Residual high-grade angina after enhanced external counterpulsation therapy[☆]

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Abstract

Objective: We evaluated the degree of residual angina on the outcomes of enhanced external counterpulsation (EECP) therapy for chronic stable angina.

Background: Angina refractory to medical therapy is common in the pool of patients who are not completely revascularized by angioplasty or bypass surgery.

Methods: We examined 902 patients enrolled from 1998 to 2001 in the Second International Enhanced External Counterpulsation Patient Registry. Baseline and outcome variables were stratified by the last recorded Canadian Cardiovascular Society class.

Results: Residual Class 3 (12.1%) or 4 (2.3%) angina was uncommon among patients with severe coronary artery disease after treatment with EECP. Prevalence of diabetes, hypertension, dyslipidemia, and heart failure was similar among the anginal post-EECP anginal classes. Multivessel coronary disease was more common in those with higher-grade angina at completion. More frequent and severe angina at entry was more common in those with the higher anginal classes at EECP ($P<.001$). There were no differences in the rates of chronic medications utilized or prior revascularization. At 3-year follow-up, rates of death, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery tended to be higher across increasing residual angina classes. The composite cardiac event rates were 34%, 33%, and 44% for those with Class 0, Class 1/2, and Class 3/4 angina at EECP completion ($P=.01$), respectively. Multivariate analysis for the composite endpoint found residual Class 3/4 angina (OR=1.59, 95% CI=1.19–2.17, $P=.002$), diabetes (OR=1.57, 95% CI=1.23–2.01, $P=.0003$), age (per decile OR=1.17, 95% CI=1.04–1.31, $P=.007$), and greater EECP augmentation (OR=0.79, 95% CI=0.65–0.96, $P=.02$) as significant predictors.

Conclusions: Residual high-grade angina after EECP occurs in those with more severe angina and multivessel disease at baseline and is associated with cardiac events over the next 3 years. These data suggest that close clinical observation and intensive management of those with high-grade angina post-EECP are warranted.
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1. Introduction

Enhanced external counterpulsation (EECP) was cleared for marketing by the Food and Drug Administration in 1995 for use in stable and unstable angina, acute myocardial infarction (MI), and cardiogenic shock and in 2002 for use in heart failure (HF) [1,2]. The Centers for Medicare and Medicaid Services approved coverage of EECP in 1999 for use in patients with angina refractory to maximal medical therapy and attempts at percutaneous and/or surgical coronary revascularization. EECP is a noninvasive counterpulsation technique that has been shown to reduce angina pectoris, to improve quality of life, and to extend time to exercise-induced ischemia in patients with symptomatic stable angina [3].

Previous studies have shown that the degree of diastolic augmentation during EECP can impact the short- and long-term antianginal benefits with this therapy [4]. While most patients have a clinical reduction in their angina and use of nitroglycerin, the outcomes of those with high-grade Class 3–4 angina after completion of EECP have not been previously described.

2. Methods

2.1. Patients

The Second International Enhanced External Counterpulsation Registry (IEPR-2) enrolled 902 consecutive patients from January 1998 to October 2001 in whom mortality was available at the 3-year time point after completion of EECP [5]. Data came from 18 clinical sites, which, on average, performed EECP, one session per day, 5 days a week, for 7 weeks on each patient. Since the IEPR was designed to collect data on as broad a range of patients as possible, the criteria for entry were only that the

patient gave informed consent and had at least 1 h of EECP treatment for chronic angina. Upon completion and exit of the EECP program, the Canadian Cardiovascular Society (CCS) anginal class was assigned by trained physiologists, nurses, and physicians who cared for the patients during EECP.

The IEPR methodology has been previously described [5]. All patients gave written informed consent prior to entry into the registry. Briefly, the registry methodology involved collecting patient demographics, medical history, coronary disease status, and quality of life assessments prior to EECP treatment. After 35 h of standard EECP treatment (Vasomedical, Inc., Westbury, NY), data were collected on CCS anginal class and interim clinical events.

2.2. Statistical analysis

Data are presented as percentages for categorical variables or as mean values and standard deviations for continuous variables. Chi-square, chi-square for trend, and one-way analysis of variance were used as test statistics as appropriate. A P value <.05 was considered statistically significant. Multivariate analysis was done using a logistic regression model with a backward selection technique. There were 902 complete cases used in the model, and there were 308 events [composite of death, MI, percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG)].

3. Results

3.1. Baseline characteristics

Baseline characteristics according to CCS group are given in Table 1. Residual Class 3 (12.1%) or 4 (2.3%) angina was uncommon among patients with severe coronary

Table 1
Baseline demographics, clinical characteristics, and cardiac medications according to the final CCS anginal class

	No angina	Class 1	Class 2	Class 3	Class 4
Number of patients	145	175	438	123	21
Demographics					
Age, in years (mean±S.D.)	67.2±10.5	65.7±10.8	66.1±10.5	67.0±11.1	64.2±11.5
Male gender (%)	82.8	80.0	73.2	72.4	76.2
White race (%)	97.9	94.2	95.4	96.7	95.0
Medical history					
Time (in years) since CAD diagnosis (mean±S.D.)	11.1±7.4	10.4±7.5	11.3±8.4	11.5±9.0	12.3±6.1
Prior PCI or CABG (%)	90.8	85.3	85.9	90.6	85.7
Prior MI (%)	77.9	71.7	70.5	69.4	71.4
Congestive HF (%)	36.4	27.9	25.4	37.3	52.4
Risk factors					
Family history of CAD (%)	87.4	77.0	81.1	80.2	85.0
Diabetes (%)	36.6	44.3	39.9	45.8	52.6
Hypertension (%)	63.4	70.1	66.7	72.7	81.0
Hyperlipidemia (%)	81.7	78.7	82.9	80.3	85.7
Non-cardiac vascular disease (%)	31.0	27.2	25.8	31.4	22.2
Current smoking (%)	8.3	7.6	5.8	9.2	5.0

Table 2
Baseline coronary disease severity, left ventricular ejection fraction, and baseline medications according to final CCS anginal class

	No angina	Class 1	Class 2	Class 3	Class 4
Number of patients	145	175	438	123	21
Coronary disease severity					
Multivessel disease (%)*	71.9	75.1	81.9	81.0	89.5
Candidate for PCI (%)	7.0	5.8	5.3	5.8	0.0
Candidate for CABG (%)	7.7	10.5	6.0	3.3	4.8
Not a candidate for either PCI or CABG (%)	89.4	87.7	92.3	92.6	95.2
Left ventricular ejection fraction, % (mean±S.D.)	42.7±13.4	46.3±14.5	46.5±14.1	46.5±12.2	42.6±11.7
Angina frequency					
Angina episodes/week (mean±S.D.)**	6.0±7.6	9.7±13.3	10.3±12.2	14.2±13.9	21.0±19.1
Any short-acting nitroglycerin use (%)**	58.7	70.9	78.1	84.3	90.5
Number of times/week (mean±S.D.)**	3.3±6.6	5.7±10.2	7.2±11.7	9.4±11.7	15.2±21.1
Baseline medications					
Beta-blockers (%)*	64.1	73.1	78.0	76.4	81.0
Calcium channel blockers (%)	38.6	45.1	45.7	48.0	57.1
Angiotensin-converting enzyme inhibitors (%)	43.4	38.3	41.3	41.5	28.6
Angiotensin receptor blockers (%)	11.1	10.9	7.1	10.6	14.3
Nitrates (%)*	73.8	81.1	81.1	87.8	85.7
Lipid lowering (%)	73.1	76.0	78.0	80.3	85.7
Antiplatelet (%)	70.3	76.6	78.9	77.7	85.0

  * $P<.01$.
  ** $P<.001$.

artery disease (CAD) treated with EECP. Prevalence of diabetes, hypertension, dyslipidemia, and HF was similar among the anginal classes. Multivessel coronary disease was more common in those with higher-grade angina at completion. In addition, more severe angina at entry was more common in those with the higher anginal classes at EECP completion, and consistent with this finding, there were threefold higher rates of anginal attacks and nitroglycerin usage. There were no differences in the rates of chronic medications utilized or prior revascularization with the exception of beta-blockers and nitrates. At baseline, beta-blockers were utilized in 64.1%, 73.1%, 78.0%, 76.4%, and 81.0% of those with no angina and those with Class 1, 2, 3, and 4 angina, respectively ($P<.01$). Nitrates were utilized in 73.8%, 81.1%, 81.1%, 87.8%, and 85.7% of those with no angina and those with Class 1, 2, 3, and 4 angina, respectively ($P<.01$; Table 2).

3.2. Procedural results and complications

The peak diastolic augmentation ratio was similar for all groups during the first (0.8±0.5 for lowest and highest CCS groups) and last hours of treatment (1.1±0.6 and 1.0±0.7, respectively). The diastolic augmentation is the increase of arterial blood pressure and retrograde aortic blood flow during diastole. Blood pressure changes are monitored by finger plethysmography. A ratio is computed, using the systolic and diastolic peak pressures. Ratios greater than 1 indicate that diastolic pressures are greater than systolic pressures. The cumulative hours of treatment were similar for all groups (35.7±2.7 and 36.0±4.0 h for lowest and highest CCS groups, respectively). Rates of adverse cardiovascular events during treatment were low. However, 14.3% of those with CCS Class 4 angina were treated for symptoms of HF during the course of EECP.
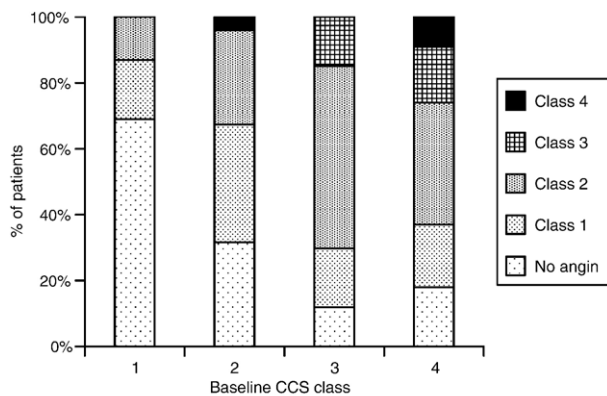

Fig. 1. Frequency of residual angina after EECP according to baseline CCS class.
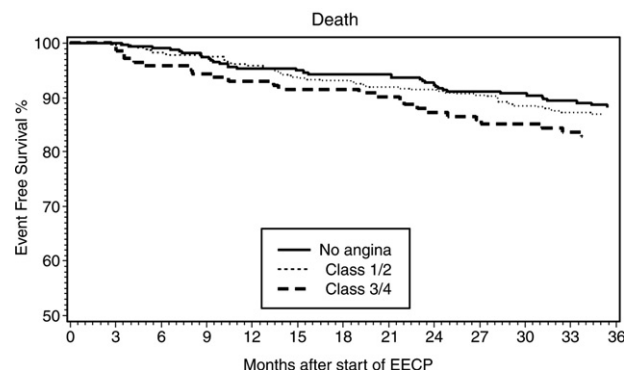

Fig. 2. Rates of death according to CCS class after completing EECP ($P=.21$).
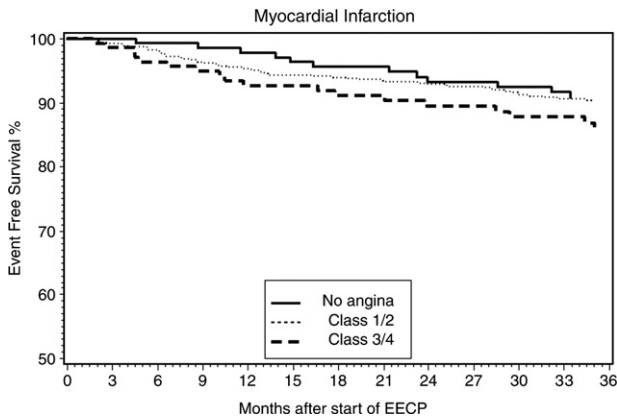
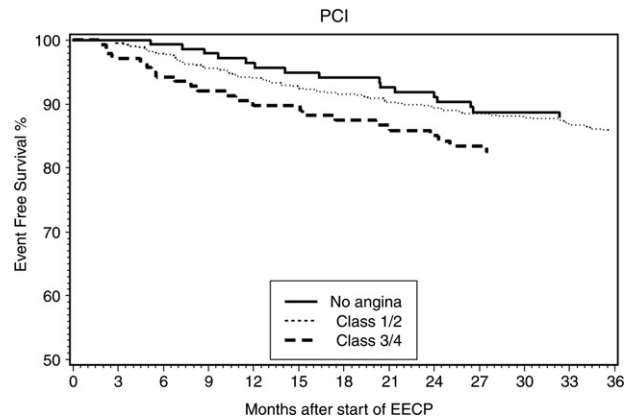Fig. 3. Rates of MI after EECP according to final CCS class (*P*=.30).

Fig. 5. Rates of PCI after EECP according to final CCS class (*P*=.32).

However, not all of these episodes required hospitalization (data not shown).

3.3. Improvement in symptoms

Fig. 1 shows the absolute reduction in angina episodes per week from baseline and at the completion of EECP for the CCS groups. Those with Class 3/4 angina more frequently finished with higher grades of angina. There were no patients with Class 1 symptoms who developed Class 3 or 4 symptoms by the end of EECP treatment.

3.4. Clinical events

Figs. 2–6 show the rates of death, MI, CABG, PCI, and the composite major adverse cardiac event (MACE) by CCS group. The composite cardiac event rates were 34%, 33%, and 44% for those with Class 0, Class 1/2, and Class 3/4 angina at EECP completion (*P*=.01), respectively. By the end of 3 years of follow-up, 11.1% and 17.7% of those with CCS Class 3 and 4 angina underwent CABG and PCI, respectively (Figs. 4 and 5). Only the composite endpoint of MACE demonstrated a separation in survival curves, indicating a worsened survival for those with CCS Class 3 and 4 at the completion of EECP (*P*=.01). Multivariate

analysis for the composite MACE endpoint found Class 3/4 angina (OR=1.59, 95% CI=1.19–2.17, *P*=.002), diabetes (OR=1.57, 95% CI=1.23–2.01, *P*=.0003), age (per decile OR=1.17, 95% CI=1.04–1.31, *P*=.007), and greater EECP augmentation (OR=0.79, 95% CI=0.65–0.96, *P*=.02) as significant predictors. Variables tested in the model and found not to be significant were gender, smoking status, baseline CCS class, ejection fraction ≤35%, hypertension, hyperlipidemia, history of HF, prior coronary bypass surgery, and total hours of EECP treatment. Multivariate analysis for death at 3 years found CCS Class 3 and 4 angina at the completion of EECP (OR=1.45, 95% CI=0.88–2.38, *P*=.15), age (per decile OR=2.02, 95% CI=1.32–3.09, *P*=.0003), male gender (OR=2.00, 95% CI=1.16–3.46, *P*=.01), ejection fraction ≤35% (OR=1.92, 95% CI=1.26–2.91, *P*=.002), and greater EECP augmentation (OR=0.68, 95% CI=0.48–0.96, *P*=.03) as significant predictors.

4. Discussion

We have demonstrated that residual Class 3 (12.1%) or 4 (2.3%) angina was infrequent among patients with severe CAD treated with EECP. Having a greater baseline degree of angina and more multivessel disease were associated with the
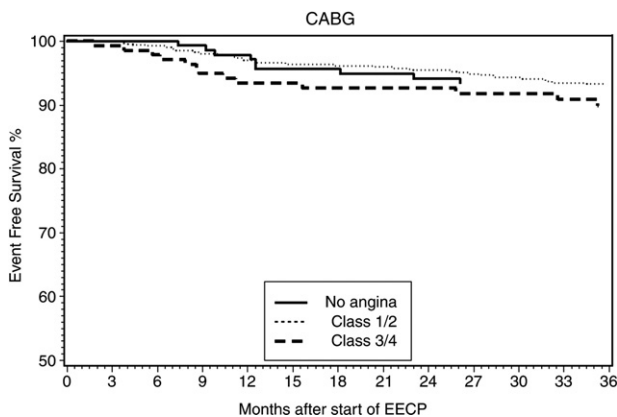

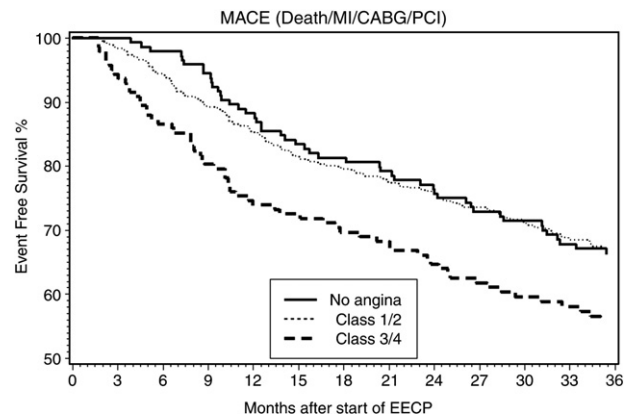Fig. 4. Rates of CABG after EECP according to final CCS class (*P*=.39).

Fig. 6. Rates of MACEs defined as death, MI, PCI, or CABG after EECP according to final CCS anginal class (*P*=.01).

CCS Class 3 or 4 angina upon completion of treatment. Importantly, higher-grade angina upon completion of EECP was a clinical sign, predicting higher rates of MACE with a trend toward higher mortality, along with diabetes, older age, and a lesser degree of augmentation during the course of EECP. In terms of mortality as a singular endpoint, CCS Class 3 or 4 angina was not a significant predictor; however, older age, male gender, reduced left ventricular ejection fraction, and a lower EECP augmentation were related to worsened survival over 3 years. The CCS Class 3 or 4 angina did not meet statistical significance in the mortality model, likely due to the sparseness of the data and relatively fewer deaths than MACEs. Revascularization for residual CCS Class 3 and 4 angina was not commonly performed post-EECP. Given that ~87% had revascularization before EECP was begun, likely patients were deemed noncandidates for future revascularization despite high-grade symptoms.

These data suggest that careful assessment of the CCS grade upon completion of EECP is important. The degree of residual anginal discomfort appears to drive additional cardiovascular events including revascularization. A prior study conducted at six Veterans Affairs General Internal Medicine Clinics, in 5558 patients with coronary disease (48% had prior revascularization), demonstrated a clear relationship between angina severity and functional limitations due to angina with mortality over the next year [6]. Importantly, none of these patients were treated with EECP during the course of their disease. In this study, the highest mortality recorded in the most symptomatic patients was 10–12% at 1 year. By comparison, the 1-year mortality rate for patients in our study was <10%, which can be attributed to >85% revascularization and to >70% statin use in all groups at baseline. Having noted this, there appears to be a residual opportunity for improved medical management in patients with high-grade angina. While rates of conventional anti-anginals at baseline were, as expected, high, the rates of medications at discharge likely could have been upward adjusted, including calcium channel blockers, beta-blockers, long-acting nitrates, and ranolazine [7]. In addition, maximal use of disease-modifying therapy with statins, angiotensin-converting enzyme inhibitors, blood pressure control, and glycemic control in diabetics would be expected to have a higher relative risk reduction in patients with more severe coronary disease [8]. In our data, the class of medications in which there appears to be the greatest opportunity for expanded use is angiotensin-converting enzyme inhibitors. A recent meta-analysis (n=33,500) from six trials targeting patients with stable coronary disease and preserved left ventricular function, randomizing to angiotensin-converting enzyme inhibitors or placebo, found a pooled 17% risk reduction in cardiovascular mortality (P=.01) [9]. These data suggest that an improved mortality could be achieved in our population where less than half received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. Mechanical therapy with EECP is thought to improve angina, and outcomes by microvascular angiogenesis in the coronary circulation are thought to improve endothelial function; thus, for those with continued severe angina, continued or repeated EECP can be considered [10,11].

We acknowledge several limitations to our study. We relied on CCS class assignment by caregivers who were not blinded to the patients' background history or course of therapy on EECP. In addition, we do not have data on the use of medications after completion of EECP. Changes in pharmacologic therapy, lifestyle modifications, or adverse outcomes after cardiac and noncardiac procedures could have played a role in the differences we observed in the composite MACE outcome at 3 years.

5. Conclusions

Residual high-grade angina after EECP is uncommon and occurs in those with more severe angina and multivessel disease at baseline and is associated with cardiac events over the next 3 years. These data suggest that close clinical observation and intensive management of those with high-grade angina are warranted.

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