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Effectiveness of Repeat Enhanced External Counterpulsation for Refractory Angina in Patients Failing to Complete an Initial Course of Therapy

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Enhanced External Counterpulsation · Refractory angina · Incomplete

Abstract
Aims: This study examined the causes and results of retreatment of patients who failed to complete an initial 35-hour Enhanced External Counterpulsation (EECP) course. ***Methods and Results:*** Data of 2,311 successive angina patients from the International EECP Patient Registry were analyzed, 86.5% completed their EECP course (Complete cohort). Of the 13.5% patients failing to complete the initial course (Incomplete cohort), 28.3% had repeat EECP within 1 year vs. 10.1% of the Complete group. The predictors of failure to complete the initial course of EECP were: female gender, heart failure, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and use of nitroglycerin. For the Complete group, 83.4% had a reduction of at least one Canadian Cardiovascular Society (CCS) class after their initial EECP course, vs. 21.7% in the Incomplete group ($p < 0.001$). After repeat treatment, 66.2% of the Incomplete group achieved at least one CCS class reduction vs. 69.4% of the Complete group (p = NS) undergoing retreatment. The independent predictors for those who return to successfully complete their second course were patients who stopped their first course because of clinical events, and candidacy for coronary artery bypass grafting at the time of initial treatment. ***Conclusion:*** The results of retreatment of those who failed to complete their initial EECP course were comparable to those who completed their initial treatment, with similar reductions of CCS angina class.

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Introduction

Enhanced External Counterpulsation (EECP) is a noninvasive medical device for the treatment of coronary artery disease (CAD). Three pairs of pneumatic cuffs are wrapped around the calves, lower and upper thighs of patients and sequential external pressure of 200–220 mm Hg is applied at the end of systole to increase diastolic coronary perfusion pressure. External pressure is released at the end of diastole to reduce afterload. The application of compression during diastole to the lower extremities also increases venous return. This increase in diastolic filling, together with systolic unloading, augments cardiac output [1, 2]. The hemodynamic objectives of EECP are to maximize diastolic augmentation and systolic unloading. Therefore, the ratio of the areas or peak amplitudes of diastolic to systolic blood pressure waveforms during treatment can be used as an index of EECP hemodynamic effectiveness [3].

EECP is commonly used to treat disabling angina in medically refractory patients who are not candidates for revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) due to unfavorable coronary anatomy, comorbidity, or high surgical risk [4]. EECP is typically prescribed for 1 h/day, 5 days/week over 7 weeks for a total treatment course of 35 h. Using this treatment protocol, typically about 75% of patients will demonstrate an improvement of one or more Canadian Cardiovascular Society (CCS) angina classes with associated improvements in functional tolerance, quality of life and myocardial perfusion [5–8]. In most patients, these results are sustained at 3 years post-therapy [9].

We have previously reported that about 18% of EECP patients undergo retreatment within 2 years after completing a full initial course of treatment. About 70% of these patients had a decrease of one or more CCS classes at the end of their retreatment [10]. However, there is little information available regarding the current clinical practice of EECP in respect to retreatment of patients who failed to complete an initial course of therapy. In particular, the reasons for retreatment, duration of retreatment, clinical predictors of retreatment, success rate of retreatment remain unclear. These issues are important in assessing the value of retreatment in this group of patients. They are also important to insurers and health care providers who must decide whether treatment beyond the initial incomplete course of EECP is indicated and whether it should be covered or not.

This study attempts to answer four questions related to the current clinical practice of EECP in patients failing to complete their initial treatment. What are the clinical predictors of failures to complete their initial course? What is the frequency of EECP retreatment? What are the reasons for the retreatment of drop-out patients? What is the success rate of retreatment, assessed immediately after retreatment and at 1-year follow-up?

Methods

The International EECP Patient Registry (IEPR) was established at the Epidemiology Data Center of the University of Pittsburgh in 1998. The IEPR is a voluntary registry prospectively collecting data regarding the use, safety and efficacy of EECP in consecutive series of patients. The design and the methodology of data collection of the registry complies with the Declaration of Helsinki, all centers and providers of EECP therapy have approval from their local institutional review board, and all patients participating in the registry must sign the consent form approved by each local institutional review board. The demographics and clinical characteristics of participating patients, their response to treatment and their short- and long-term outcomes are tracked. No payments are made to either patients or providers for their participation. The first phase of the IEPR enrolled >5,000 patients from over 50 participating centers.

In the present study sequential refractory angina patients without previous EECP treatment enrolled in the IEPR with 1-year follow-up post-initial EECP were included. The criteria for entry included only that the patients give informed consent and have at least 1 h of EECP treatment. For analysis, patients were divided into two groups, those who had completed a full initial EECP course of ≥35 h (Complete), and those patients who received less than 30 h of initial treatment (Incomplete). Demographics, baseline characteristics, treatment course, and initial results were recorded for all patients. The characteristics and results of patients retreated within 14 months of the first hour of EECP were examined (1-year after completion of treatment).

A Cox Proportional Hazards model was used to determine the independent predictors of return for retreatment within 14 months of treatment initiation. Patients were censored at death or loss to follow-up, but not for CABG, PCI or MI. This model included all baseline characteristics to start and a backwards selection technique was used. Statistical significance was defined as $p < 0.05$ level.

Results

There were 2,311 successive angina patients enrolled in the IEPR between January 1998 and August 2001 from 47 sites providing 14-month follow-up. Of this group, 2,000 (86.5%) completed their course of treatment; 311 (13.5%) patients did not complete their first course of treatment. Fourteen (14) patients died during the initial

Table 1. Patient characteristics by whether they completed their initial full 30–35 h course of EECP treatment

Variable	Incomplete (n = 311)	Complete (n = 2,000)
Age, years	65.6 ± 11.7	66.4 ± 10.6
Male gender, %***	65.6	75.2
White race, %*	91.2	94.8
Time since CAD diagnosis, years	11.1 ± 8.9	11.1 ± 8.2
Family history of CAD, %	78.4	78.9
Hx of diabetes, %*	49.2	42.6
Hx of hypertension, %	72.1	70.9
Hx of hyperlipidemia, %	81.8	82.1
Noncardiac vascular disease, %	36.5	32.6
Multivessel CAD, %	75.5	76.5
LV ejection fraction, %***	43.9 ± 15.2	47.2 ± 14.4
Prior myocardial infarction, %	70.4	70.2
Congestive heart failure, %***	48.0	32.0
Prior PCI, %	68.4	68.6
Prior CABG, %	71.7	70.4
Prior PCI/CABG, %	89.1	88.9
Candidate for PCI, %	9.6	13.3
Candidate for CABG, %	11.9	12.4
Not candidate for PCI/CABG, %	87.0	84.1

* $p < 0.05$, *** $p < 0.001$ comparing Incomplete vs. Complete groups.

CABG = Coronary artery bypass surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; LV = left ventricular; PCI = percutaneous catheter intervention.

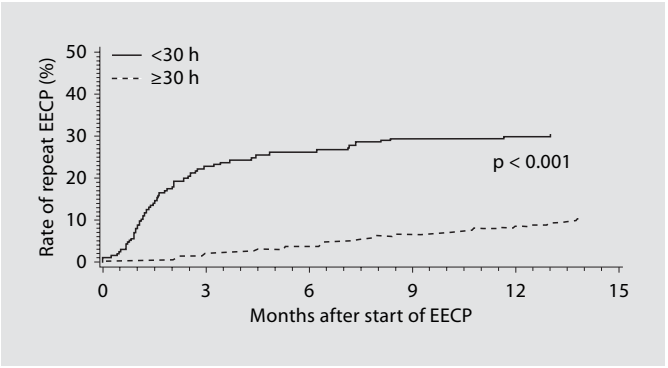

Fig. 1. Rate of repeat EECP by completion of first course of treatment.

treatment period, 11 from the Incomplete group and 3 from the Complete group. Of the remaining 300 Incomplete patients, 85 (28.3%) patients had repeat EECP treatment within 1 year vs. 202/1997 (10.1%) of the Complete group. The rate of repeat EECP by completion of first course of treatment is shown in figure 1.

There were no differences in the average age of Incomplete patients vs. the Complete patients (65.6 ±11.7 vs. 66.4 ± 10.6 years). However, there were less white (91.2 vs. 94.8%, $p < 0.05$), and less male gender (65.6 vs. 75.2%, $p < 0.001$) patients in the Incomplete cohort. The medical history in these groups of patients were essentially similar: 11.1 years since they were diagnosed with CAD, 68% with prior PCI, 71% with prior CABG, 70% with prior MI, 78% had family history of premature CAD, 33% with noncardiac vascular disease, 71% hypertension, 82% hyperlipidemia, and 91% past or current smoker. There were more diabetes mellitus (49 vs. 42%, $p < 0.05$) and congestive heart failure (HF) patients (48 vs. 32%, $p < 0.001$) in the Incomplete vs. Complete group. Most patients in both cohorts were being treated with multiple medicines for their CAD: aspirin (77%), lipid lowering agents (74%), long-acting nitrates (81%), beta-blockers (72%), calcium channel blockers (45%). The Incomplete group used more angiotensin converting enzyme inhibitors (47 vs. 40%, $p < 0.05$) and angiotensin receptor blockers (12 vs. 9%, $p < 0.05$). Overall the EECP patients were a high-risk population, with 89% having had prior PCI/CABG, and with 85% no longer considered as candidates for further invasive revascularization. Details of the medical history are recorded in table 1.

At baseline, distributions of angina functional class as measured by CCS for the two groups are shown in figure 2. The severity of CAD was greater in the Incomplete group. The Incomplete group had more CCS classes III and IV patients than the Complete group (91.6 vs. 87.6%, $p < 0.01$). The average left ventricular ejection fraction was significantly less in the Incomplete group (43.9 vs. 47.2%, $p < 0.001$), with more angina episodes per week (12.9 ± 15.5 vs. 10.6 ± 12.8), and more use of nitroglycerin (9.2 ± 12.9 vs. 6.8 ± 11.3 times/week, $p < 0.001$).

The average hours of initial treatment course for the Incomplete group were 12.9 ± 8.2 vs. 36.5 ± 4.7 for the Complete group. The EECP hemodynamic effectiveness index (Diastolic/systolic ratios) during EECP treatment were significantly less in the Incomplete than in the Complete group (peak amplitude 0.7 ± 0.5 vs. 0.8 ± 0.5, $p < 0.01$; area 0.9 ± 0.6 vs. 1.0 ± 0.6, $p < 0.05$). Distributions of CCS angina class within 1 week after the initial course of EECP treatment for the Incomplete were significantly difference from the Complete group ($p < 0.001$), as shown in figure 2. For the Complete group, 83.4% of the patients reduced at least one CCS class after their EECP treatment with only 18.1% of the patients remaining in CCS class III

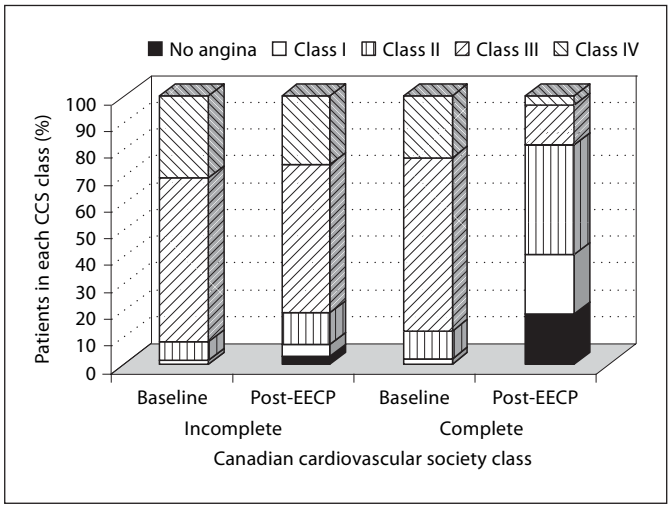

Fig. 2. Distribution of angina functional class at baseline and after the initial course of EECP treatment for those who failed to complete the course (n = 311) and those who completed the full 30–35 h course (n = 2,000).

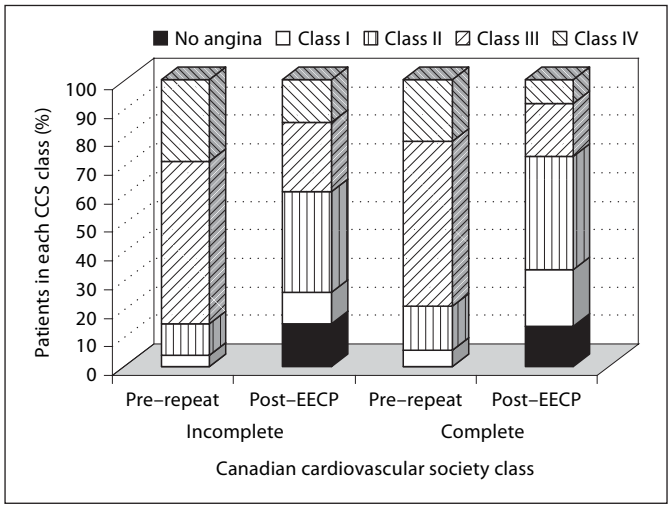

Fig. 3. Distribution of CCS class before and after the repeat EECP treatment course for those who failed to complete the initial course and those who completed the full 30–35 h treatment.

or IV. This was significantly different from the Incomplete group in which only 21.7% of the patients achieved a reduction of at least one CCS class and in which 80.7% remained in class III/IV ($p < 0.001$). Mean decrease in angina episodes/week and percent of patients discontinuing the use of nitroglycerin were 6.8 ± 12.7 and 27.9% in the Incomplete and 8.1 ± 11.6 and 56.6% in the Complete group.

For the Incomplete group, 38.3% of patients discontinued their treatment due to personal reasons, 54.7% due to clinical events (emergency PCI/CABG, MI, unstable angina, exacerbation of or new HF), and 7.1% for unknown reasons. Using logistic regression model, the predictors of failure to finish the prescribed 30 or more hours of treatment were: female vs. male (odds ratio = 1.55; 95% confidence limits = 1.19–2.03), HF vs. no HF (odds ratio = 1.77; 95% confidence limits = 1.36–2.29), use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (odds ratio = 1.33; 95% confidence limits = 1.03–1.73), and use of nitroglycerin (odds ratio = 1.02; 95% confidence limits = 1.00–1.02).

For the 85 Incomplete patients returning for retreatment the mean time to return was 74 ± 78 days, significantly less than the 233 ± 119 days for the 202 patients from the Complete group ($p < 0.001$). The average hours for the course of retreatment for the Incomplete was 27.3 ± 13.8 h, with 62.7% completing a 30–35 h course during their second treatment. The cumulative EECP treatment in the Incomplete group was greater than 30 h in 80% of treated patients (mean of 38.7 ± 13.5 total cumulative hours). In comparison, the average hours of repeat treatment for the Complete group was 25.9 ± 12.8 h, and 54.4% completed more than 30 h in their second treatment (mean of 62.8 ± 14.7 total cumulative hours).

After repeat treatment, 66.2% of patients in the Incomplete group achieved at least one CCS angina class reduction vs. 69.4% after repeat treatment in the Complete group (p = NS), as shown in figure 3. Prior to the second treatment 85.2% of Incomplete group patients had CCS class III/IV angina; post-treatment this improved to 39.2% ($p < 0.001$) of patients. The number of angina episodes/week significantly decreased after repeat treatment compared with pre-repeat treatment in both the Incomplete (from 8.3 ± 8.9 to 4.3 ± 7.3, $p < 0.05$) and the Complete group (from 8.8 ± 11.0 to 3.7 ± 7.1, $p < 0.001$). However, despite the comparable reduction of at least one CCS angina class angina episodes between the Incomplete and Complete groups, the percentage of patients using nitroglycerin in the Incomplete group remained relatively high at 56.8% after the second treatment as compared to a nitroglycerin usage rate of 34.6% in those who had just completed an initial treatment course of 30–35 h.

The independent predictors for returning to successfully complete a second course after failing to complete a first course (by Cox regression model with patients cen-

Table 2. Status at 1 year by whether patient completed the original course of EECP treatment

Variable	Incomplete (n = 311)	Complete (n = 2,000)
Death, %	11.3	5.0
Nonfatal myocardial infarction, %	6.4	4.6
CABG, %	5.1	2.8
PTCA, %	8.7	5.1
Repeat EECP, %	19.0	7.8
Medical treatment only, %	35.4	69.5
No information available, %	14.1	5.4

Events are hierarchical.

CABG = Coronary artery bypass surgery; PCI = percutaneous coronary intervention.

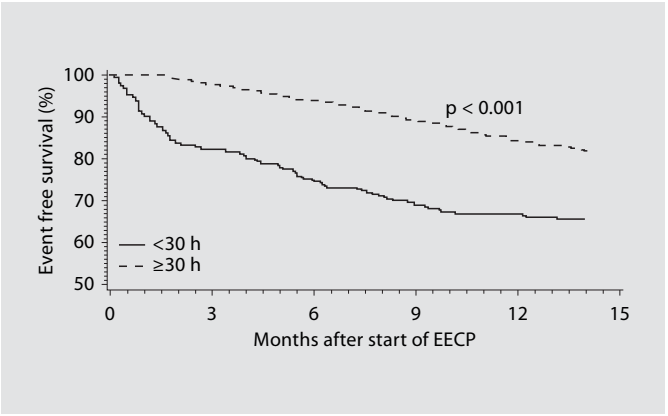

Fig. 4. Freedom from death/MI/PCI/CABG by completion of initial EECP course of treatment.

sored at death or lost to follow-up but not for PCI, CABG or MI) were patients who stopped their first course because of clinical events (when compared with those who failed to complete due to personal reasons) (hazard ratio = 2.43; 95% confidence limits = 1.38–4.29), and candidacy for CABG at time of initial course (hazard ratio = 0.31; 95% confidence limits = 0.10–1.00).

At 1-year follow-up, the status of the 311 patients in the Incomplete group compared to the 2,000 Complete group patients is shown in table 2. The Incomplete patients had significantly more events (death, MI, PCI, CABG) by 1 year than did those who finished the initial treatment (31.5 vs. 17.5%, $p < 0.0001$). Freedom from death/MI/PCI/CABG by completion of initial EECP course of treatment is shown in figure 4.

Discussion

Patients included in the IEPR are predominately high risk, unrevascularizable CAD patients. EECP was generally well-tolerated even in these high-risk patients. While most patients (86.6%) completed the prescribed course (30–35 h) of therapy, a small number of patients stopped treatment for clinical events (7.1%) or by choice (8.8%). An incomplete initial course was the variable showing the strongest association with retreatment. Also, while CCS angina class improved in 75% of patients completing treatment, with 53% discontinuing nitroglycerin use, 25% of patients did not improve their angina class. Persistent and increasing angina were also major reasons for retreatment. The group completing the initial course of therapy had fewer cardiovascular events at 14-month follow-up than the group who did not complete treatment. Similarly, patients achieving angina reduction during their first course of therapy had fewer major cardiovascular events than those who did not complete the initial course of treatment.

Retreatment courses tended to be more abbreviated than the initially prescribed treatment (26.5 ± 13.2 vs. 33.3 ± 9.6 h). It is likely that reimbursement guidelines influenced both the referral of patients for retreatment and the duration of retreatment prescribed. Commonly third party payers will approve an initial full course of 30–35 h of treatment and have variable policies regarding the 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 treatments) and approve a limited (10–12 h) amount of additional EECP treatment unless sufficient time has elapsed between treatments (6 months–1 year). The rationale most commonly cited for these decisions is that retreatment is most likely to be effective in those patients demonstrating an initial response to treatment. Retreatment for incomplete initial treatment in particular may have been influenced by prior payer approval for a 35-hour course of treatment both in terms of referral for retreatment and in the duration of the retreatment prescribed.

Conclusions

While EECP is a well-tolerated and effective treatment for patients with severe angina not responding to medical therapy and not amenable to revascularization about 14% of patients fail to complete therapy due to medical events and for personal reasons. In current practice as evidenced by the IEPR about 13% of treated patients (26.6% of those not completing and 10% of those completing an initial course of EECP) undergo retreatment within 14 months of the initial treatment. The major reasons for retreatment include an incomplete initial course and persistent or significantly increased angina. Baseline characteristics predicting return include: CHF, prior PCI, and hypertension in those patients completing initial treatment and initial lack of angina reduction in the group of patients not completing the initial course of therapy. Retreatment with EECP can offer reduction of angina to those not completing their original treatment. Retreatment results were comparable to initial treatment results with a similar proportion of patients completing therapy and a similar proportion of patients demonstrating benefit in reduction of CCS angina class. The course of retreatment tended to be more abbreviated than the initial prescribed course of therapy.

Conflict of Interest

William E. Lawson Speaker's bureau of Vasomedical, Inc., Westbury, NY, USA. *Gregory Barsness* none declared. Andrew D. Michaels: Medical director of the International EECP Patient Registry, speaker's bureau of Vasomedical, Inc., Westbury, NY, USA. *Ozlem Soran* Speaker's bureau of Vasomedical, Inc., Westbury, NY, USA. *Elizabeth D. Kennard* none declared. Sheryl F. Kelsey: none declared. *John C.K. Hui* Chief Technology Officer, Senior Vice President and Board member of Vasomedical, Inc.

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