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Enhanced External Counterpulsation as Initial Revascularization Treatment for Angina Refractory to Medical Therapy

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Key Words

External counterpulsation · Registry · Angina · Noninvasive circulation assist device · Revascularization

Abstract

Enhanced external counterpulsation (EECP) is effective in patients with angina refractory to medical therapy or revascularization. However, as a noninvasive treatment it should perhaps be considered the first-line treatment with invasive revascularization reserved for EECP failures or high-risk patients. The International EECP Patient Registry was used to analyze a cohort of patients with prior percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) (n = 4,454) compared with a group of patients (PUMPERS) who were candidates for PCI and/or CABG and chose EECP as their initial revascularization treatment (n = 215). The PUMPERS responded to treatment with EECP with decreased anginal episodes and nitroglycerin use and with improvement in their Canadian Cardiovascular Society functional class, similarly to previously revascularized patients. Treatment with EECP resulted in sustained, and often progressive, reduction in angina over the succeeding 6 months. Given the findings of this study, it is interesting to speculate on the possibility of using EECP as the primary revascularization intervention after medical therapy proves unsatisfactory.

Background

Enhanced external counterpulsation (EECP) has become increasingly used as a noninvasive treatment option for angina pectoris patients refractory to medical therapy who are not candidates for revascularization. Patients treated with EECP therapy have demonstrated an improvement in Canadian Cardiovascular Society (CCS) functional angina class, increased exercise tolerance, and a reduction in nitroglycerin use. Objective measures of coronary ischemia have demonstrated improved time to ST segment depression, stress myocardial perfusion [1–4], PET scan myocardial perfusion at rest and after dipyridamole [5]. These benefits have been demonstrated to be durable in many patients for up to 5 years after treatment [6, 7].

EECP studies have demonstrated a greater improvement in stress myocardial perfusion in patients with single- or double-vessel disease or multiple conduits with prior coronary artery bypass graft (CABG) compared to patients with unrevascularized severe triple-vessel disease [8, 9]. Also, patients undergoing EECP after prior CABG demonstrate improvement equal to post-percutaneous coronary intervention (PCI) patients. This is noted despite the post-CABG patients having more extensive disease and greater left ventricular dysfunction at the time of EECP treatment [10]. These findings support an 'open-vessel hypothesis', i.e. that a patent vessel is necessary to transmit the increased diastolic pressure and flow gener-

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ated by EECP to the distal coronary circulation and promote the recruitment or development of collaterals.

Current health care policies usually limit reimbursement for EECP to patients with angina refractory to medical therapy who are not candidates for CABG or PCI. Because of this, the patients currently selected for EECP treatment tend to be those with extensive severe disease, a group in which it has been historically hardest to show benefit.

There are no data evaluating the strategy of EECP used as the primary revascularization (no prior CABG or PCI) for patients with medically refractory angina. As an effective and noninvasive treatment, EECP should perhaps be considered prior to invasive revascularization procedures, particularly in limited coronary disease with preserved left ventricular function where the main benefit of revascularization is angina relief and improved quality of life.

Patients selecting EECP as primary revascularization, often with limited coronary disease, may demonstrate a greater benefit than the more commonly treated refractory angina patient with extensive coronary artery disease. The effect of EECP in decreasing oxidative stress, normalizing endothelial dysfunction, and promoting favorable remodeling may be particularly beneficial in the earlier stages of atherosclerotic disease [11]. Less extensive disease might favor collateral formation or recruitment as per the patent-vessel hypothesis. It is also possible, however, that the absence of the additional conduits provided by prior CABG might limit the potential for distal transmission of the increased pressure and flow generated by EECP, thus limiting recruitment and development of collaterals. Primary treatment with EECP might also, in a fashion analogous to angioplasty compared to CABG, lead to an increased infarct mortality when compared to CABG due to fewer distal conduits and less well developed collaterals resulting in larger infarcts.

The International EECP Patient Registry (IEPR) was initiated in 1998 to determine the baseline characteristics, safety and acute and long-term outcome of EECP therapy in consecutive series of patients undergoing treatment for chronic angina in a wide variety of clinical settings [12]. Patients are being followed for 3 years after a course of treatment. As of July 2001 there were 89 clinical sites, both in the United States and abroad that had enrolled over 5,000 patients into the registry. While most patients treated in the International EECP registry have angina refractory to medical therapy and are not revascularization candidates, the IEPR also includes patients who were candidates for CABG and/or PCI and chose EECP as their primary revascularization therapy. This subgroup of patients were given the acronym 'PUMPER' representing Primary Utilization to improve Myocardial Perfusion with Enhanced external counterpulsation Revascularization, and the effectiveness of this approach was analyzed in the following report.

Methods

The IEPR was used to analyze a cohort of patients enrolled into the registry prior to September 2000 who had data with respect to previous CABG and PCI, as well as judgment as to suitability for such interventions as determined by their referring physicians at the time when patients began their EECP treatment. The group with prior PCI and/or CABG revascularization (non-PUMPER) was compared (patient characteristics, treatment course, results, morbidity and mortality) with the group of patients choosing EECP as their initial revascularization treatment (PUMPER). All patients had reached their 6 months' post-treatment follow-up time-point to be included in the analysis.

Statistical Methods

Data on proportions were calculated as percentages of the number of patients having a response for that attribute. Continuous variables were expressed as mean value and standard deviation for those patients reporting that variable. Comparisons of proportions in the two groups having an attribute were done using χ^2 or Fisher's exact tests. Comparison of continuous variables was performed using the Wilcoxon t test approximation. All statistical analysis was carried out using the SAS® system.

Results

Of the 4,454 patients in the registry suitable for analysis, 4,239 (95%) had undergone revascularization at some time prior to EECP (non-PUMPER). Of those who had previously undergone revascularization, 79.3% had prior CABG, 75% had prior PCI, 54% had both. Only 16% of these patients were considered suitable for further invasive revascularization at the time of beginning EECP. In contrast, 215 patients (5%) had no previous revascularization (PUMPER), and were usually also considered suitable either for CABG (90%) or PCI (70%) at the time of beginning EECP. Demographics, medical history and risk factors are shown in table 1. Both groups were composed of predominantly white males with a mean age of 66.5 years for the non-PUMPER and 67.4 years for the PUMPER. PUMPER were significantly more likely to be nonwhite, had significantly fewer risk factors than the non-PUMPER group, and had fewer concomitant conditions such as congestive heart failure and diabetes. As shown in table 1, the PUMPER group had coronary artery disease of more recent onset (5.1 vs. 11.6 years, $p < 0.001$)

Table 1. Demographics, medical history, risk factors, coronary disease, angina and nitroglycerin use before EECP treatment

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Demographics		
Age (mean), years	66.4 ± 10.7	67.1 ± 11.0
Male, %	75.4	72.9
White race, %**	94.0	86.4
Risk factors, %		
Family history	77.0	73.2
Diabetes***	43.3	32.0
Hypertension	69.6	65.9
Hyperlipidemia**	79.0	68.6
Smoking (past or current)*	71.7	62.7
Medical history		
Prior myocardial infarction, %***	71.3	40.0
Non-cardiac vascular disease, %***	31.5	19.8
Congestive heart failure, %***	32.9	13.0
LVEF, mean %***	46.2	52.5
Duration of CAD, years***	11.6 ± 8.1	5.1 ± 6.6
Multivessel disease (≥ 70% stenosis), %***	78.2	52.0
Prior treatment, %		
Prior CABG or PCI	100.0	0
Prior EECP	4.4	0
Suitability for revascularization		
Candidate for CABG***	12.7	89.8
Candidate for PCI***	12.8	70.1
Candidate for neither***	83.6	0
CCS angina class, %***		
Class I	2.6	9.3
Class II	13.5	33.0
Class III	59.3	44.2
Class IV	24.6	13.0
Unstable angina, %	3.4	2.3
Angina episodes/week***	10.4 ± 13.1	6.4 ± 9.7
Nitroglycerin use, %***	71.4	46.9
Number of times/week*	9.8 ± 12.4	7.1 ± 10.5

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

and less multivessel disease (52.0 vs. 78.2%, $p < 0.001$). PUMPER had less severe angina (class III/IV angina in 57.2 vs. 83.9%, $p < 0.001$) and less nitroglycerin use (46.9 vs. 71.4%, $p < 0.001$). Angina characteristics and nitroglycerin use are summarized in table 1.

Patients underwent a mean treatment time of 34 h. There was no significant difference in the course of treatment completion rates of PUMPER versus non-PUMPER (88.8 vs. 82.8%). The magnitude of the hemodynamic effect produced by EECP was significantly higher in the PUMPER group as assessed by the effectiveness ratio [13], which is defined as the ratio of peak diastolic to systolic pressure as measured by finger plethysmograph (peak ratio at end of treatment 1.33 vs. 1.09, $p < 0.001$). Table 2 summarizes the details of the treatment and of angina class and nitroglycerin use after treatment. Immediately after treatment course completion, a reduction of CCS angina class was seen in 75.0% of PUMPER vs. 72.7% of non-PUMPER, a nonsignificant difference. Episodes of angina, nitroglycerin use and frequency of nitroglycerin use were reduced substantially in both groups.

Six-month follow-up data were completed for 79.9% of non-PUMPER and 76.7% of PUMPER. Table 3 summarizes the angina characteristics and nitroglycerin use at 6 months. A significant difference was found in the proportion of patients who had maintained their angina reduction. For PUMPER, 89% reported angina that was less than or the same as that immediately post-EECP, and

Table 2. Post-EECP results

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Hours of treatment (mean)	33.8	34.3
Completed treatment, %	82.8	88.8
Diastolic augmentation		
First-hour peak ratio***	0.8 ± 0.5	0.9 ± 0.5
Last-hour peak ratio***	1.1 ± 0.6	1.3 ± 0.6
CCS angina class, %**		
No angina	17.1	35.7
Class I	22.4	27.0
Class II	32.8	21.4
Class III	21.3	11.2
Class IV	7.1	5.6
Angina decreased by one or more classes, %	73.0	74.8
Decrease in angina episodes/week***	7.6 ± 11.6	5.2 ± 9.3
Nitroglycerin use, %	17.4	15.2
Decrease in frequency of nitroglycerin use/week*	7.0 ± 11.0	5.9 ± 10.5

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Results at 6 months after EECP treatment

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Completed 6-month follow-up	3,388 (79.9%)	165 (76.7%)
CCS angina class, %**		
No angina	25.1	51.9
Class I	20.8	19.2
Class II	29.8	20.5
Class III	18.2	7.6
Class IV	6.1	0.5
Angina episodes/week***	4.7 ± 7.8	1.9 ± 3.4
Angina same or less than post-EECP, %**	79.4	89.0
Overall success, %[a] ***	77.1	83.9
Nitroglycerin use, %***	45.3	19.5
Frequency of use/week	6.2 ± 8.6	3.4 ± 3.6

[a] Angina reduction from before to after EECP and no worsening at 6 months.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

83.9% reported less angina than they had before EECP. For the non-PUMPER group, the figures were 79.4 and 77.1% ($p < 0.01$ and $p < 0.05$, respectively). Adverse cardiac events occurring both during the treatment period and out to 6 months are shown in table 4. The frequency of major events (death/myocardial infarction/CABG/PCI) during the treatment period was very low for both groups, and although higher during the 6 months' follow-up period (6.3% for PUMPER, 10.8% for non-PUMPER, p = NS) was not significantly different between the two groups. At 6 months, revascularization had been performed in 6.1% of non-PUMPER and 5% of PUMPER. Interestingly, the non-PUMPER group patients were more likely to undergo PCI (4.2 vs. 0.6%, $p < 0.05$) and the PUMPER group was more likely to undergo CABG (4.4 vs. 1.9%, $p < 0.05$) despite the significantly higher prevalence of multivessel coronary artery disease in the non-PUMPER group. There was no significant difference in the revascularization rates at 6 months despite 100% of the PUMPER being candidates for revascularization versus only 16% of the non-PUMPER. At the end of the 6-month follow-up, myocardial infarctions (1.0 vs. 3.3%,

Table 4. Adverse events

	After EECP[1]		During follow-up[2]	
	non-PUMPER	PUMPER	non-PUMPER	PUMPER
Patients, n	4,239	215	3,388	165
Death, %	0.3	0.0	2.9	3.2
Myocardial infarction, %	0.7	0.9	3.3	1.0†
CABG, %	0.2	0.9*	1.9	4.4†
PCI, %	1.0	0.0	4.2	0.6†
Death/MI/CABG/PCI, %	1.9	1.4	10.6	8.0
Any hospitalization, %	–	–	21.9	8.8†††

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ comparing events after EECP.

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ comparing events during follow-up.

[1] Occurring during the period of EECP treatment and up to 5 days after the last day of treatment.

[2] Occurring from the 6th day after treatment to 6 months.

$p < 0.05$) and hospitalizations (8.8 vs. 21.9%, $p < 0.001$) were significantly lower for the PUMPER group; mortality was similar in both groups.

Discussion

Trials comparing medical versus surgical revascularization for coronary artery disease have focused on survival. Surgical revascularization has demonstrated benefit in the patient with three-vessel disease and in one- or two-vessel disease involving the proximal left anterior descending artery. The greatest absolute reduction in mortality is seen in patients with depressed left ventricular function. Those patients with preserved left ventricular function and one- or two-vessel disease not involving the left descending anterior artery would be expected to demonstrate only a marginal survival benefit from CABG. Extensive algorithms have been developed using clinical and angiographic variables to estimate surgical survival benefit, but are consistent with little evidence of benefit in the low-risk (1% annual mortality) patient [14]. Evidence-based survival benefit from angioplasty is even more problematic.

In view of the above, EECP may have a role in the patient who continues to have disabling angina refractory to medical therapy but who, on the basis of limited coronary artery disease and preserved left ventricular function, would not be expected to show a mortality benefit with surgery. It may also have a role in the patient who does not wish to be exposed to the risks of CABG or PCI (e.g., cognitive deficits, stroke, death, perioperative myocardial infarction). Depending on its effectiveness in improving myocardial perfusion, EECP revascularization may also benefit patients in moderate or higher cardiac risk groups. EECP is a noninvasive technique, potentially widely accessible, and robust in its effectiveness in relieving angina.

Though there were initial concerns regarding the potential for exacerbating peripheral arterial insufficiency, precipitating heart failure, and in causing pulmonary emboli, clinical follow-up of over 5,000 patients has shown EECP to be safe and effective. Indeed, EECP has been successfully used in patient groups at increased risk for traditional revascularization (women, elderly including patients >100 years old [15], diabetics [16], end-stage renal disease, depressed left ventricular function [17]).

While the PUMPER group would be expected, from the clinical and angiographic information collected, to have a lower annual cardiac mortality than the non-PUMPER group, they are still largely a moderate-risk group, and as such, they still may not represent the low-risk medically refractory patient who would demonstrate the greatest benefit/risk from EECP. The comparison of the PUMPER and non-PUMPER groups can, however, provide information regarding the relative efficacy, durability and morbidity and mortality of the two groups. While PUMPERs demonstrated a significantly greater hemodynamic effect from EECP during treatment, immediate post-treatment benefits in angina reduction and improvement in angina functional class were similar in both groups. However, at 6 months' follow-up the PUMPER were found to be significantly more likely to maintain or further reduce their angina (fig. 1). While no significant differences were found in major adverse cardiac events

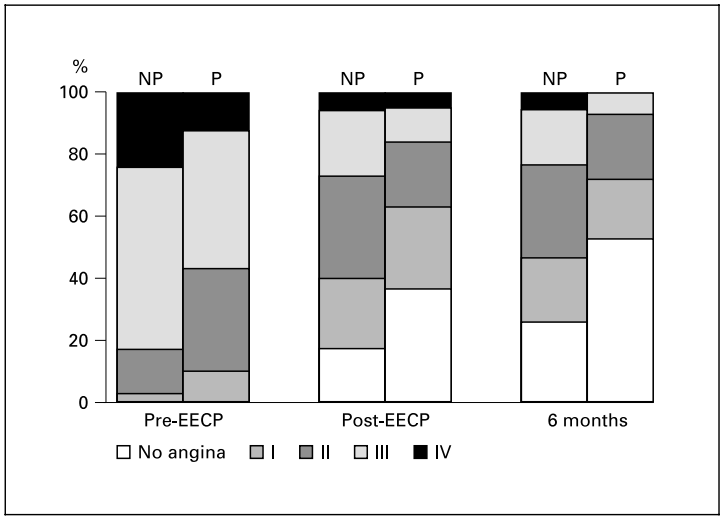

Fig. 1. CCS functional class before EECP, immediately after EECP, and at 6 months after EECP in the non-PUMPER (NP) and PUMPER (P) groups.

between the groups, there were significantly greater and more durable relief of angina, less myocardial infarctions, and fewer hospitalizations in the PUMPER group at 6 months. These findings may support there being a greater success in revascularization in the PUMPER group, which had less extensive coronary disease.

Conclusions

Previously unrevascularized angina patients who are candidates for elective CABG or PCI respond to treatment with EECP with decreased anginal episodes and nitroglycerin use and with improvement in their CCS functional class, similarly to previously revascularized patients. Treatment with EECP resulted in sustained, and often progressive, reduction in angina over the succeeding 6 months. It is interesting to speculate, given the findings of this study, on the proper role of EECP in treating angina patients. Should EECP, a noninvasive therapy, be used as the primary 'revascularization' intervention after medical therapy proves unsatisfactory? Does EECP 'revascularization' alter the risk of cardiac events and mortality sufficiently to justify its use as an alternative in moderate- or high-risk patients? Or should EECP continue to be reserved for patients refractory to medical therapy who are poor candidates for surgical revascularization? While the current study leaves these questions unanswered, it will hopefully promote interest in the appropriately designed study to test these questions. Long-term follow-up will be performed on current study participants to evaluate the duration of benefit and the impact on morbidity, mortality and resource utilization associated with using EECP as the initial treatment for angina.

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