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Frequency and Efficacy of Repeat Enhanced External Counterpulsation for Stable Angina Pectoris (from the International EECP Patient Registry)

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We assessed the frequency, efficacy, predictors, and long-term success of repeat enhanced external counterpulsation (EECP) therapy in relieving angina in a large cohort of patients who had chronic angina pectoris and had undergone a full course of EECP. Within 2 years of the initial course of EECP, the rate of repeat EECP was 18%, which occurred at a mean interval of 378 days after initial EECP. Of those who underwent repeat EECP, 70% had a decrease of ≥1 angina class at the end of repeat EECP with similar decreases in nitroglycerin use. ©2005 by Excerpta Medica Inc. **(Am J Cardiol 2005;95:394–397)**

Enhanced external counterpulsation (EECP) is used to manage disabling angina in medically refractory patients who are not candidates for conventional coronary revascularization. EECP (Vasomedical, Westbury, New York) is a noninvasive technique that has been shown to decrease angina pectoris and extend time to exercise-induced ischemia in patients who have stable angina.[1] In addition to relieving myocardial ischemia, EECP is associated with improved quality of life.[2,3] It uses sequential inflation of 3 sets of pneumatic cuffs wrapped around the lower extremities. The cuffs are inflated sequentially at the onset of diastole, producing aortic counterpulsation, diastolic augmentation, and increased coronary artery blood flow.[4] At the onset of systole, external pressure in the cuffs is released, producing a decrease in systolic pressure. A typical course of EECP involves 1 to 2 hours daily, for a total of 35 hours of therapy. The frequency and efficacy of repeat EECP therapy have not previously been investigated. This report examines the frequency, clinical patient characteristics, and early and long-term outcomes of repeat EECP in a large cohort of patients who had refractory angina pectoris. These issues are important for assessing the durability of initial therapy and the success rate of repeat therapy.

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The International EECP Patient Registry (IEPR) enrolls consecutive patients who undergo EECP for chronic angina. The IEPR began in January 1998, and >5,000 patients have been enrolled from >100 centers in the United States and other countries. Because the registry aims to collect data on as broad a range of patients as possible, the criteria for entry are only that the patient give informed consent and have ≥1 hour of EECP therapy for chronic angina.

The IEPR methods has been previously described.[5] All patients gave written informed consent before entry into the registry. Briefly, the IEPR methods involve collecting patient demographics, medical history, coronary disease status, and quality-of-life assessments before EECP therapy. After completion of EECP, data are collected on anginal status according to the Canadian Cardiovascular Society classification, medication use, and adverse clinical events. Quality of life was assessed by patients with a 5-point scale for health status, quality of life, and satisfaction with

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0002-9149/05/$–see front matter
doi:10.1016/j.amjcard.2004.09.041

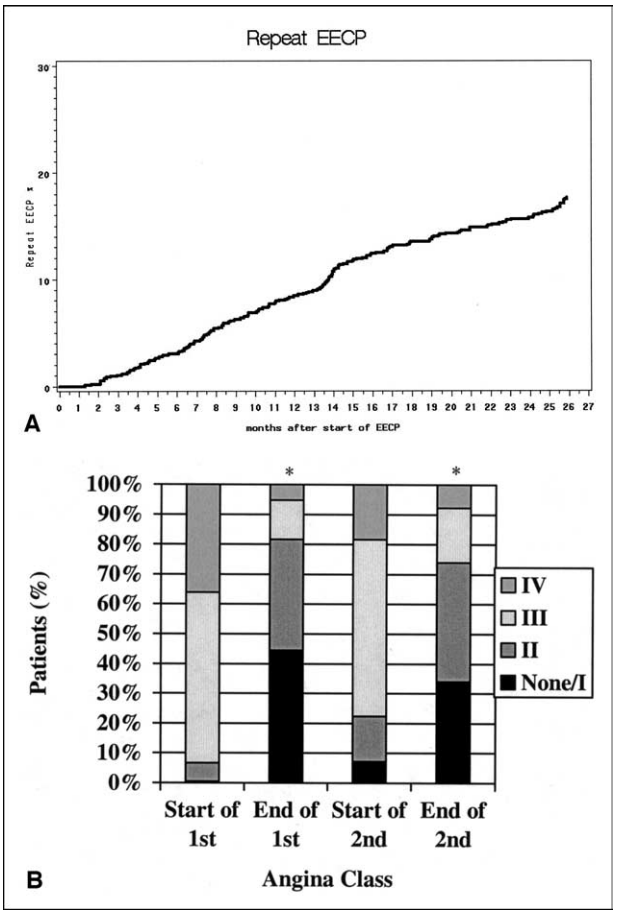

FIGURE 1. ***(A)*** **Cumulative rate of repeat EECP.** ***(B)*** **Angina classes at baseline, immediately after EECP, before repeat EECP, and after repeat EECP among patients who underwent repeat EECP. *p <0.01 versus course before therapy.**

TABLE 1 Patient Characteristics Before First Hour of Enhanced External Counterpulsation by Repeat Treatment

Variable	Patients With Repeat EECP (n = 194)	Patients Without Repeat EECP (n = 998)
Age (yrs)	67 ± 11	66 ± 11
Men	77%	76%
Caucasian	97%	96%
Previous percutaneous coronary intervention	74%	68%
Previous coronary bypass*	79%	70%
Previous myocardial infarction	69%	72%
Congestive heart failure	33%	30%
Noncardiac vascular disease	30%	31%
Diabetes mellitus	38%	42%
Hypertension*	77%	69%
Hyperlipidemia	82%	83%
Smoker, current or previous*	62%	70%
Angina class‡		
I	1%	12%
II	6%	8%
III	57%	68%
IV	36%	22%
Angina episodes/wk‡	11 ± 10	15 ± 16
Nitroglycerin use†	84%	75%
Nitroglycerin frequency/wk†	9 ± 12	13 ± 14
Medications		
β blockers	81%	75%
Calcium blockers	52%	47%
Angiotensin-converting enzyme inhibitors	42%	41%
Angiotensin receptor blockers	12%	9%
Nitrates	83%	80%
Lipid-lowering agents	76%	76%
Aspirin/antiplatelet agents	78%	77%
Candidate for coronary angioplasty*	15%	10%
Candidate for coronary bypass	12%	10%

*p <0.05; †p <0.01; ‡p <0.001.

TABLE 2 Variables Associated With Repeat Enhanced External Counterpulsation Within Two Years

Variable	Repeat EECP Rate*	p Value†
All patients	18%	
Age <65 yrs	17%	0.96
Men	18%	0.64
Women	16%	
Severe (class III/IV) angina	18%	0.12
Previous coronary bypass	20%	0.01
Previous percutaneous coronary intervention	19%	0.05
Hypertension	19%	0.01
Smoker	16%	0.03

*Kaplan-Meier rates at 791 days after the first day of EECP.
†Log-rank test.

quality of life. Patients are interviewed by telephone 6 and 12 months after the last EECP session and yearly thereafter for 3 years to record anginal status, quality of life, and cardiac events.

In statistical analyses, data are presented as percentages for categorical variables or as mean ± SD for continuous variables. Differences between groups were examined with chi-square test for categorical variables and unpaired *t* test for continuous variables. Repeat rates for EECP were estimated with Kaplan-Meier survival analysis; the log-rank test was used to test differences between groups. Comparisons between first and second courses of EECP were made with McNemar's test or paired *t* test. A 2-tailed p value <0.05 was considered statistically significant.

This study examined 1,192 patients from 29 sites who underwent a first course of EECP for chronic angina pectoris, completed a full course of 35 hours, and were enrolled in the IEPR at sites that reported ≥85% follow-up status at 2 years. Patients were 66 ± 11 years old, and 76% were men. Most had previous revascularization, and only 14% were considered suitable for further invasive revascularization. Anginal symptoms were severe, with 90% reporting Canadian Cardiovascular Society class III or IV at baseline, with a mean angina frequency of 11 episodes/week. Nitroglycerin was used by 81% of patients, β blockers by 76%, calcium channel blockers by 48%, and hypolipidemic agents by 76%. After the initial course of EECP, 86% of patients reported a decrease of ≥1

TABLE 3 Angina Symptom Relief After First and Second Courses of Enhanced External Counterpulsation for Patients Undergoing Repeat Treatment

	First Course	Second Course
Angina class before EECP‡		
I	1%	7%
II	6%	15%
III	57%	59%
IV	36%	18%
Mean hours of EECP therapy‡	38 ± 7	29 ± 13
Angina class after EECP		
0/I	45%	34%
II	37%	40%
III	13%	18%
IV	5%	8%
Angina decreased ≥1 class‡	89%	70%
Episodes angina/wk before EECP‡	15 ± 16	10 ± 12
Episodes angina/wk after EECP‡	3 ± 5	4 ± 7
Nitroglycerin use before EECP†	85%	77%
Nitroglycerin use after EECP	42%	51%
Nitroglycerin frequency/wk before EECP	13 ± 14	11 ± 11
Nitroglycerin frequency/wk after EECP‡	2 ± 4	7 ± 9

*p <0.05;†p <0.01; ‡p <0.001.

TABLE 4 Angina Severity at Two-year Follow-up

	Repeat EECP	
	Yes (n = 181, 94%)	No (n = 878, 88%)
Days from first EECP course	795 ± 47	
Days from second EECP course	414 ± 217	
Angina class‡		
0/I	31%	52%
II	28%	31%
III	31%	15%
IV	10%	2%
Episodes/week†	6 ± 10	3 ± 7
Nitroglycerin use‡	63%	45%
Frequency/wk	8 ± 12	7 ± 11

Values are means ± SD or percentages.
†p <0.01; ‡p <0.001.

Canadian Cardiovascular Society class and nitroglycerin use was discontinued by 57% of patients.

Within 2 years of finishing therapy, 194 patients (Kaplan-Meier rate 18%; Figure 1) underwent a repeat course of EECP. Among those patients who underwent repeat EECP, 152 (78%) had available data on the second course. Reasons for repeat EECP were persistent angina in 38% of patients and increasing angina in 62%. Time to repeat EECP was 378 ± 207 days (range 40 to 791). Repeat EECP occurred ≤1 year in 62% of patients (Figure 1).

Table 1 lists demographic characteristics of those patients who returned for repeat EECP compared with those who did not return. There were few significant differences between groups. Baseline characteristics associated with a higher rate of return are presented in Table 2. Age and gender were not associated with differences in rates, but previous revascularization (coronary artery bypass grafting or percutaneous coronary intervention), history of hypertension, and nonsmoking were associated with a higher rate of return. The rate of repeat EECP for patients who reported an initial anginal decrease was 19% compared with 12% for those who had no initial decrease ($p = 0.07$). Among those who underwent repeat EECP, 70% demonstrated a significant decrease in angina (Figure 1 and Table 3), and, although this was significantly less than the 89% of patients who had initially achieved a decrease in angina, the distribution of Canadian Cardiovascular Society class after a second course was not statistically different from that after the first course. At 2-year follow-up, anginal symptoms remained significantly worse in patients who had repeat EECP (Table 4). Fifty-nine percent of patients who had repeat EECP also had class 0 to 2 angina compared with 82% of those who did not undergo repeat EECP ($p <0.001$). Nitroglycerin use was more common in patients who underwent repeat EECP (63%) than in those who did not (45%, $p <0.001$).

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This report documents the incidence and clinical outcomes of patients who underwent repeat EECP for chronic stable angina pectoris. Compared with patients who did not undergo a second course, those who did had more severe angina and a higher incidence of previous revascularization, but there was little difference with respect to age, gender, risk factors for coronary disease, incidence of heart failure, medication use, or quality of life.

A minority of patients (18%) enrolled in a second course of EECP for persistent or increasing angina. Repeat EECP most commonly occurred ≤1 year of completing the initial course. Patients who underwent repeat EECP had a decrease in angina and a concomitant decrease in nitroglycerin use after the second course of therapy. Those patients who showed a greater symptomatic response to initial therapy may have been more willing to undergo a second course of therapy, or physicians may have been more likely to refer patients who had been treated successfully for a repeat course if recurrent symptoms developed. At 2 years, those patients who underwent a second course of therapy had worse angina compared with those who did not undergo a second course. Patients who underwent repeat EECP did benefit from the 2 courses of therapy but they did not sustain the symptomatic improvement.

With any interventional therapy for symptomatic ischemic heart disease, it is important to understand the frequency and efficacy of repeat therapy. The 18% rate for repeat EECP in this cohort of patients who had refractory angina is comparable to the rate of repeat revascularization with bare metal stents. In the SIRIUS study, patients who had a single de novo lesion were assigned at random to receive bare stenting versus sirolimus-coated stenting. Patients assigned to the bare stent arm had a 17% rate of target vessel revascularization at 9 months compared with the 4% rate in those assigned to the sirolimus stent arm.[6] In the Arterial Revascularization Therapies Study

(ARTS) trial, which randomized patients who had multivessel disease to coronary artery bypass grafting or percutaneous coronary intervention with bare stents, the 1-year rates for repeat revascularization were 16% for percutaneous coronary intervention and 2% for coronary artery bypass grafting.[7] Thus, the repeat EECP rate is comparable to the repeat revascularization rate with bare stenting but appears higher than that for coronary artery bypass grafting or for single lesions with drug-eluting stents. It is noteworthy that the rate of repeat EECP was low in this cohort of highly symptomatic patients who had multivessel disease in whom further conventional revascularization was not feasible.

Reimbursement guidelines may have influenced the referral of patients for retreatment and the duration of retreatment prescribed. Commonly, third-party payers will approve an initial full course of 35 hours of therapy but have variable policies regarding approval for retreatment. Policies range from no retreatment coverage to full-course approval. Most coverage decisions are based on medical necessity (and lack of alternative therapies) and approve a limited (10 to 12 hours) period of additional EECP unless sufficient time has elapsed between courses (6 months to 1 year). The rationale most commonly cited for these decisions is that retreatment is most likely to be effective in those patients who have demonstrated an initial response to therapy. Retreatment for incomplete initial treatment in particular may have been influenced by previous payer approval for a 35-hour course of therapy in terms of referral for retreatment and in the duration of the retreatment prescribed. In this study, we did not collect medical insurance data.

One limitation of this analysis is the lack of a control group to assess the extent of reported improvement due to other interventions (i.e., medical therapy, lifestyle modifications, or coronary revascularization) or to a "placebo effect" that may be expected in a population of highly symptomatic patients enthusiastic for an emerging novel therapy. One study compared clinical demographics and clinical outcomes from patients who had been enrolled in the IEPR and those who had been enrolled in the National Heart, Lung, and Blood Institute Dynamic Registry and underwent elective percutaneous coronary intervention.[8] However, there are significant challenges in identifying a proper comparison group and interpreting differences in outcomes from different registries. Self-reported angina severity based on mail or telephone interview is subject to potential bias, although coordinators in the IEPR were trained in the assessment and definitions of follow-up symptoms. Selection and survival bias may have accounted for differences among patients who were or were not available for 2-year follow-up. To minimize these potential biases, we only reported on patients from sites with ≥85% follow-up retention.

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