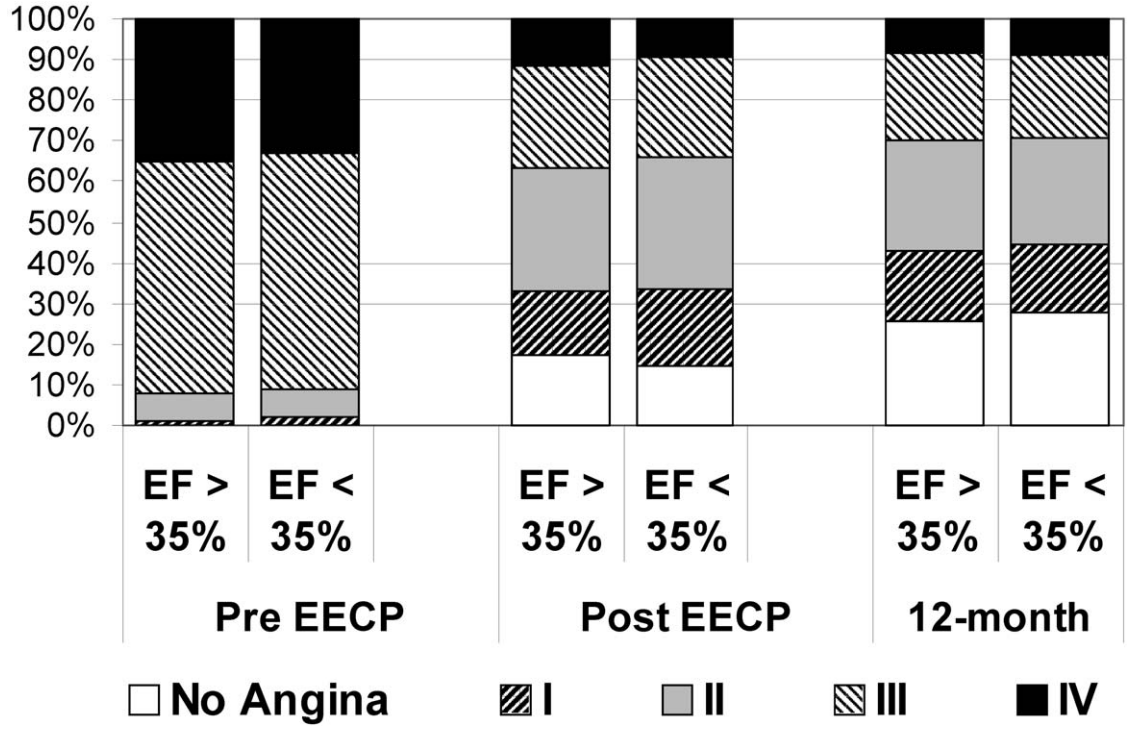

Fig. 1. Effect of enhanced external counterpulsation on Canadian Cardiovascular Society anginal class in cohorts with severe systolic dysfunction (ejection fraction [EF] ≤35%) and those with preserved systolic function (EF >35%).

EECP, safety of treatment, and durability of benefit are the subjects of an ongoing prospective, single blinded, randomized clinical trial (Prospective Enhanced External Counterpulsation Congestive Heart Failure Trial [PEECH]).

The patients with a history of heart failure and preserved left ventricular systolic function may represent a cohort in which diastolic dysfunction is playing a significant role in heart failure. What may be surprising is that both patients

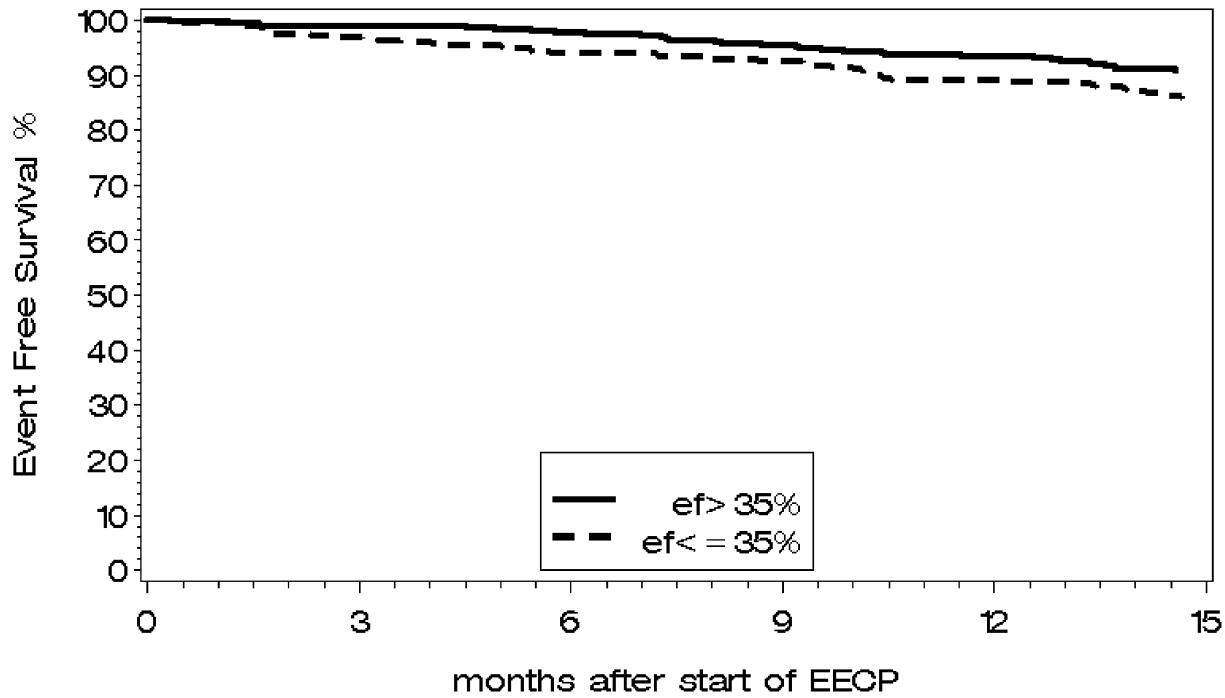

Fig. 2. Death at 1-year follow-up was 9.2% in the diastolic dysfunction group and 14.1% in the systolic dysfunction congestive heart failure patients ($P = .039$).

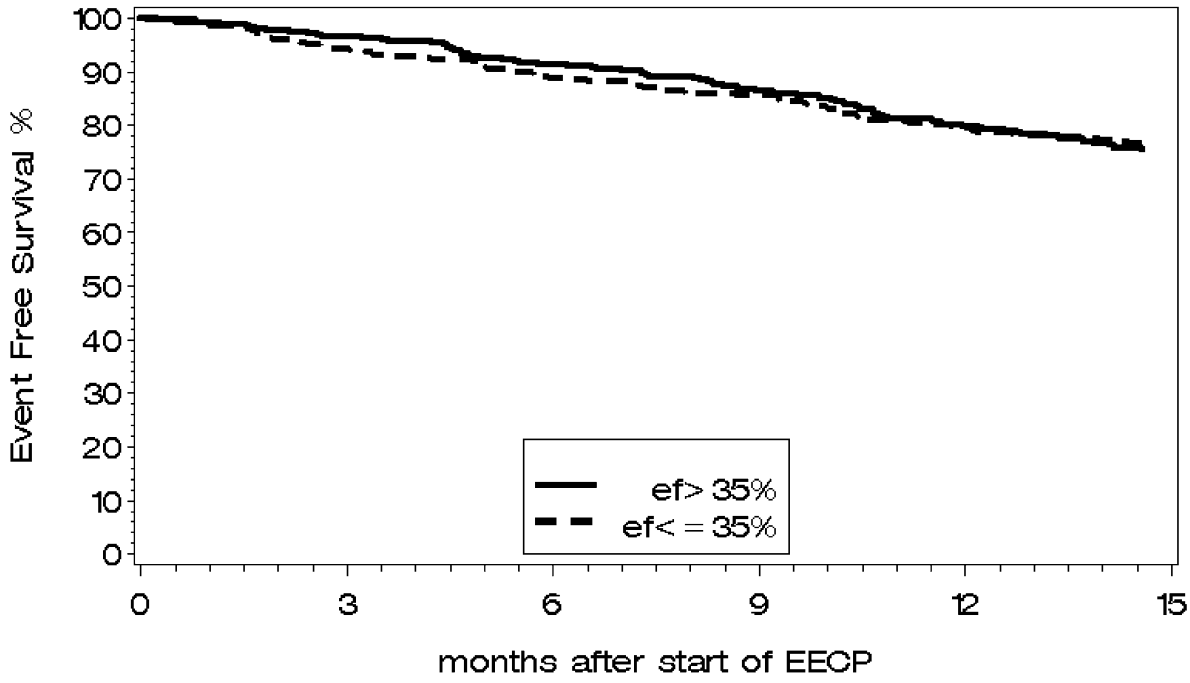

Fig. 3. Kaplan-Meier life table analysis of Major Adverse Cardiac Events (MACE: death/myocardial infarction, angioplasty, coronary bypass) in diastolic versus systolic dysfunction congestive heart failure patients.

with a history of heart failure and severe systolic dysfunction and those with a history of heart failure and preserved systolic function demonstrate a relatively high incidence of major adverse cardiovascular events in follow-up, although all-cause mortality is significantly higher in those with systolic dysfunction. This finding is concordant with reports that the prognosis with heart failure associated with diastolic dysfunction is almost as limited as the prognosis for patients with heart failure resulting from severe systolic dysfunction. And our options for effective treatment of diastolic dysfunction are fewer and less effective than the therapies available for treating severe systolic dysfunction. Given the severity of the disease suffered by these patients, the treatment and 12-month follow-up MACE are within expectations. Although it is clear that EECP benefits anginal symptoms in heart failure patients regardless of the degree of left ventricular dysfunction, more rigorous evaluation of the impact of EECP on clinical outcomes will require a randomized trial.

Table 3. Events Occurring During the Course of EECP Therapy by LV Systolic Function

	LVEF ≤35%	LVEF >35%	*P* Value
Patients in cohort	355	391	
Mean treatment hours	32.0 ± 11.2	32.3 ± 10.5	.26
Completed course	79.3	76.9	.51
Angina class decreased	75.8	78.1	.97
Unstable angina	4.2	4.6	.80
MI	0.8	1.0	1.00
Exacerbation of CHF	5.4	3.1	.12
CABG	0.6	0.5	1.00
PCI	0.6	0.5	1.00
Death	1.7	0.8	.32
Skin breakdown	2.8	1.5	.23
Musculoskeletal problems	2.5	1.0	.11
MACE	3.1	2.3	.50

CABG, coronary artery bypass grafting; MACE, major adverse cardiac event (death, MI, CABG, PCI); MI, myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina. All other abbreviations, see Table 1.

Data are percentages of patients reporting or mean values ± S.D.

Limitations of Study

The definition of systolic and diastolic dysfunction as clinical heart failure with EF >35% defining diastolic dysfunction and EF ≤35% defining systolic dysfunction may limit the generalizability of these findings. Patients were

Table 4. Kaplan-Meier Event Rates at 15 Months After First Hour of EECP

	LVEF ≤35%	LVEF >35%	*P*-Value
Patients in cohort	355	391	
Death	14.1	9.2	.039
MI	6.3	8.7	.300
PCI	5.8	7.3	.043
CABG	1.5	3.5	.103
MACE	23.8	24.4	.98

CABG, coronary artery bypass grafting; MACE, major adverse cardiac event (death, MI, CABG, PCI); PCI, percutaneous coronary intervention. All other abbreviations, see Table 3.

not defined by the NYHA as to severity of congestive heart failure at baseline. There was also no measurement of ejection fraction on follow-up. No detailed information on hospitalization or emergency room utilization during the follow-up period was available. Complete follow-up for all patients was not available, but compliance was reasonable considering that the registry enrolls mainly referral patients who are more difficult to contact after the treatment.

Conclusions

Patients with heart failure despite preserved systolic function were more likely to be female, have hypertension, and noncardiovascular disease. However, the benefits of EECP in angina patients with a history of heart failure were similar regardless of the degree of systolic dysfunction, with most patients responding to treatment. Major adverse cardiovascular events at 1 year were comparable in both cohorts despite marked differences in baseline left ventricular ejection fraction. The angina reduction after EECP in heart failure patients with systolic dysfunction and with preserved systolic function were sustained in the majority of patients at 1 year.

References

1. Lawson WE, Hui JCK, Soroff HS, Zheng ZS, Kayden DS, Sasvary D, et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am J Cardiol 1992;70:859–62.
2. Arora RR, Chou TM, Jain D, Fleischman B, Crawford L, McKiernan T, 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;33:1833–40.
3. Lawson WE, Hui JCK, Zheng ZS, Oster Z, Katz JP, Dervan JP, et al. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am J Cardiol 1995;75:840–1.
4. Lawson WE, Hui JCK, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study. Clin Cardiol 2000;23:254–8.
5. Lawson WE, Hui JCK, Lang G. Treatment benefit in the Enhanced External Counterpulsation Consortium. Cardiology 2000;94:31–5.
6. Stys TP, Lawson WE, Hui JCK, Fleishman B, Manzo K, Strobeck JE, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol 2002;89:822–4.
7. Soran O, Kennard ED, Kelsey SF, Holubkov R, Strobeck J, Feldman AM, et al. Enhanced external counterpulsation as treatment for chronic angina in patients with left ventricular dysfunction: a report for the IEPR. Congest Heart Fail 2002;8:297–302.
8. Lawson WE, Kennard ED, Holubkov R, Kelsey SF, Strobeck JE, Soran O, for the IEPR investigators, et al. Benefit and safety of enhanced external counterpulsation in treating coronary artery disease patients with a history of congestive heart failure. Cardiology 2001;96:78–84.
9. Wu GF, Qiang SZ, Zheng ZS, Zhang MQ, Lawson WE, Hui JCK. A neurohormonal mechanism for the effectiveness of enhanced external counterpulsation. Circulation 1999;100:I–832(#4390).
10. Qian XX, Wu WK, Zheng ZS, Zhan CY, Yu BY, Lawson WE, et al. Effect of enhanced external counterpulsation on nitric oxide production in coronary disease. J Heart Dis 1999;1:193.
11. Qian XX, Wu WK, Zheng ZS, Yu BY, Lou HC, Lawson WE, et al. Effect of enhanced external counterpulsation on lipid peroxidation in coronary disease. J Heart Dis 1999;1:116(461).
12. Vilkas D, Suresh K, Lawson W, Hui JCK, D'Ambrosia D. Does enhanced external counterpulsation improve cardiac function in ischemic cardiomyopathy? J Investigative Med 2002;50:180A.
13. Lawson W, Pandey K, Hui JCK, Suresh K, D'Ambrosia D, Vilkas D. Benefit of enhanced external counterpulsation in ischemic cardiomyopathy, cardiac or peripheral effect? J Card Fail 2002;8:S41.