Comparison of Patients Undergoing Enhanced External Counterpulsation and Percutaneous Coronary Intervention for Stable Angina Pectoris

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Enhanced external counterpulsation (EECP) has recently emerged as a treatment option for angina in selected patients suitable for revascularization with percutaneous coronary intervention (PCI). We compared baseline characteristics and 1-year outcome in 2 cohorts of PCI candidates presenting with stable symptoms: 323 patients treated with EECP in the International EECP Patient Registry (IEPR), and 448 NHLBI Dynamic Registry patients treated with elective PCI. Compared with patients receiving PCI, IEPR patients had a higher prevalence of many risk factors including prior PCI (53.0% vs 33.3%, p <0.001), prior coronary artery bypass grafting (42.1% vs 18.6%, p <0.001), prior myocardial infarction (56.4% vs 27.8%, p <0.001), history of congestive heart failure (16.8% vs 9.2%, p <0.01), and history of diabetes (37.9% vs 23.5%, p <0.001). Left ventricular ejection fraction was lower among IEPR patients (mean 50.3% vs 59.2%, p <0.001). At 1 year, survival was comparable in the 2 cohorts (98.7% IEPR vs 96.8% PCI, p = NS), as were rates of coronary artery bypass grafting during follow-up (4.5% IEPR vs 5.7% PCI, p = NS). At 1 year, 43.7% of IEPR patients reported no anginal symptoms compared with 73.4% of Dynamic Registry patients (p <0.001). Rates of severe symptoms (Canadian Cardiovascular Society class III, IV, or unstable) at 1 year were 15.5% among IEPR patients and 9.5% in the Dynamic Registry (p = 0.02). PCI candidates suitable for and treated with EECP had 1-year major event rates comparable to patients receiving elective PCI. Although PCI was associated with substantially lower rates of 1-year symptoms, EECP may be a safe treatment option for selected patients with obstructive coronary disease. ©2002 by Excerpta Medica, Inc.

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Use of enhanced external counterpulsation (EECP) as a treatment for angina and myocardial infarction has steadily increased worldwide in the past 5 years, after reports of sustained benefit.[1–3] The International EECP Patient Registry (IEPR) was initiated in 1998 to document the safety, acute and long-term efficacy, and evolution of EECP in consecutive patients treated in clinical practice.[4] In the initial published series of 978 IEPR patients, 22% were classified as candidates for percutaneous coronary intervention (PCI) at the time EECP treatment was started. The use of PCI for anginal symptoms has also been constantly increasing, as intracoronary stents and other developments have increased feasibility and acute effectiveness of catheter-based intervention.[5,6] The National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry of Coronary Interventions was started in 1997 to assess contemporary PCI practice. The first cohort of patients underwent PCI from July 1997 until February 1998. This report compares patients in the 2 registries, examining baseline characteristics and 1-year outcome of consecutive PCI candidates treated in the setting of stable symptomatic angina.

METHODS

Study protocols: The University of Pittsburgh serves as the Coordinating Center for both the IEPR and NHLBI Dynamic Registry, whose protocols are briefly described below.

IEPR: All clinical centers using EECP as a treatment modality were invited to join the voluntary IEPR; this registry enrolled all consecutive patients undergoing at least 1 hour of EECP treatment with no clinical or other exclusions. All centers were approved by their institutional review boards for IEPR participation (if required), and all registry patients gave informed written consent for participation. All registry patients were treated with EECP equipment (Vasomedical, Inc., Westbury, New York) using a regimen previously described. In general, treatment was applied 1 to 2

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TABLE 1 Baseline Patient Characteristics by Registry

Variable	IEPR (n = 323)	PCI (n = 448)
Age (yrs)	65.7 ± 10.5	64.5 ± 11.6
Age >65 yrs	54.8%	48.7%
Male gender‡	79.9%	72.3%
Medical history		
Prior PCI*	53.0%	33.3%
Prior coronary artery bypass grafting*	42.1%	18.6%
Prior myocardial infarction*	56.4%	27.8%
Congestive heart failure‡	16.8%	9.2%
Risk factors		
Diabetes mellitus*	37.9%	23.5%
Systemic hypertension	62.5%	60.8%
Hyperlipidemia	67.9%	65.5%
Angina at time of index procedure (CCS class)*		
I	9.6%	5.3%
II	26.0%	41.4%
III	47.1%	48.3%
IV	17.3%	5.1%
Left ventricular ejection fraction (%)*	50.3 ± 10.8	59.2 ± 12.6
Ejection fraction category*		
<35%	10.7%	6.0%
36 49%	24.4%	12.0%
>50%	64.9%	82.0%
Extent of coronary disease		
Lesions reported in 2 native vessels	29.1%	33.5%
Lesions reported in 3 native vessels	29.1%	23.1%

*p <0.001; †p <0.01; ‡p <0.05.

hours/day, 5 to 6 days/week, with a minimum total of 35 hours defining a full course of treatment. At enrollment, patient demographics, medical history, disease characteristics, and symptoms were collected. At the last hour of treatment, status, the degree of diastolic augmentation achieved, untoward clinical events, and symptomatology were recorded. After the last treatment, telephone follow-up of clinical events, hospitalizations, and anginal status began at 6 months, and 1, 2, and 3 years.

NHLBI Dynamic Registry: The design of the Dynamic Registry, which includes 17 centers (14 of which participated in earlier NHLBI registries of balloon angioplasty), has been previously reported.[6] All centers were approved by their institutional review boards for IEPR participation if required. As in the IEPR, there are no exclusion criteria; consecutive patients undergoing insertion of a guide catheter as the first step of intended PCI have demographic, symptom, and medical histories collected at study entry, with procedure outcome and any in-hospital events collected at discharge. Patients who provided written informed consent for follow-up are contacted at a 1-year anniversary by phone or mail regarding events during follow-up and symptomatic status in the last 6 weeks.

Patients in the analysis: For this analysis, all patients undergoing initial EECP treatment from the opening of the IEPR until March 1, 2000, were considered; this cutoff date was selected to allow sufficient follow-up information in the study database. Of these 2,187 patients, 323 (14.8% of the entire cohort) who received index EECP treatment in the setting of stable exertional angina, and were classified as PCI candidates at time of index EECP, are included in this analysis.

In the Dynamic Registry, 448 consecutively enrolled patients who gave informed written consent for follow-up and underwent elective PCI for stable symptoms, without myocardial infarction in the previous 30 days, were included in this study (23.2% of the entire cohort of 1,931 patients).

Outcome measures: Mortality included death from all causes. In the Dynamic Registry, repeat visits to the catheterization laboratory during hospitalization for index PCI are not treated as repeat PCI procedures. One-year angina refers to the patient's self-reported level of exertional angina. In the IEPR, angina at time of follow-up contact was classified as Canadian Cardiovascular Society (CCS) classes I through IV, with unstable symptoms included in the class IV category. In the Dynamic Registry, patients who reported angina in the 6 weeks before contact had symptoms classified according to CCS class if symptoms were stable, with unstable symptoms classified separately. For maximum comparability, stable CCS class IV and unstable angina are considered as a single category throughout this report.

Statistical methods: Chi-square tests (including the Mantel-Haenszel chi-square for ordered categories) and *t* tests, as appropriate, were used to compare characteristics of IEPR and Dynamic Registry patients. One-year event rates were calculated using the Kaplan-Meier approach, and unadjusted comparisons of survival curves were performed using the log-rank test. In these exploratory analyses, a 2-sided p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics: Compared with patients receiving PCI in the Dynamic Registry, a larger proportion of IEPR patients were men (Table 1). Prior coronary intervention was more prevalent among IEPR patients at study entry, as was history of myocardial infarction, congestive heart failure, and diabetes mellitus. Whereas most patients in each cohort presented with either CCS class II or III angina, class I symptoms as well as class IV angina occurred more often among IEPR patients. Mean ejection fraction was significantly lower in the IEPR cohort (95% CI for difference in mean ejection fraction between PCI and IEPR cohorts, 6.9% to 10.8%); more than one third of IEPR patients had ejection fractions <50%. An accurate comparison of extent of coronary disease between the 2 cohorts is precluded by different criteria for significant disease in a vessel (≥70% stenosis in the IEPR, and ≥50% in the Dynamic Registry). Thus,

TABLE 2 Baseline Patient Characteristics by Registry According to Previous Intervention

Variable	Previous Intervention		No Previous Intervention	
	IEPR (n = 221)	PCI (n = 187)	IEPR (n = 102)	PCI (n = 261)
Age (yrs)[‡,¶]	64.6 ± 10.3	67.5 ± 10.7	68.2 ± 10.4	62.4 ± 11.8
Age >65 yrs[¶]	51.1%	59.4%	62.8%	41.0%
Male gender	82.4%	77.0%	74.5%	69.0%
Medical history				
Prior PCI	76.9%	79.7%		
Prior coronary artery bypass grafting[‡]	61.6%	44.6%		
Prior myocardial infarction[‡,¶]	65.6%	41.3%	36.3%	18.2%
Congestive heart failure	20.0%	13.9%	9.8%	5.8%
Risk factors				
Diabetes[‖]	39.4%	30.3%	34.7%	18.6%
Systemic hypertension	64.7%	61.8%	57.6%	60.1%
Hyperlipidemia	70.5%	71.2%	62.4%	61.2%
Angina at the time of index procedure (CCS class)[‡]				
I	9.1%	2.8%	10.8%	7.0%
II	23.1%	37.9%	32.4%	43.8%
III	47.5%	55.9%	46.1%	43.0%
IV	20.4%	3.4%	10.8%	6.2%
Left ventricular ejection fraction (%)[‡,¶]	49.1 ± 10.7	55.5 ± 13.6	53.2 ± 10.3	61.1 ± 11.6
Ejection fraction category				
<35%	12.8%	11.2%	6.0%	3.4%
36 49%	30.5%	16.9%	10.7%	9.6%
>50%	56.7%	71.9%	83.3%	87.0%
Extent of coronary disease				
Lesions reported in 2 native vessels	34.4%	26.9%	17.7%	38.0%
Lesions reported in 3 native vessels[§]	33.9%	44.0%	18.6%	8.9%

*p <0.05; †p <0.01; ‡p <0.001 within patients with previous intervention.
§p <0.05; ‖p <0.01; ¶p <0.001 within patients without previous intervention.

while the proportion of patients with disease reported in multiple vessels was similar in the 2 cohorts, it is possible that the actual extent of the disease was somewhat more severe in IEPR patients.

Table 2 lists baseline characteristics for patients stratified according to history of prior intervention (coronary artery bypass grafting or PCI) at entry. Of note, among patients without prior revascularization, those treated with EECP were, on average, older, whereas among patients with prior intervention, those in the IEPR cohort were slightly younger. The between-registry differences with respect to prior myocardial infarction and mean ejection fraction observed in the overall comparison of Table 1 also remained significant within the subgroup comparisons.

Outcome of initial procedure: Among the 323 patients treated with EECP, 85.8% completed a full course of treatment. Reasons for failure to complete EECP treatment included disruption of treatment due to medical event or voluntary discontinuation of treatment by the patient. Among the 448 patients treated with PCI, 92.1% had a successful initial procedure, defined as a reduction of stenosis in all attempted lesions by at least 20% to a final stenosis <50%, without occurrence of death, myocardial infarction, or emergency coronary artery bypass grafting during post-PCI hospitalization.

Events and status at one year: Survival during follow-up was comparable in the 2 cohorts (p = NS by log-rank test), with 1-year Kaplan-Meier rates of 98.7% among IEPR patients (95% CI for 1-year mortality, 0.5% to 3.5%) and 96.8% among the PCI cohort (95% CI for 1-year mortality, 1.9% to 5.4%). One-year rates of coronary artery bypass grafting were also comparable (p = NS) at 4.5% among IEPR patients (95% CI, 2.7% to 7.7%) and 5.7% for PCI patients (95% CI, 3.9% to 8.3%).

A substantially higher proportion of Dynamic Registry patients underwent PCI during follow-up (Figure 1); 1-year PCI rates were 6.3% in the IEPR (95% CI, 4.0% to 9.9%) and 17.2% in the Dynamic Registry (95% CI, 14.0% to 21.1%). Repeat EECP, an outcome not monitored in the Dynamic Registry, was reported in 9.1% of IEPR patients (95% CI, 6.2% to 13.0%) during the first year.

A larger proportion of IEPR patients alive and contacted at 1 year reported use of calcium channel blockers, long-acting nitrates, and angiotensin receptor blockers compared with Dynamic Registry patients (Table 3). Higher 1-year calcium channel blocker and long-acting nitrate use among IEPR patients were also found among patients with previous intervention (calcium channel blocker use, 50.3% IEPR vs 39.9% PCI [p = 0.051]; nitrate use, 58.2% IEPR vs 35.3% PCI [p <0.001]) as well as patients without prior intervention (calcium channel blocker use, 51.4% IEPR vs 29.3% PCI [p <0.001]; nitrate use, 40.5% IEPR vs 26.9% PCI [p = 0.025]).

Of note, among patients with anginal symptoms at 1 year, nearly twice as many Dynamic Registry patients reported use of short-acting nitroglycerin as did IEPR patients. This difference was also noted among

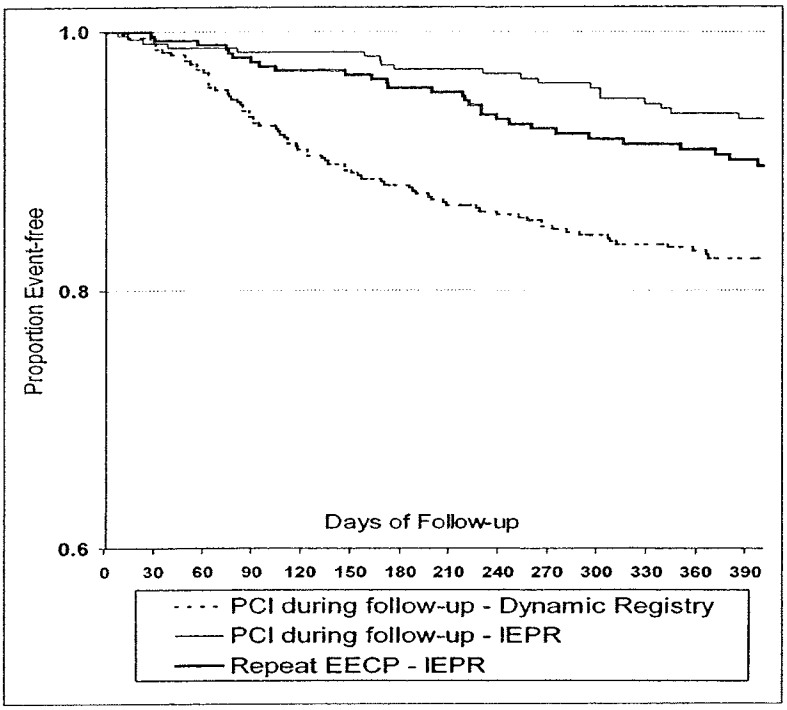

FIGURE 1. Kaplan-Meier curves for freedom from PCI during follow-up by registry (p <0.001 for comparison of IEPR vs Dynamic Registry freedom from PCI curves by log-rank test), and for freedom from repeat EECP (this outcome was monitored for IEPR patients only).

TABLE 3 Medication Use and Angina Status at One-Year Follow-Up by Registry (in patients alive and contacted at one year)

Variable	IEPR (n = 251)	PCI (n = 422)
Medication use		
β Blockers	53.8%	54.7%
Calcium channel blockers*	50.6%	33.7%
Long-acting nitrates*	53.0%	30.3%
ACE inhibitors	26.7%	28.0%
Angiotensin-receptor blockers‡	5.6%	1.9%
Short-acting nitroglycerin for angina (in patients with angina at 1 year)*	43.3%	82.2%
Angina status (CCS class)‡		
No angina	43.7%	73.4%
Class		
I	22.0%	5.1%
II	18.8%	12.1%
III	11.8%	5.1%
IV/unstable	3.7%	4.4%

*p <0.001; †p <0.01 for comparison of proportions.
‡p <0.001 for comparison of prevalence of any angina, and p = 0.02 for prevalence of class III or IV/unstable angina.

patients with previous intervention (proportion of those with 1-year symptoms using nitroglycerin, 42.5% IEPR vs 81.6% PCI [p <0.001]) and among those without prior intervention (46.4% IEPR vs 82.8% PCI, p <0.001).

Table 3 shows that 43.7% of IEPR patients and 73.4% of patients in the Dynamic Registry alive and contacted at 1 year reported no anginal symptoms (p <0.001 for comparison). When present, symptoms were generally mild or moderate (class I or II) among IEPR patients, with more severe symptoms relatively infrequent in either cohort. Class III, IV, or unstable symptoms were reported in 15.5% of patients initially treated with EECP and in 9.5% of patients in the PCI cohort, a statistically significant difference (p = 0.02).

Because baseline angina status was not equivalent in the 2 cohorts, it is informative to compare 1-year symptoms according to angina severity at the time of the index procedure. Figure 2 shows anginal status at 1 year among patients alive and contacted according to baseline symptom severity. As was the case for the overall comparison, prevalence of 1-year symptoms was significantly higher among IEPR patients within all baseline symptom subgroups. This was also the case within other important subgroups examined: patients with previous intervention (1-year symptom rates of 63.9% IEPR vs 30.0% PCI, p <0.001), patients without previous intervention (38.4% IEPR vs 24.3% PCI, p = 0.02), men (57.9% IEPR vs 24.7% PCI, p <0.001), and women (50.0% IEPR vs 31.6% PCI, p = 0.03).

DISCUSSION

This exploratory comparison of symptomatic PCI candidates treated with EECP to patients treated with PCI points out important differences in clinical presentation. Compared with patients treated with PCI, stable symptomatic patients receiving EECP who were also PCI candidates tended to present with a markedly higher risk profile. Although most patients in both cohorts presented with class II or III symptoms, more IEPR patients had very mild or very severe angina at the time of treatment. IEPR patients also tended to have more left ventricular dysfunction.

Despite the higher risk profile among IEPR patients, their 1-year mortality rate was relatively low, and comparable to PCI patients. Although assessment of any risk-adjusted EECP survival benefit is not appropriate in this report due to the small numbers of events and limitations of data collection and comparability, the similarly observed survival suggests that EECP may be a safe treatment option for selected PCI candidates. The need for subsequent invasive intervention, either catheter-based or surgical, was also quite low in patients treated with EECP.

PCI was clearly (and not surprisingly) superior to EECP in terms of eradicating anginal symptoms at 1 year after the procedure. In addition, severe or unstable symptoms occurred in approximately 16% of IEPR patients versus 10% of the PCI cohort. The

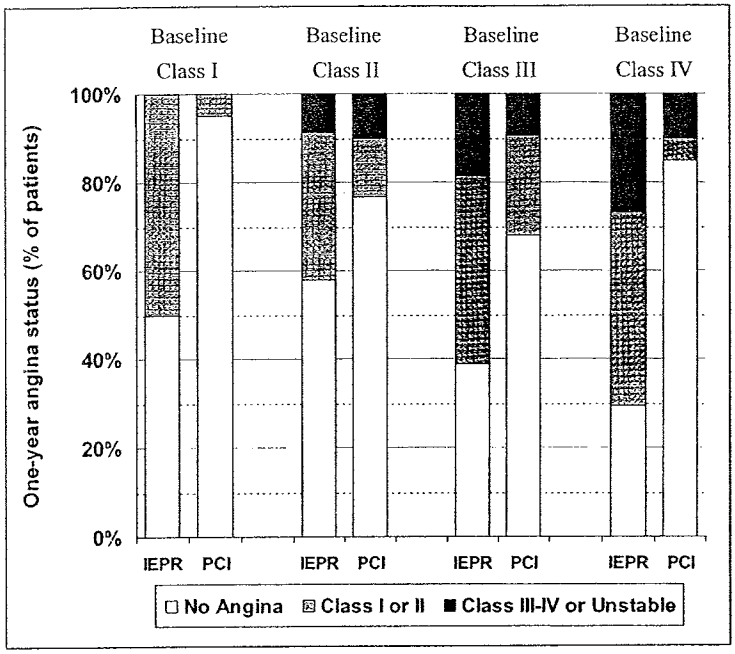

FIGURE 2. Angina status at 1-year follow-up by registry and baseline angina class. p = 0.001 for comparison by registry of prevalence of any angina at follow-up among patients who were in class I at baseline; p = 0.004 for class II; p <0.001 for classes III and IV; p = NS for comparison by registry of prevalence for classes III to IV or unstable angina at follow-up among baseline classes I, II, and IV patients; and p = 0.02 within class III patients.

increased likelihood of anginal symptoms after the procedure may be viewed by some patients who are considering undergoing EECP as an acceptable "price to pay" to avoid or defer a more invasive revascularization approach, in the same fashion that some patients eligible for PCI and coronary artery bypass grafting opt to have initial PCI despite the greater efficacy of coronary artery bypass grafting in relief of long-term symptoms in the setting of extensive CAD.[7]

Several important limitations are inherent in this comparison of patients from 2 registries enrolling at primarily different centers. Data collected are limited and occasionally (as in the case of vessel disease) not directly comparable between studies, precluding meaningful estimation of any risk-adjusted treatment benefit. Designation of an IEPR patient as a PCI candidate was generally not performed by a PCI op-erator, who would be most qualified to make this determination based on detailed angiographic and clinical evidence. Finally, self-reported angina based on mail or telephone interview is subject to potential bias, although coordinators in both registries were trained in the assessment and definitions of follow-up symptoms.

Despite these limitations, our comparison suggests that in selected patients with symptomatic coronary disease suitable for treatment with PCI, EECP may be a safe treatment option. Whereas freedom from angina 1 year after EECP is less than observed with PCI, most patients treated with EECP report some reduction in angina severity. In addition to use as an initial therapy for patients without prior intervention, EECP may have a potential role as a treatment to optimize the results of previous revascularization procedures. We hope that the findings of this report and others will facilitate the planning of future clinical trials to definitively address the role of EECP in clinical practice.

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