Analysis of Baseline Factors Associated With Reduction in Chest Pain in Patients With Angina Pectoris Treated by Enhanced External Counterpulsation

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Data from the International Enhanced External Counterpulsation (EECP) Patient Registry were analyzed to determine which patient characteristics influence improvement in angina class with EECP treatment. Patients with severely disabling angina at baseline, men, and those without a history of smoking are more likely to improve their angina class after EECP, whereas those with diabetes mellitus, prior bypass surgery, and heart failure were less likely to benefit. ©2003 by Excerpta Medica, Inc.

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Enhanced external counterpulsation (EECP) is a noninvasive medical device for treating patients with coronary disease. Three pairs of pneumatic cuffs are applied to the lower extremities and inflated and deflated in synchrony with the cardiac cycle. The cuffs are sequentially inflated (applying 250 to 300 mm Hg of external pressure) at the onset of ventricular diastole, returning blood in the lower extremities to the central circulation, producing aortic diastolic augmen-

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TABLE 1 Patient Characteristics and Medical History Before Enhanced External Counterpulsation (EECP)

Variable	(n = 4,592)
Age (yrs) (range)	66.7 ± 10.8 (30 101)
Men	75.1%
White	93.5%
Duration of coronary artery disease (yrs)	10.8 ± 8.2
Prior myocardial infarction	67.3%
Congestive heart failure	31.6%
Unstable angina pectoris	3.2%
Prior coronary angioplasty	65.0%
Prior coronary bypass	67.3%
Prior revascularization	85.7%
Multivessel coronary disease	75.2%
Left ventricular ejection fraction (%)*	46.5 ± 13.9
Diabetes mellitus	41.4%
Hypertension	70.0%
Hyperlipidemia	79.4%
Noncardiac vascular disease	30.3%
Past or present smoking	70.6%

*Ejection fraction was <35% for 18.7% of patients.

tation, and increasing venous return and cardiac output.[1] The cuffs are deflated at the end of ventricular diastole, decreasing peripheral resistance to flow and providing left ventricular unloading.[2] EECP is typically used to treat patients with angina refractory to conventional medical therapy and poor candidates for revascularization with angioplasty or bypass surgery. EECP has consistently been shown to be effective in treating patients with angina using various measures, including: improved functional class,[3,4] reduced anginal symptoms,[5,6] improved quality-of-life indexes,[7–9] improved stress radionuclide perfusion,[10,11] increased exercise time,[12,13] and increased time to ST-segment depression.[14] Treatment with EECP has also been demonstrated to increase nitric oxide levels and decrease malondialdehyde, a marker of lipid peroxidation, as well as to decrease endothelin-1 levels.[15–17] The benefit of EECP has been shown to be sustained at 3 and 5 years after treatment by radionuclide stress testing and quality-of-life measures.[18,19]

The International EECP Patient Registry (IEPR) was organized to evaluateá across a broad range of providers and patientsá the patterns of use, safety, and efficacy of EECP by consecutively tracking the results and side effects of EECP therapy at participating centers (currently 106). This report summarizes the results of the IEPR. We characterized the patientsá demographics, evaluated the safety and effectiveness of EECP, and determined which patient characteristics predict a successful response to treatment with EECP.

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The IEPR at the Epidemiology Data Center of the University of Pittsburgh Graduate School of Public Health was initiated in January 1998 to sequentially trackà across a broad spectrum of participating providersá the demographics, entry characteristics, and outcomes of all patients with angina treated with EECP. The IEPR has completed enrollment of 5,000 patients who will be followed for 3 years. Patients who underwent their first EECP were used for the present analysis.

EECP was typically prescribed for 35-hour sessions, 1 hour/day, over a period of 7 weeks. During treatment sessions, patients were routinely monitored by electrocardiography, pulse oximetry, finger plethysmography; a nurse was in attendance, and a supervising physician was immediately available. An initial history and subsequent interval history was obtained before each treatment, at the end of therapy, and at 6 months after treatment. Interval end points included an evaluation of Canadian Cardiovascular Society (CCS) anginal functional class, angina frequency, nitroglycerin use, changes in medications, quality of life, and interim events (major adverse cardiovascular events such as death, myocardial infarction, and revascularization). Success was defined as a decrease of at least 1 CCS angina class after a course of treatment.

Univariate associations between patient baseline characteristics and angina reduction were examined using chi-square tests for categoric variables and Wilcoxon tests for continuous variables. Significance was defined as $p < 0.05$. Logistic regression analysis was used to determine independent predictors decreases in angina class. All factors showing an association with reduction in angina with a p value of <0.2 were put into the model and a backward selection technique was used to determine significant independent predictors. Additional analyses were done to determine independent predictors of a decrease in angina class for those with and without severe (CCS class III or IV) angina.

As of June 2002, there were 5,000 patients enrolled from 106 EECP treatment sites (6 international and 100 in the United States).[20] Only patients with no previous EECP treatment on enrollment in the Registry were analyzed in this report (n = 4,592). Patients completed a mean of 34 ± 10 hours of treatment, with 83.1% completing the course as prescribed. Patientsá characteristics, medical history, and cardiovascular risk factors at the start of EECP are listed in Table 1. Cardiac medications included β blockers (65.7%), calcium channel blockers (46.1%), angiotensin-converting enzyme inhibitors (38.3%), angiotensin receptor blockers (10.0%), long-acting nitrates (74.8%), lipid-lowering medications (67.5%), and aspirin (70.9%).

Major adverse cardiovascular events occurring over the course of therapy were low and included death in 0.3% of patients, myocardial infarction in 0.9%, coronary bypass in 0.2%, and angioplasty in 0.8%. Exacerbation of heart failure was noted in 1.9% of patients and unstable angina in 2.8%. These latter events were not attributed to EECP by the investigators. There were no reported incidences of pulmonary embolism. Minor adverse events included 1.4% of patients with skin breakdown and 1.0% with musculoskeletal problems attributable to EECP treatment. No clinically important arrhythmias were reported, suggesting that arrhythmias are not a major concern during EECP.

It is well known that the amplitude or area under

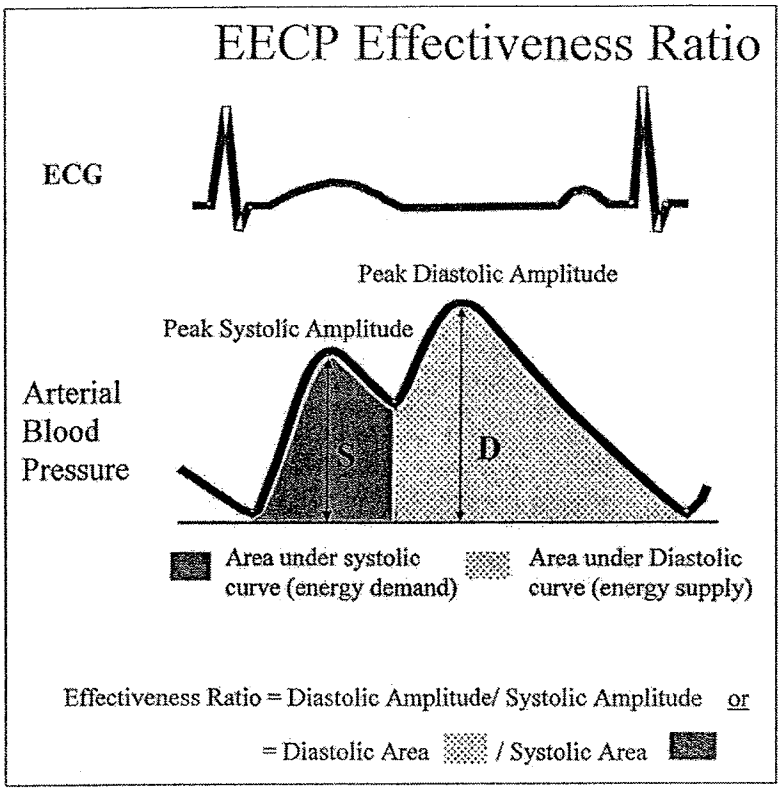

FIGURE 1. Operation of EECP and hemodynamic effectiveness. ECG = electrocardiogram.

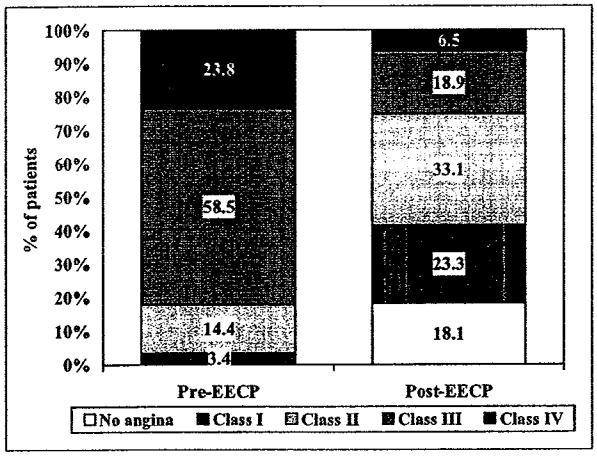

FIGURE 2. Changes in CCS angina class before and after EECP.

the systolic blood pressure waveform represents myocardial workload and the amplitude or area under the diastolic waveform reflects coronary perfusion pressure and myocardial oxygen supply. Therefore, the ratio of peak diastolic amplitude to peak systolic amplitude could potentially serve as an index of myocardial energy supply and demand, an indicator of the hemodynamic effectiveness of EECP treatment. A diagram of the calculation of the EECP effectiveness index is given in Figure 1. The average peak amplitude effectiveness index for the 4,592 patients analyzed in this study during the first hour of EECP treatment was 0.80 ± 0.5 and the last hour was 1.07 ± 0.6, an improvement of 33.8% ($p < 0.01$ using paired *t* test).

Angina status by the CCS classification for before and after treatment is shown in Figure 2. Patients in the IEPR cohort responded to EECP treatment; angina functional class improved ≥1 class(es) in 73% of treated patients, ≥2 classes in 38.2%, ≥3 classes in 17.3%, did not change in 26.0%, and worsened in 1.1%. Mean angina episodes per week at baseline were 10.1 ± 12.9 and decreased to 2.5 ± 5.8 episodes/week after EECP treatment. Baseline nitroglycerin use was 9.5 ± 11.9 times/week before EECP and decreased to 2.7 ± 6.5 times/week after EECP.

As shown in Figure 2, most patients (82.3%) were in CCS classes III or IV at baseline, and 75.5% of these patients reduced their angina by at least 1 class after EECP. Those with less severe angina (class I or II) still had a significant decrease in angina after EECP (61.9% of patients). Other factors that showed some association with a decrease in angina are listed at the top of Table 2. These included men, having never smoked, and the absence of heart failure, diabetes mellitus, and a prior coronary bypass. However, it should be noted that even patients with heart failure and diabetes mellitus, who were likely to have more extensive vascular disease and more severe ventricular dysfunction, achieved a success rate (as measured by a decrease in CCS class) of approximately 70%. Age and cardiac risk factors other than diabetes mellitus and smoking were not significant predictors. Using logistic regression modeling, significant independent predictors of angina reduction were higher angina class at baseline, men, and no history of smoking. Diabetes mellitus, heart failure, and prior coronary bypass were all associated with less angina reduction. Table 3 lists odds ratios and confidence intervals for these attributes.

Stratifying the model by severe (class III or IV) angina produced the results that are listed in Table 4. For patients with severe angina, the only significant independent predictor of angina reduction was the absence of heart failure. For patients with less severe (class I or II) angina, the only significant independent predictor of improvement in angina was history of smoking. Both diabetes mellitus and prior bypass surgery were associated with less angina reduction.

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A benefit from EECP was seen in all patient subgroups. Although patients with diabetes mellitus, heart failure, and prior bypass surgery showed less benefit with regard to the decrease of CCS angina class, the

TABLE 2 Reduction of Angina by at Least One Class Using Predictive Factors

Predictive Factor	Prevalence of Factor	Success Rate With Factor	Success Rate Without Factor	p Value
Class III or IV angina	82.3%	75.5%	61.9%	<0.001
Men	75.1%	73.8%	70.9%	0.056
Never smoked	29.4%	75.3%	72.1%	0.025
Diabetes mellitus	41.4%	71.1%	74.5%	0.010
Heart failure	31.6%	70.0%	74.7%	0.001
Prior bypass surgery	67.3%	72.6%	74.4%	0.200

TABLE 3 Odds Ratios for Predictors of Success* in Patients (n = 4,287) Who Underwent Enhanced External Counterpulsation (EECP)

Attribute	Odds Ratio	95% Confidence Interval
CCS angina class II vs I	2.03	1.41–2.92
CCS angina class III vs I	3.64	2.59–5.11
CCS angina class IV vs I	4.08	2.84–5.85
Men	1.24	1.06–1.46
Never smoked	1.26	1.08–1.47
Diabetes mellitus	0.75	0.65–0.87
Heart failure	0.84	0.73–0.96
Prior coronary bypass	0.83	0.71–0.96

*Success in EECP is defined as patients who have a decrease of ≥1 CCS angina class.

TABLE 4 Odds Ratios for Independent Predictors of Success* by Initial Severity of Angina in Patients Who Underwent Enhance External Counterpulsation (EECP)

Patient CCS Angina Classification Before EECP	Attribute	Odds Ratio	95% Confidence Interval
Class III or IV	Congestive heart failure	0.73	0.62–0.85
	Diabetes mellitus	0.69	0.51–0.94
Class I or II	Prior coronary bypass	0.67	0.50–0.90
	Never smoked	1.40	1.00–1.81

*Success in EECP is defined as patients who have a decrease of ≥1 CCS class.

overall success rate in these subgroups was approximately 70%. In practice, this translates into broad clinical utility across the usual patient subgroups. Overall, EECP was effective in improving angina by at least 1 CCS anginal class in 73% of patients. The importance of heart failure in these patients is emphasized by the finding that for the patients with the most severe angina, heart failure is the only independent factor associated with a decrease in angina class. Heart failure is often a reflection of extensive, established vascular disease and irreversible myocardial injury. Improvement in this setting may be limited or may require different dosing (additional hours of treatment). Previous IEPR reports showed only 77.9% of patients with heart failure completed therapy versus 86.2% of patients without heart failure.[20] Whether this reflects less treatment, less benefit, or dropout because of a lack of benefit remains to be determined. Despite this, over 77% of patients with heart failure achieve a decrease in angina class. In preliminary reports, EECP has increased maximal oxygen uptake and exercise tolerance in patients with heart failure.[21] This will be explored in the ongoing randomized multicenter trial of EECP in patients with heart failure patients (Prospective Evaluation of EECP in Congestive Heart Failure [PEECH]).

For the patients presenting with more mild or moderate angina, the presence of diabetes mellitus and prior coronary bypass assumes importance in determining treatment effect. It is not surprising that diabetes mellitus and prior coronary bypass emerged as predictors of a lower likelihood of benefit because both are clearly correlated with more extensive vascular disease. In addition, diabetics demonstrate impaired angiogenesis and endothelial function, and a propensity to atherothrombosis. It is somewhat surprising that a history of non-smoking predicted benefit. Most of the cardiovascular effects of smoking are relatively transient (vasoconstriction, endothelial damage, desaturation, hypercoagulability); the risk of ex-smokers eventually returns to the norm of non-smokers. The collected data do not permit further refinement of participantsá smoking habits. Further study is needed to clarify the relation of smoking to outcome.

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