

## Effectiveness of Enhanced External Counterpulsation in Patients with Left Main Disease and Angina

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### Summary

**Background:** Enhanced external counterpulsation (EECP) is a noninvasive device that uses three pairs of sequentially inflated pneumatic cuffs applied to the lower extremities and synchronized with the heart beat to provide diastolic augmentation, increase coronary blood pressure and flow, venous return and cardiac output, and decrease afterload.

**Hypothesis:** This study examines the safety and effectiveness of EECP therapy in patients with significant left main coronary artery disease (LMD).

**Methods:** In all, 2,861 patients enrolled in the International EECP Patient Registry (IEPR) were divided into three groups, those without LMD (n = 2,377), those with LMD and prior CABG (n = 431), and those with unbypassed LMD (n = 53).

**Results:** Patients with LMD, with or without prior CABG, were significantly more likely to have triple-vessel disease (98.1 and 88.7%, respectively) than patients without LMD (41.9%). Post-EECP, 74% without LMD, 75% with LMD with prior CABG, and 65% with unbypassed LMD improved their Canadian Cardiovascular Society (CCS) angina by at least one class (p = NS). There were no differences in the mean decrease in weekly angina episodes (7.1 vs. 8.0 vs. 7.6)

and in the mean frequency of weekly nitroglycerin use (6.6 vs. 8.1 vs. 8.9). At 6-month follow-up, the CCS class improved further in all three groups, and there was a further reduction in mean weekly angina episodes (4.7 vs. 4.6 vs. 5.3) and nitroglycerin use (6.5 vs. 6.8 vs. 8.2). Kaplan-Meier life table analysis 8 months after starting EECP demonstrated a major cardiovascular event rate of 11.2% in patients without LMD, 15.6% in LMD with CABG, and 24.3% in LMD without prior CABG. Late mortality in unbypassed LMD was 13.2% (confidence interval [CI] 3.3–23.1) versus 4.8% (CI 2.7–7.1) in LMD with CABG, and 2.8% (CI 2.1–3.5) without LMD (p = 0.0039 by log-rank test).

**Conclusion:** Enhanced external counterpulsation is equally effective in relieving angina in patients with or without LMD. However, the significantly increased late mortality in patients with LMD without prior CABG suggests that early revascularization should be considered in these patients.

**Key words:** left main disease, enhanced external counterpulsation, angina

### Introduction

Enhanced external counterpulsation (EECP)<sup>1</sup> is a noninvasive device that uses three pairs of sequentially inflated pneumatic cuffs applied to the lower extremities and synchronized with the heart beat to provide diastolic augmentation, increase coronary blood pressure and flow, venous return and cardiac output, and decrease afterload.<sup>2–4</sup> Currently, EECP is used primarily for medically refractory angina in patients who are not good candidates for revascularization. Typically, patients are prescribed a 1-h treatment session daily over a 7-week period for a total course of 35 h.

Previous results have demonstrated EECP to be effective in reducing anginal symptoms,<sup>5</sup> increasing time to ST-segment depression,<sup>6</sup> increasing exercise time,<sup>7,8</sup> and improving quality of life.<sup>9,10</sup> Myocardial perfusion at rest and with exercise has been demonstrated to improve after EECP by both positron emission tomography (PET) scan and radionuclide imaging.<sup>11,12</sup> The benefit of EECP is durable, and has been demonstrated up to 5 years post treatment.<sup>13–17</sup> There are data to

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support multiple mechanisms of EECp action, including collateral recruitment,<sup>14</sup> angiogenesis and arteriogenesis, altering vasomotor tone in favor of vasodilation,<sup>15,16</sup> and normalizing endothelial function.<sup>17</sup>

Previous studies have demonstrated that surgical revascularization (CABG) prior to EECp increases the likelihood of improving baseline stress perfusion defects.<sup>14</sup> This report examines the short- and intermediate-term results of treating a particularly high-risk subset of patients with significant left main coronary artery disease (LMD). The objectives were to determine whether treatment with EECp is as safe and effective in relieving angina in patients with LMD as in those without LMD, and to evaluate the safety and effectiveness of EECp in treating patients with LMD without prior CABG. The major reasons for not operating in LMD had to do with patient preference, physician recommendations, and the patient-physician interaction. The mean left ventricular ejection fraction (LVEF) was comparable and in the mild to moderate systolic dysfunction range in all three groups.

## Methods

The International EECp Patient Registry I (IEPR) collects data on patient characteristics, safety, and short- and long-term outcomes.<sup>18</sup>

TABLE I Patient characteristics and medical history pre EECp

|  | No left main | Left main, no CABG | Left main, prior CABG |
|--|--------------|--------------------|-----------------------|
| Patients in cohort                                       | 2,377        | 53                 | 431                   |
| Age (years) <sup>b</sup>                                 | 65.7 ± 10.8  | 71.4 ± 11.2        | 67.3 ± 9.8            |
| Gender (% male)  | 73.5         | 77.4               | 83.5                  |
| Race (white) %   | 93.1         | 96.2               | 96.0                  |
| Duration of coronary artery disease (years) <sup>c</sup> | 9.9 ± 7.9    | 7.3 ± 7.7          | 13.7 ± 7.4            |
| Prior MI (%) <sup>b</sup>                                | 65.3         | 54.7               | 72.9                  |
| History of heart failure (%)                             | 28.2         | 41.5               | 39.8                  |
| Prior PCI (%)  | 65.5         | 56.6               | 65.2                  |
| Prior CABG (%)   | 62.9         | 0                  | 100                   |
| Candidate for PCI (%) <sup>c</sup>                       | 14.8         | 23.1               | 5.9                   |
| Candidate for CABG (%) <sup>c</sup>                      | 16.8         | 23.1               | 7.5                   |
| LV ejection fraction (%)                                 | 47.2 ± 13.7  | 46.3 ± 16.2        | 43.0 ± 13.1           |
| Diabetes mellitus (%) <sup>a</sup>                       | 41.2         | 56.6               | 41.4                  |
| Hypertension (%)   | 70.2         | 69.8               | 68.9                  |
| Hyperlipidemia (%)                                       | 78.6         | 66.0               | 81.8                  |
| Vascular disease (%)                                     | 25.3         | 39.6               | 32.2                  |
| Past or present smoking (%)                              | 71.7         | 64.2               | 75.9                  |

<sup>a</sup> = p < 0.05.

<sup>b</sup> = p < 0.01.

<sup>c</sup> = p < 0.001 testing LM, no CABG vs. LM, prior CABG.

Abbreviations: CABG = coronary artery bypass graft, MI = myocardial infarction, PCI = percutaneous coronary intervention, LM = left main, EECp = enhanced external counterpulsation.

The IEPR study population included 2,861 patients with angiographic data and no previous EECp treatment. Significant LMD was defined as a stenosis ≥ 70%. The cohort of patients was subdivided into three groups for analysis: those without LMD, those with LMD with prior CABG, and those with unbypassed LMD.

Demographic information was obtained at entry and interval histories were obtained at the end of treatment and at 6-month follow-up. At each data point, information was obtained on the Canadian Cardiovascular Society (CCS) angina functional class, angina frequency, nitroglycerin use, medication changes, and major adverse cardiovascular events (MACE: death, MI, revascularization with angioplasty [PCI] or CABG).

## Statistical Analysis

Discrete variables were analyzed by chi-squared testing and continuous variables by Wilcoxon rank sum test. Significance was defined as p < 0.05. Kaplan-Meier life table analysis was used to determine the rate of MACE at 8 months after the start of EECp therapy.

## Results

Of the 2,861 patients, 484 (17%) had LMD; 431 patients had LMD with prior CABG, and 53 patients had unbypassed LMD. Patient characteristics, medical history, and cardiovascular risk factors at the start of EECp are shown in Table I. The majority of patients were treated with statins, aspirin, beta blockers, and nitrates. The previously bypassed patients with LMD were significantly more likely to be taking nitrates (82.6 vs. 66.0%; p < 0.01) and lipid-lowering drugs (74.9 vs. 51.9%; p < 0.001) than the unbypassed patients with LMD. The patients with left main CAD were significantly more likely to have triple-vessel disease (88.7 and 98.1%, respectively, for unbypassed and previously bypassed) than patients without LMD (41.9%). Angiographic data are shown in Table II.

TABLE II Coronary stenosis ≥ 70% or graft closed

|                                | No left main<br>n = 2,377 | Left main,<br>no CABG<br>n = 53 | Left main,<br>prior CABG<br>n = 431 |
|--------------------------------|---------------------------|---------------------------------|-------------------------------------|
| Left main                      | 0                         | 100                             | 100                                 |
| Left anterior descending (LAD) | 74.3                      | 70.6                            | 90.1                                |
| Left circumflex (LCx)          | 63.0                      | 60.8                            | 85.0                                |
| Right coronary artery (RCA)    | 72.0                      | 75.0                            | 87.9                                |
| LAD graft                      | 22.1                      | NA                              | 18.8                                |
| LCx graft                      | 31.2                      | NA                              | 30.2                                |
| RCA graft                      | 35.2                      | NA                              | 37.8                                |

Abbreviations: CABG = coronary artery bypass graft, N = number, NA = not applicable.

### Treatment Course and Adverse Events

Although most patients completed the prescribed course of EECP treatment, there was a nonsignificant trend toward fewer unbypassed patients with LMD completing and a higher percentage of this group not completing because of clinical events (Table III). These clinical events included nonsignificant higher rates of unstable angina, MI, exacerbation of congestive heart failure, revascularization, and death. A significantly higher percentage of the patients with unbypassed LMD had a major adverse cardiovascular event (death, MI, or revascularization) during treatment.

### Clinical Outcome

#### Canadian Cardiovascular Society Angina Class

The CCS classification improved comparably in all groups, as shown in Figure 1. There were also no significant differences among the groups without LMD, unbypassed LMD, and bypassed LMD in mean decrease in weekly anginal episodes (7.1 vs. 7.6 vs. 8.0, respectively), mean difference in frequency of nitroglycerin use per week (6.6 vs. 8.9 vs. 8.1, respectively), or nitroglycerin discontinuation (84.7 vs. 80.6 vs. 83.2%, respectively).

#### Long-Term Clinical Outcome

At 6-month follow-up, the improvement achieved immediately post EECP treatment continued to increase as more patients from Class II through IV moved to Class I and even no angina, as shown in Figure 2. In addition, there were continued decreases in mean weekly anginal episodes, numbers of patients using nitroglycerin, and frequency of nitroglycerin use, although there were no statistically significant intergroup differences. At 6 months, the weekly anginal episodes count was

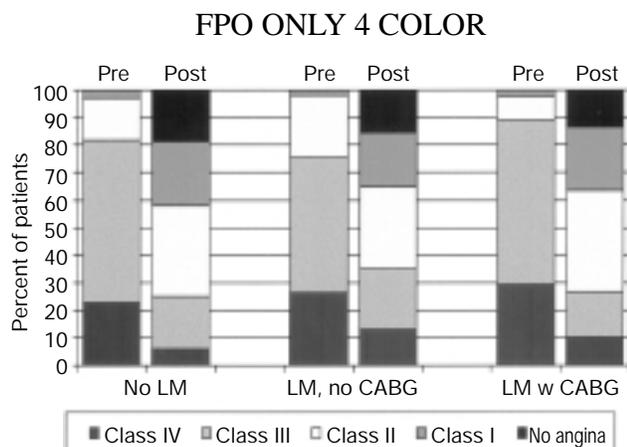


FIG. 1 Changes in Canadian Cardiovascular Society class pre and post enhanced external counterpulsation. LM = left main, CABG = coronary artery bypass graft.

TABLE III Treatment course and adverse events

|  | No left main<br>n = 2,377 | Left main, no CABG<br>n = 53 | Left main, prior CABG<br>n = 431 |
|--|---------------------------|------------------------------|----------------------------------|
| Treatment hours (mean)                       | 34.3 ± 10.0               | 31.3 ± 11.9                  | 34.4 ± 9.5                       |
| Completed as prescribed (%)                  | 83.9                      | 75.5                         | 83.4                             |
| Stopped for clinical event (%)               | 7.9                       | 17.0                         | 9.5                              |
| Unstable angina (%)                          | 2.8                       | 5.8                          | 2.3                              |
| Myocardial infarction (%)                    | 0.6                       | 1.9                          | 1.2                              |
| Congestive heart failure (%)                 | 1.9                       | 3.8                          | 2.3                              |
| CABG   | 0.1                       | 1.9                          | 0.5                              |
| PCI  | 0.8                       | 1.9                          | 0.9                              |
| Death  | 0.3                       | 1.9                          | 0.7                              |
| Any MACE (death, MI, PCI, CABG) <sup>a</sup> | 1.7                       | 7.6                          | 2.5                              |

<sup>a</sup>p < 0.05 testing unbypassed left main vs. left main with prior CABG and no left main.

Abbreviations: N = number, MACE = major adverse coronary events. Other abbreviations as in Table I.

4.7 vs. 5.3 vs. 4.6, respectively, for the groups without LMD, unbypassed LMD, and LMD with prior CABG; nitroglycerin use was 41.6 vs. 41.0 vs. 45.4%; and the frequency of nitroglycerin usage per week was 6.5 vs. 8.2 vs. 6.8.

Follow-up of the three groups of patients for MACE (death, MI, CABG, PCI) was performed using Kaplan-Meier life table analysis (Fig. 3 and Table IV). There was an early and diverging difference in MACE among the three groups. There was a notable and statistically significant increased rate of MACE in the patient group with unbypassed LMD. Of particular concern was the very high comparative death rate in these

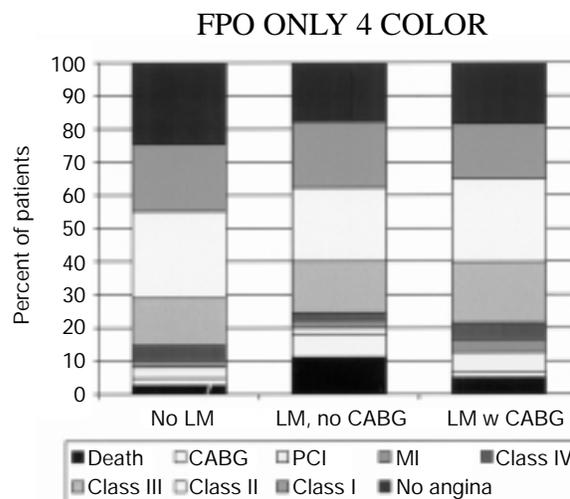


FIG. 2 At 6-month follow-up, the improvement achieved immediately post enhanced external counterpulsation treatment not only remains stable, but improved further as more patients from Class II through IV moved to Class I and even no angina. MI = myocardial infarction, PCI = percutaneous coronary intervention. Other abbreviations as in Figure 1.

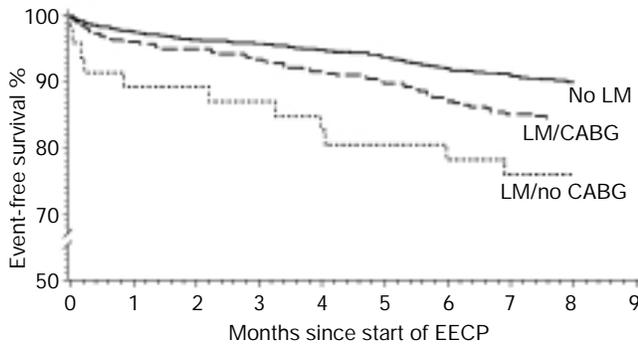


FIG. 3 Freedom from major adverse coronary events (death, myocardial infarction, revascularization) from start of enhanced external counterpulsation (EECP) through 8 months. Abbreviations as in Figures 1 and 2.

patients. Late mortality in the patients with unbypassed LMD was 13.2% (CI 3.3–23.1), versus 4.8% (CI 2.7–7.1) in those with bypassed LMD, and 2.8% (CI 2.1–3.5) in the patients with CAD without LMD ( $p = 0.0039$  by log-rank test).

## Discussion

Patients with unbypassed LMD constituted 1.85% of patients with CAD and 11% of patients with LMD studied in the IEPR. There is no evidence of CABG selection bias on the basis of LVEF; the mean EF is higher in patients with unbypassed than in those with bypassed LMD. Except for a higher incidence of diabetes mellitus (56.6 vs. 41.4%) and, of course, a history of prior surgical revascularization, there were no markers of increased surgical risk in patients with unbypassed compared with those with bypassed LMD. A significantly greater proportion of the patients with unbypassed LMD were believed to be candidates for revascularization with CABG or PCI by their physicians than those in the other groups.

Reasons for not operating are often dependent on the patient, physician recommendations, and the patient–physician interaction. It is important to remember that the IEPR is a prospective registry of usual practice and not a randomized trial with restrictive inclusion criteria. The variability in practice thus captured is important in assessing the impact of different

practices on outcomes. The IEPR includes a diverse group of patients and practice patterns. This diversity is the strength of the prospective registry as it reflects real world practice and experience and also provides insights into the relative value of different approaches. It has been unclear whether patients with angina and LMD would benefit symptomatically, because by definition they have an occluded proximal conduit. According to the patent vessel hypothesis, a proximally patent conduit is necessary for transmitting the increased coronary pressure and flow to the distal circulation to promote collateral recruitment and development and to effect endovascular function. In this context, the patients with LMD and, to an even greater degree, those with unbypassed LMD would be less likely to benefit than the patients without LMD. There was, however, a comparable response in all groups as assessed by improvement in angina functional class and nitroglycerin use. From the perspective of angina reduction, EECP was safe and effective, with or without LMD and independent of prior CABG.

A second concern with patients with LMD was the safety of EECP, particularly if chosen as an alternative to revascularization. The cohort with unbypassed LMD is comprised of high-risk patients. The average age was 71.4 years, 56.6% had diabetes, 54.4% had prior infarction with an average EF of 46.3% (EF < 35% in 25%, and 41.5% had a history of congestive heart failure), left main and triple-vessel CAD was present in 88.7%, and class III/IV angina in 81.2%. Only 29.4% were amenable to revascularization, either by PCI or CABG. The decision of whether a patient was a candidate for revascularization was made by the patient's treating cardiologist. It was a real-life decision, made by the physician with the most detailed knowledge and interaction with the patient. While the initial experience during EECP showed a significant difference in the composite, but not individual MACE from the cohort without LMD and that with bypassed LMD, the longer-term follow-up sounds a note of caution. Long-term composite MACE, and particularly mortality, was notably higher in the patient with unbypassed LMD.

There are no recent trials of medically treated LMD because of the historical mortality rate of 15–20% in most series.<sup>19,20</sup> This is despite clear improvements in medical therapy, including statins to decrease progression, antiplatelet agents to lessen thrombotic events, and angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-

TABLE IV Adverse event rates (95% confidence interval) at 8 months after start of EECP

|              | No left main<br>n = 2,377 | Left main, no CABG<br>n = 53 | Left main, prior CABG<br>n = 431 | p Value <sup>a</sup><br>(log-rank test) |
|--------------|---------------------------|------------------------------|----------------------------------|---|
| Death (%)    | 2.8 (2.1, 3.5)            | 13.2 (3.3, 23.1)             | 4.8 (2.7, 7.1)                   | 0.0039                                  |
| MI (%)       | 2.5 (1.8, 3.2)            | 5.0 (0.0, 11.7)              | 4.9 (2.7, 7.1)                   | 0.83                                    |
| CABG (%)     | 2.3 (1.7, 3.0)            | 6.8 (2.4, 11.2)              | 2.0 (0.6, 3.4)                   | 0.080                                   |
| PCI (%)      | 3.6 (2.8, 4.2)            | 4.8 (0.0, 11.4)              | 6.3 (3.8, 8.8)                   | 0.58                                    |
| Any MACE (%) | 11.2 (9.9, 12.5)          | 24.3 (11.8, 36.8)            | 15.6 (11.9, 19.3)                | 0.09                                    |

<sup>a</sup> Comparing “left main, no CABG” with “left main, prior CABG”.

Abbreviations as in Tables I and II.

blockers, and aldosterone antagonists to treat left ventricular dysfunction. With drug-eluting stents clearly decreasing restenosis rates, there is strong interest in stenting unprotected left main coronary stenoses, particularly in patients at high risk for CABG. Results in the recent but pre drug-eluting stent era have demonstrated 100% procedural success with a 9% left main stent procedure-related mortality in patients at high risk for CABG (and no mortality in patients at low risk for CABG).<sup>21</sup> The 1–6 month mortality rates were 2% in patients at high risk and 2.6% in those at low risk for CABG. These mortality rates are comparable to the 4.6% noted in the CASS registry. However, angiographic restenosis was 23% and target lesion revascularization was required in 17.4%. The future use of drug-eluting stents may benefit early mortality while minimizing late restenosis and associated morbidity and mortality.

It is not surprising that long-term mortality was driven by significant left main stenosis, a known powerful determinant of survival. Any potential beneficial effects of EECP on patient's symptoms and myocardial perfusion cannot overcome this defining anatomical problem. The increased mortality over the cohort without LMD was noted despite a substantially increased revascularization rate in both cohorts with LMD at follow-up.

The number of patients in the cohorts with LMD is relatively small. Since CABG is indicated for LMD, the patients with unbypassed LMD may represent a group of patients both less likely to seek medical care and less trusting and willing to follow their physician's recommendations. This may also have influenced the observed outcomes.

## Conclusions

Enhanced external counterpulsation can be performed safely and effectively in patients with and without LMD. Comparable immediate benefits in anginal improvement were seen independent of the presence of LMD. Similarly, patients with unbypassed LMD exhibit comparable benefit in obtaining relief from angina after EECP to that in patients with previously bypassed LMD. During active treatment with EECP, there was a nonsignificant trend toward increased events and revascularization in the patients with unbypassed LMD. However, in long-term follow-up, unbypassed LMD emerged as a significant indicator of increased mortality and MACE in comparison with patients without LMD, and with patients with bypassed LMD. While EECP appears to ameliorate angina independent of anatomy, it does not normalize the high mortality associated with unrevascularized left main coronary disease.

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