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Two-Year Outcomes in Patients with Mild Refractory Angina Treated with Enhanced External Counterpulsation

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Summary

Background: In the International Enhanced External Counterpulsation Patient Registry (IEPR), approximately 85% of the patients treated are in Canadian Cardiovascular Society (CCS) class III–IV with no option for further invasive coronary revascularization procedures.

Hypothesis: This study sought to determine whether it is clinically important to establish whether the observed durable reduction in disabling severe angina with enhanced external counterpulsation (EECP) treatment can be extended to those with less severe CCS class II angina, who also have no option for further revascularization.

Methods: This study evaluated the immediate response, durability and clinical events over a 2-year period after EECP treatment in 112 patients with Canadian Cardiovascular Society (CCS) class II angina versus 1,346 patients with class III–IV angina using data from the International EECP Patient Registry (IEPR).

Results: Treatment with EECP significantly (by at least one CCS class) reduced angina frequency, nitroglycerin use, and improved quality of life in both groups. At 2-year follow-up, 74% of class II and 70% of class III–IV patients remained free of major adverse cardiovascular events (MACE) and continued to demonstrate a durable CCS class improvement over baseline.

Conclusion: The robust effectiveness of EECP as a noninvasive device, together with its relatively low start-up and recurrent costs, makes it an attractive consideration for treating patients with milder refractory angina in addition to the patient with severely disabling angina treated in current practice.

Key words: noninvasive, 2-year outcome, enhanced external counterpulsation, angina

Introduction

Enhanced external counterpulsation (EECP) is a noninvasive device for the treatment of patients with coronary artery disease. It consists of three pair of pneumatic cuffs wrapped around the lower extremities. The cuffs inflate sequentially at the beginning of diastole and deflate during systole, producing systolic unloading and diastolic augmentation as well as increasing venous return.[1] Enhanced external counterpulsation has been shown to be effective in treating disabling angina in patients refractory to medical or surgical therapy, consistently reducing angina in about 75% of patients treated.[2–4] In the International EECP Patient Registry (IEPR), approximately 85% of the patients treated are in Canadian Cardiovascular Society (CCS) class III–IV with no option for further invasive coronary revascularization procedures.[5] As outlined in the American College of Cardiology/American Heart Association

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(ACC/AHA) guidelines for stable angina, treatment is aimed at complete, or nearly complete, elimination of anginal chest pain and a return to normal activities.[6] It is clinically important to establish whether the observed durable reduction in disabling severe angina with EECP treatment can be extended to those with less severe CCS class II angina, who also have no option for further revascularization.

In patients with limited revascularization possibilities, treatment with EECP is an attractive alternative possibility if sustained benefit can be demonstrated. This treatment ameliorates the neurohumoral and endovascular dysfunction[7] that promotes clinical vascular disease. There is increasing interest in the use of EECP in patients with established coronary disease for whom EECP might be used as an alternative to traditional revascularization, extending to a potential role in secondary and primary prevention of cardiovascular events.[7]

Currently, EECP treatment is largely restricted to patients with refractory and severely disabling angina partly because of reimbursement coverage of only patients with CCS class III and IV angina by the Centers for Medicare and Medicaid Services (CMS). The present study was conducted to evaluate the potential benefit of EECP in treating refractory patients with less severely disabling (CCS class II) angina. The immediate response to treatment of patients with CCS class II angina receiving a course of EECP and the durability of response and clinical events over a 2-year follow-up were evaluated and contrasted to the more commonly EECP-treated patients with severe disabling angina.

Methods

Data of consecutive patients treated with EECP in various centers ranging from single cardiologist practices to teaching medical centers were collected in the IEPR at the University of Pittsburgh, as described previously.[8,9] Briefly, the IEPR was initiated in January 1998 and has enrolled over 5,000 patients from more than 100 centers throughout the world. All patients had angina, received one or more hours of EECP treatment, and gave informed consent for follow-up. At entry, data were collected on demographics, medical history, coronary disease status, quality of life and medications. Typically, EECP was prescribed as a course of treatment of 1–2 h/day, 5 days/week, and lasting 4–7 weeks for a cumulative total of 35 h. This standard treatment course was not mandated for inclusion in the IEPR and could be altered by the patient's clinical course and response to therapy. Patients were included in this study regardless of whether they completed the original planned course of treatment.

Post-treatment follow-up included evaluation of symptom status, medication use, adverse clinical events, additional interventions, and quality of life. Major adverse cardiovascular events (MACE) were defined as including all cause mortality, nonfatal myocardial infarction, and revascularization with angioplasty or bypass surgery. Follow-up was performed at subsequent visits or by phone interview at 6 months and 1, 2, and 3 years after the last EECP treatment.

Statistical Analysis

Discrete variables were analyzed by chi-square testing and continuous variables by Wilcoxon rank sum test. Significance was defined at $p < 0.05$. Kaplan-Meier life table analysis was used to determine the rate of MACE up to 790 days after the start of EECP therapy.

Results

A cohort of 1,458 patients from 30 sites with 2-year follow-up data was analyzed. There were 112 patients (8%) in CCS class II and 1,346 (92%) in class III and IV. The average total EECP treatments were 34.5 ± 7.9 h in class II and 33.6 ± 9.9 h in class III and IV. In the class II group, 10% of the patients failed to complete the 30 or more hours of EECP treatment as prescribed (5% because of personal reasons, 5% because of clinical events). In the class III and IV group, 16% failed to complete the EECP treatment course (7% because of personal reasons, 9% because of clinical events).

Both CCS class II and class III–IV cohorts were comprised of high-risk groups of patients who were not candidates for revascularization, had mild-to-moderate left ventricular dysfunction (13 ± 9% in class II and 14 ± 20% in class III/IV had ejection fractions < 35%), and a high prevalence of diabetes mellitus and multivessel disease (Table I). There were demographic and clinical differences noted between the patient cohorts with CCS class II and class III–IV angina. The class II cohort had a significantly greater proportion of men, and fewer

TABLE I Demographics and clinical characteristics by angina class

	CCS class II	CCS class III/IV
Number of patients	112	1,346
Age (years) ± SD	66 ± 12	66 ± 11
Male gender (%) [a]	85	74
Systolic HBP (%) [a]	62	72
Hyperlipidemia (%)	82	83
Diabetes mellitus (%)	38	43
Smoking past or present (%) [a]	64	73
CAD duration (years) ± SD	10 ± 8	12 ± 8
Prior MI (%)	68	72
Multivessel CAD (%)	72	79
Heart failure (%) [b]	22	34
LV ejection fraction (%) ± SD	49 ± 13	46 ± 14
Prior revascularization (%)	84	90
Noncardiac vascular disease (%)	24	32
Family history of CAD (%)	77	80
Not candidate for revascularization	76	87

[a] $p < 0.05$.
[b] $p < 0.01$.
Abbreviations: SD = standard deviation, CCS = Canadian Cardiovascular Society, HBP = home blood pressure, CAD = coronary artery disease, MI = myocardial infarction, LV = left ventricular.

TABLE II Medications (% of patients) at baseline and post-enhanced external counterpulsation (EECP) treatment by CCS class

	Baseline		Post EECP	
Medications	Class II	Class III/IV	Class II	Class III/IV
Beta blockers	77	77	75	78
Ca channel blockers	44	48	40	47
ACE inhibitors [a, c]	30	44	31	44
ARB	12	10	10	9
Nitrates (long acting) [b, d]	64	83	60	81
Lipid lowering	77	77	80	78
Aspirin	78	78	83	80

[a] $p < 0.01$.
[b] $p < 0.001$ comparing groups at baseline.
[c] $p < 0.01$.
[d] $p < 0.001$ comparing groups post EECP.
There was no significant difference in medication comparing baseline with post-EECP treatment for both class II and class III/IV groups.
Abbreviations: CCS = Canadian Cardiovascular Society, Ca = calcium, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker.

patients with hypertension, heart failure, and history of smoking. Medications were essentially the same in both groups except for a significantly lower use of angiotensin-converting enzyme (ACE) inhibitors and long-acting nitrates (Table II) and prn SL nitroglycerin use (Table III) in the cohort with CCS class II angina. Medication use, except for SL nitroglycerin use, did not change significantly during the course of EECP.

Treatment with EECP significantly reduced angina frequency (Table IV), percent of patients taking SL nitroglycerin routinely, and frequency of SL nitroglycerin use (Table III), and improved quality of life measures (Table V) in both groups immediately post treatment. These effects were largely sustained and remained significantly improved over baseline at 2 years post treatment. Despite qualitatively similar results, angina frequency and SL nitroglycerin use remained significantly greater in the patients in CCS class III–IV at all time points (Tables III, IV). Reduction of CCS angina class after EECP treatment and at 2-year follow-up was significant for both groups ($p < 0.001$). Angina was reduced at least one CCS class in 61% of patients in class II immediately post therapy compared with 78% of patients in CCS class III–IV ($p < 0.001$). The difference in patients who remained free of MACE or repeat EECP treatment remained significant at 2 years: 70% of those in class II demonstrated a persistent reduction of at least one angina class compared with 81% of those in class III–IV ($p < 0.05$). Figure 1 illustrates the distribution of CCS angina class at baseline, immediately post EECP therapy, and at 2 years post therapy.

Major adverse cardiovascular events were uncommon during therapy (2.7% in class II and 2.1% in class III–IV) and not significantly different between the two cohorts. At 2-year follow-up, MACE had occurred in 26% of patients in class II and 30% of those in class III–IV (p = NS; Table VI). A Kaplan-Meier plot of major cardiovascular event-free survival rate up to 790 days after the first day of EECP treatment in CCS class II versus class III–IV is shown in Figure 2. In this group of high-risk patients, 74% of class II and 70% of class III–IV patients remained free of MACE (death, myocardial infarction [MI], revascularization; p = NS) and continued to demonstrate a durable CCS class improvement over baseline.

TABLE III Sublingual (SL) nitroglycerin use (percentage of patients using SL nitroglycerin over the course of a week) and frequency of SL nitroglycerin use (number of times/week)

	Baseline	Immediately post EECP	Two years post EECP
% of patients			
CCS II (%)	61	23	43
CCS III and IV (%)	79	41	50
P value	<0.001	<0.001	NS
Frequency of use			
Class II	4.1 ± 8.2	1.1 ± 3.0	1.9 ± 4.4
Class III and IV	8.4 ± 12.5	2.4 ± 6.2	3.4 ± 9.0

Percentage of patients and frequency of SL nitroglycerin was significantly different between groups ($p < 0.001$) at all time points, and use of SL nitroglycerin significantly decreased in both groups post treatment ($p < 0.001$). This effect was sustained for all angina classes at 2 years post treatment ($p < 0.001$).
Abbreviations as in Table II.

TABLE IV Weekly angina frequency (number of episodes/ week)

	Baseline	Immediately post EECP	Two years post EECP
CCS II	6.7 ± 10.2	1.7 ± 4.9	2.4 ± 4.2
CCS III–IV	12.2 ± 13.8	3.1 ± 7.0	4.1 ± 8.7

Angina frequency was significantly higher in CCS III–IV at all time points ($p < 0.001$) and was significantly improved in both groups with treatment ($p < 0.001$). This effect was sustained in both groups at 2 years post treatment ($p < 0.001$).
Abbreviations as in Table II.

TABLE V Percentage of patients demonstrating improvement in quality-of-life measures by time and angina class

	Immediately post EECP		Two years post EECP	
	CCS II	CCS III–IV	CCS II	CCS III–IV
Health (%)	58	52	38	48
Quality of life (%)	60	52	44	51
Satisfaction (%)	56	57	39	53

There was a significant improvement from baseline in all measures of quality of life sustained at 2 years post treatment ($p < 0.001$).
Abbreviations as in Table II.

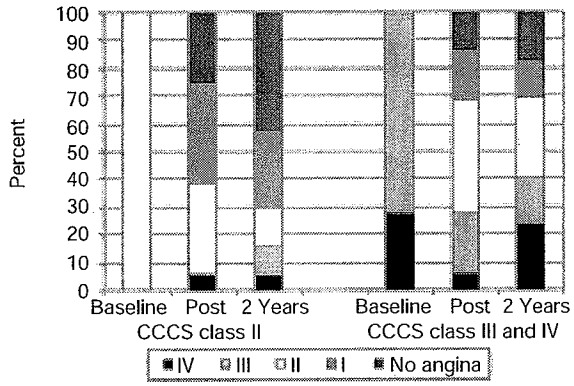

FIG. 1 Distribution of Canadian Cardiovascular Society (CCS) angina classes at baseline, after enhanced external counterpulsation treatment and at 2-year follow-up of patients with CCS class II and class III–IV angina, including patients with major adverse cardiovascular events (death, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft).

TABLE VI Major adverse cardiovascular events by time and angina class

	Immediately post EECP		Two years post EECP	
	CCS II	CCS III–IV	CCS II	CCS III–IV
Death (%)	0	0.4	4.6	10.8
MI (%)	0	0.7	6.5	8.8
CABG (%)	0	0.3	9.6	5.2
PCI (%)	2.7	0.8	12.9	12.6
MACE (%)	2.7	2.1	25.7	30.1

Individual events are not mutually exclusive. There was no significant difference between CCS class II and CCS class III/IV cohorts at 2 years in overall events.

Abbreviations: CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, MACE = major adverse cardiovascular events. Other abbreviations as in Table I and II.

Discussion

While there were no significant differences in the individual major cardiovascular endpoints at 2 years between the CCS class II and CCS class III–IV cohorts, there was also no significantly higher rate of combined MACE in the CCS class III–IV group. This is consistent with the paucity of differences between the two cohorts at baseline that would have predicted a greater risk of MACE in the CCS class III–IV group. The CCS angina class is a relatively minor predictor of prognosis and freedom from events compared with the extent and severity of coronary artery disease and left ventricular dysfunction. Despite this, CCS angina class has been shown to be linearly associated with increasing rates of percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG), as well as all-cause mortality and nonfatal MI.[10–12]

Revascularization has demonstrable mortality benefits in certain defined subsets of patients with coronary artery disease (e.g., left main, triple-vessel with compromised ventricular function). However, perhaps the major objective in most patients undergoing revascularization has been the relief of angina and improvement in quality of life. Successful sustained relief of angina with revascularization by angioplasty and bypass surgery is limited by procedural success, completeness of revascularization, and complications, which include death. In about 20% of patients after bypass surgery, overall quality of life does not improve, and approximately 25% of patients have recurrent angina within a year after surgery. Predictors of recurrent angina have included past angioplasty, heart failure, and time from surgery. Predictors of limited physical function post revascularization have included age > 75 years, female gender, diabetes, peripheral vascular disease, heart failure, and angina. Predictors of poor quality of life have included female gender, diabetes, peripheral vascular disease, and low ejection fraction. The strongest independent predictors of improvement in the quality of life 1 year after angioplasty include baseline angina frequency and physical functioning. The benefits of invasive revascularization are closely related to baseline CCS class.[13–15]

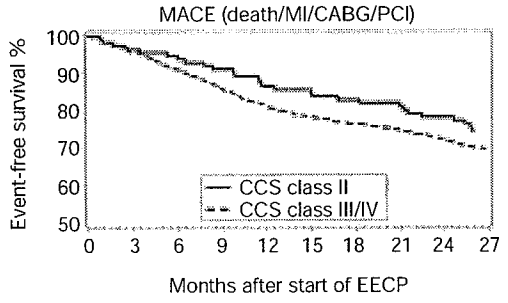

FIG. 2 Kaplan-Meier plot of major cardiovascular event-free survival by initial CCS class II versus class III–IV. Abbreviations as in Figure 1.

Enhanced external counterpulsation was effective in producing significant durable (2-year) improvement in the severity and frequency of angina, nitroglycerin use, and the quality of life in both CCS class II and class III–IV angina cohorts. As has been reported for invasive revascularization, the greatest improvement at 2 years post EECP was noted in the patients most severely disabled at baseline (CCS class III–IV). There was a low drop-out rate and low incidence of treatment complications in both groups, which may be contrasted with periprocedural morbidity and mortality associated with traditional revascularization.

The stated goal of angina treatment is to minimize angina. Preliminary cost-effectiveness analyses using Markov processes have shown EECP to provide a favorable cost-effectiveness ratio over medication alone, the additional use of EECP approximating $3,126 per quality-adjusted life year. However, the cost effectiveness is greatest in patients with severely disabling angina; in patients with less severe angina, the same re-

sources (35 h of EECP) produces a significant but lesser cost effectiveness.

Conclusions

In patients who have CCS class II angina and who are refractory to medical therapy and poor candidates for revascularization, EECP is effective in producing a sustained reduction in the severity and frequency of angina and improved quality of life. The benefit and durability are largely comparable with those seen in patients with severely limiting angina (CCS class III–IV). The robust effectiveness of EECP as a noninvasive device, together with its relatively low start-up and recurrent costs, makes it an attractive consideration for treating patients with milder refractory angina in addition to the patient with severely disabling angina treated in current practice.

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