**Predictors of Benefit in Angina Patients One Year after Completing Enhanced External Counterpulsation: Initial Responders to Treatment versus Nonresponders**

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**Introduction**

Enhanced external counterpulsation (EECP) is a non-invasive treatment used for patients with angina refractory to medical therapy who are not revascularization candidates. The system consists of three sets of cuffs wrapped around the calves, lower and upper thighs of the patients. The pneumatic cuffs are sequentially inflated at the onset of diastole, causing diastolic augmentation and increasing venous return, cardiac output and coronary blood flow. Cuff deflation is timed to end diastole, to reduce vascular resistance, and provides systolic unloading, which further increases the cardiac output [1, 2].

EECP has been shown to be effective in reducing both angina and myocardial ischemia in patients not responding to medical therapy and without revascularization alternatives [3–12]. Many of these patients are high risk because of age, extensive coronary disease, extensive previous revascularization, severity of left ventricular dysfunction or comorbidity. In small patient cohorts, EECP has been shown to have extended benefit, with continued reduction in angina, improvement in quality of life and persistent reduction in major adverse cardiovascular events (MACE) for up to 5 years after treatment [18, 19].
The objective of the current analysis was to compare 6-month and 1-year outcomes and to determine predictors of 1-year angina status in patients who demonstrated initial clinical improvement (responders) versus those who did not show immediate benefit (nonresponders) after completing a course of EECP for chronic angina. Data were obtained from the International EECP Patient Registry (IEPR). The IEPR is a prospective study that tracks consecutive patients enrolled from a diverse group of providers and centers to evaluate patterns of use and efficacy of EECP treatment. All participating patients gave informed consent. The registry is voluntary, with no payments made to either patients or treatment centers.

**Methods**

The IEPR is coordinated at the Epidemiology Data Center of the University of Pittsburgh Graduate School of Public Health. It collects and analyzes data on consecutive patients treated with EECP at participating centers. Information collected includes patient demographics, clinical characteristics and both immediate and long-term outcomes.

Enhanced external counterpulsation was typically prescribed as a course of 1-hour daily sessions, 5 days a week for 7 weeks, for a total treatment of 35 h. EECP was performed under continuous medical supervision with monitoring of the electrocardiogram, pulse oximeter and finger plethysmogram. Demographics, medical history and angina status were obtained at baseline. Telephone follow-up was performed at 6 and 12 months after treatment. Information collected included an evaluation of Canadian Cardiovascular Society (CCS) angina functional class, angina frequency and nitroglycerin use, changes in medications, quality of life and interim events – MACE: death, myocardial infarction (MI), angioplasty (percutaneous coronary intervention; PCI), coronary bypass surgery (coronary artery bypass grafting; CABG). The present study included consecutive patients receiving at least 30 h of treatment. Patients were divided into two groups: those patients with a reduction of at least one CCS angina class after EECP (responders) and those not showing reduction in angina (nonresponders).

**Statistical Analysis**

Discrete variables were analyzed by χ² testing and continuous variables by the unpaired t test. Significance was defined as p < 0.05. Kaplan-Meier survival analysis was used to estimate rates of MACE. Logistic regression analysis was used to determine independent predictors of acute angina reduction and 1-year benefit (continued or new angina reduction with no invasive revascularization), and the Cox proportional hazards model was used to determine predictors of MACE at 1 year.

**Results**

A cohort of 2,007 consecutive EECP patients completing at least 30 h of EECP with information available on acute angina reduction and 1-year follow-up was analyzed. The mean number of hours of treatment was 36.6 ± 4.9. The patient demographic characteristics, cardiac history and angina status at entry are shown in table 1. Medications at baseline are listed in table 2.

**Clinical Outcome**

CCS angina class was reduced by at least one class in 1,665 patients (83.0%) immediately after completion of the course of EECP (responders); 342 patients (17.0%) had no initial reduction in angina (nonresponders). In the cohort responding to EECP with reduction in angina class, weekly angina episodes decreased from 10.4 ± 13.1 to 1.7 ± 3.9 (p < 0.001). The nonresponding cohort also...
demonstrated a smaller but still significant decrease in weekly angina episodes from 11.5 ± 13.1 at baseline to 5.8 ± 9.2 after treatment (p < 0.05). The frequency of nitroglycerin usage/week decreased significantly in the responders from 9.3 ± 12.3 to 1.6 ± 4.5 (p < 0.001), but not significantly in the nonresponders from 10.5 ± 12.9 to 5.2 ± 8.0. Improvement in quality of life was reported in 63% of responders versus 37% of nonresponders (p < 0.001).

The only significant, independent predictor of lack of initial response to EECP was baseline angina class (I, II, III versus IV with odds ratios 5.0, 4.8, 1.4 and CI 2.4–10.4, 3.2–7.0 and 1.0–2.0, respectively).

At 1 year after the completion of EECP, 15% of nonresponders had undergone invasive revascularization (CABG or PCI) versus 8% of responders (p = 0.0001). In addition, 6% of nonresponders versus 5% of responders died (p = not significant) (table 3). For the remaining patients free of MACE, there was a persistent reduction in CCS angina class over baseline at 1-year follow-up, as shown in figure 1. Interestingly, the initial group of nonresponders to EECP demonstrated increasing reduction in CCS angina class over time. In both initial responders and nonresponders there was a sustained reduction in angina episodes per week at 6 months: 2.8 ± 6.1 and 5.8 ± 8.9 for responders and nonresponders, respectively. At 12 months, the number of angina episodes per week was 3.1 ± 6.4 and 5.4 ± 8.6. Frequency of nitroglycerin usage per week remained decreased at 6 and 12 months in the responders group (6.1 ± 8.4 and 6.0 ± 7.8, respectively). For nonresponders, the frequency of nitroglycerin usage per week tended to drift back to baseline (8.3 ± 11.9 at 6 months and 8.7 ± 11.9 at 1 year). However, there was a parallel reduction in both responders and nonresponders alike in the use of nitroglycerin from baseline to 6 and 12 months (responders: from 71.7 to 41.4 to 45.2%; nonresponders: from 72.5 to 63.6 to 61.2%).

The patient-rated quality of life measures as shown in figure 2 demonstrated a large improvement immediately after EECP in the responders, which remained improved at 6-month and 12-month follow-up. However, for the nonresponders, even though there was some improvement in quality of life measures immediately after EECP, there was a gradual drift back to levels before EECP at 6 and 12 months.

Overall, 72% of the responders and 37% of the nonresponders survived to 1 year without MACE and with angina less than that reported before EECP therapy. Logistic regression analysis showed independent factors predicting this benefit to be: initial response to treatment

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Fig. 1. CCS angina class in responders and nonresponders: before EECP, immediately after EECP, 6 and 12 months after EECP follow-up (patients alive with no CABG or PCI who reported angina status at 1 year; n = 1,597).

Table 3. MACE rates for initial nonresponder and responder groups at 6 and 12 months after EECP follow-up

<table>
<thead>
<tr>
<th>Cohort</th>
<th>6 months, %</th>
<th>12 months, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponders responders</td>
<td>4.2</td>
<td>6.0</td>
<td>0.42</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponders responders</td>
<td>3.0</td>
<td>4.3</td>
<td>0.13</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponders responders</td>
<td>6.4</td>
<td>11.2</td>
<td>0.0002</td>
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<tr>
<td>MACE1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponders responders</td>
<td>14.0</td>
<td>22.8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Rates are Kaplan-Meier estimates; p values are log-rank tests to 12 months. Responder was defined as a reduction of at least one angina class immediately after EECP.

1 Death/MI/CABG/PCI.
(odds ratio 4.5; 95% CI 3.5–5.8), baseline angina class of CCS class I (odds ratio 2.1; 95% CI 0.93–4.81), class II (odds ratio 0.62; 95% CI 0.43–0.87) and class III (odds ratio 0.80; 95% CI 0.62–1.01) compared with CCS class IV, and no history of congestive heart failure (odds ratio 1.41; 95% CI 1.14–1.74).

Major Adverse Cardiovascular Events

Patients received an average of 36.6 ± 4.9 h of treatment, with 95.6% completing the prescribed course of treatment. During the course of treatment (or in the 5 days immediately following the last treatment), MACE were uncommon, occurring in 0.7% of patients (MI 0.3%, PCI 0.3%, CABG 0%, death 0.1%). The most frequent cardiovascular events during treatment included unstable angina in 1.7% and decompensated heart failure in 0.9%.

There were significant differences in the frequency of MACE differentiating the EECP responders and nonresponders (table 3). At 12 months, the frequency of PCI (11.2 vs. 5.8%; p = 0.0001) and cumulative MACE (22.8 vs. 16.1%; p = 0.0001) were significantly increased in nonresponders. The rates of death (6.0 vs. 5.0%; p = 0.42), CABG (4.3 vs. 2.8%; p = 0.13) and MI (5.6 vs. 5.0%; p = 0.81) were similar in both groups.

Independent predictors of MACE at 1 year included left ventricular ejection fraction (hazard ratio 0.92; CI 0.85–0.99 for 10% increase), diabetes mellitus (hazard ratio 1.40; CI 1.12–1.75) and baseline angina class versus patients in CCS class IV (hazard ratio 0.47, CI 0.15–1.47 for class I; hazard ratio 0.60, CI 0.39–0.94 for class II; hazard ratio 0.88, CI 0.69–1.14 for class III). As demonstrated by the Kaplan-Meier plot (fig. 3), separation of the curves occurred early after treatment and progressively increased over time after treatment.

Discussion

Initial and follow-up reduction in angina was higher than previously reported because the current cohort included only patients completing 30 or more hours of treatment, whereas previous reported data included patients with fewer than 30 h of EECP [1, 3, 4]. Patients failing to substantially complete the course of EECP demonstrate much less reduction in angina. It is unclear whether patients fail to improve because they do not complete the course of therapy or do not complete the course of therapy because they are not benefiting from EECP. The current study compares two groups of patients completing 30 h of treatment, one group responding to EECP (as defined by a reduction of at least one CCS class) and the other group demonstrating no initial benefit (nonresponders). It is of interest, despite the lack of initial response, that the nonresponders still demonstrated benefit over their baseline status at 1-year follow-up. While this may reflect the unpredictable clinical course of patients with angina, a course characterized by exacerbations and
spontaneous improvements, it is also consistent with recent findings demonstrating continued improvement in endothelial function after EECP [16] and prior studies demonstrating continued improvement in quality of life after treatment [22]. However, while symptoms improved in a substantial portion of initial nonresponders at 1 year, MACE at 1 year was overall significantly higher in the nonresponding group.

It is probable that there is a significantly positive benefit to the 30 or more hours of contact patients experienced. It has been well demonstrated that recurrent patient visits may improve health and quality of life measures as an independent variable. The substantial contact with health care providers during EECP probably has the benefit of reinforcing hygienic measures and improving compliance with health care measures. Prior studies have also suggested that EECP has a positive impact on psychosocial functioning [22], related in part to the improvement in cardiovascular health.

Patients with the most disabling angina have the most potential for benefit from EECP, as measured by reduction in angina class. However, factors such as durability of benefit and reduction of adverse cardiovascular events are as important as the initial improvement in this cohort of patients. The current study examines benefit in terms of angina class and freedom from MACE. When examined in this fashion, CCS class IV patients continue to demonstrate a substantial benefit. The relative risk:benefit ratio would support the current treatment paradigm as cost-effective.

Conclusions

One-year angina reduction without MACE was achieved in 72% of initial responders to EECP treatment. However, a surprising 37% of initial nonresponders demonstrated similar benefit at 1 year. Predictably, patients not responding to EECP demonstrated a higher frequency of MACE at 1 year, including significant increase in the rate of PCI. Factors predicting 1-year benefit included the absence of a history of congestive heart failure and baseline angina status.

Acknowledgement

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References


