Enhanced External Counterpulsation for the relief of angina in patients with diabetes: Safety, efficacy and 1-year clinical outcomes

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Background Patients with diabetes are at greater risk for coronary events, yet they are less likely to benefit from revascularization than those without diabetes. Enhanced external counterpulsation has recently emerged as a treatment option for select patients with chronic stable angina.

Methods We examined baseline characteristics, angina response, and cardiac outcomes of patients with diabetes mellitus treated with Enhanced External Counterpulsation (EECP) for chronic stable angina. Data were collected from patients enrolled in the International EECP Patient Registry (IEPR) before and after a course of EECP, and at 1 year after completion of treatment.

Results Of 1532 IEPR patients studied, 43% had diabetes mellitus at baseline. Patients with diabetes were experiencing, on average, 11 episodes of angina per week. Most had been revascularized with prior percutaneous coronary intervention or coronary artery bypass graft surgery (86%) and most were considered unsuitable for either additional procedure (87%). Treatment was completed as prescribed in 79% of patients (mean, 32 hours). Immediately after EECP, 69% of patients with diabetes demonstrated a reduction in angina of ≥1 Canadian Cardiovascular Society angina class. After 1 year, maintenance of angina reduction was reported in 72% of patients with diabetes. Quality of life was significantly improved. Despite a high-risk profile among the diabetic group in this study, 1-year mortality was similar to coronary intervention registry populations.

Conclusion This study suggests that in select patients with diabetes, EECP can be a safe, effective, well-tolerated treatment option for the relief of angina. (Am Heart J 2003;146:453–8.)

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Coronary artery disease starts earlier, is often more advanced at presentation and progresses more rapidly in patients with diabetes (DM). Despite a substantial decline in mortality from coronary artery disease in recent years, smaller declines in mortality in patients with DM have been realized.[1] Most previous studies have shown that diabetes is associated with higher rates of restenosis after angioplasty,[2–4] increased graft occlusion after bypass surgery,[5] and increased short[6–9] and long-term[2,3,6,7,10–13] morbidity and mortality after both forms of revascularization. The risk of complications after repeat revascularization procedures is increased particularly in patients with diabetes.[14,15]

The search for improved therapeutic options for patients with chronic angina has yielded a wide range of coronary revascularization techniques and procedures. In 1995 the Food and Drug Administration cleared Enhanced External Counterpulsation (EECP) for the treatment of angina. The results of MUST-EECP, a multicenter, randomized, masked, sham-controlled study, confirmed that EECP was safe and effective in treating chronic angina.[16] Further research has shown objectively that EECP improves myocardial perfusion[17–19] and that improvement in angina and quality of life may be sustained for many years.[17,20,21]

This report describes a prospective observational study of patients with diabetes undergoing EECP for

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Table I. Baseline characteristics of EECP patients by diabetes status

	No diabetes (n = 867)	Diabetes (n = 665)	*P*
Age (y)	66.3 ± 11.0	65.6 ± 10.3	NS
Male (%)	78.9	65.4	.001
White (%)	93.5	91.4	NS
Prior PCI (%)	63.9	67.6	NS
Prior CABG (%)	69.6	67.4	NS
Prior PCI or CABG (%)	86.9	86.1	NS
Congestive heart failure (%)	24.8	39.6	.001
Noncardiac vascular disease (%)	22.0	35.1	.001
Candidate for PCI (%)	12.0	9.1	NS
Candidate for CABG (%)	15.1	9.9	.01
Candidate for neither (%)	82.3	87.3	.01

*Data are mean ± SD or percentages. *CABG*, Coronary artery bypass surgery; *NS*, not significant; *PCI*, percutaneous coronary intervention.

treatment of angina who were enrolled in the International EECP Patient Registry (IEPR).

Methods

The EECP device consists of 3 paired pneumatic cuffs applied to the lower extremities. Cuffs are inflated sequentially (applying 250–300 mm Hg of external pressure) during diastole, returning blood from the legs to the central circulation, producing aortic diastolic augmentation, increasing both venous return and cardiac output. The cuffs are then deflated at end-diastole, reducing peripheral resistance and providing left ventricular unloading. Daily 1- to 2-hour treatment sessions are typically administered for a total treatment course of 35 hours.

The IEPR began in January 1998, and currently >5000 patients with chronic angina have been enrolled from >80 centers in the United States and other countries. The study group consisted of 1532 patients enrolled in the registry from 44 clinical sites between January 1998 and September 2000 and thus had reached their 1-year follow-up time point. Registry methodology has been described previously.[22] All treatment was carried out using EECP equipment (Vasomedical, Westbury, NY).

Patients were defined as having diabetes if they reported a physician diagnosis of diabetes; the validity of this method has been demonstrated previously.[23] Data on demographics, medical history, coronary disease status and medication were collected on patients before EECP treatment. No attempt was made to maintain current medication regimens throughout the study, although patients referred for EECP were considered "optimally medically managed." Angina severity was assessed using the Canadian Cardiovascular Society classification system.[24] Angina frequency and sublingual nitroglycerin use were recorded as the number of weekly episodes or doses averaged over the prior 6-week period. Patients were asked to assess their current quality of life, health, and satisfaction with quality of life on 5-point Likert scales (1 = excellent, 2 = very good, 3 = good, 4 = fair, 5 = poor). During the visit for the final EECP session, data were collected on angina status, medication, quality of life, and adverse clinical events. Events occurring in the time interval between the first session and 5 days after the last EECP session were defined as having occurred in the 'post-EECP' period. Events occurring after this but within 1 year of the last EECP session were defined as having occurred in the 1-year follow-up period. Major adverse cardiac events were defined as death, myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention. Patients were interviewed by telephone at 6 months and 12 months after the final EECP treatment session to record angina status, quality of life, cardiac and other events.

Results are presented as percentages or means (± SD). The χ^2 or Fisher exact test was used to compare categorical data, and the Wilcoxon rank-sum test was used for continuous variables. A P value of $<.05$ was considered statistically significant for comparison of groups. Events occurring up to 12 months (mean 333 days [± 104 days]) from the start of EECP therapy have been analyzed. Calculations were performed using the SAS (Cary, NC) statistical package.

Results

Baseline characteristics

Of 1532 patients analyzed, 43% reported a physician diagnosis of diabetes. At baseline, patients in groups with and without diabetes were experiencing, on average, 11 angina episodes per week and required 10 to 11 sublingual doses of nitroglycerin per week. More than 86% of patients in both groups had previous revascularization procedures (Table I). Patients with diabetes were more likely to have a history of heart failure, and a greater proportion of patients with diabetes were considered unsuitable for repeat revascularization procedures. There was a statistically significant difference between groups in terms of sex: the group with diabetes had more female patients. In addition, family history of coronary artery disease (DM vs no diabetes [ND], 80% vs 74%, $P < .01$), hypertension (81% vs 63%, $P < .001$) and noncardiac vascular disease (35% vs 22%, $P < .001$) were reported more often in the group with diabetes. Mean (SD) left ventricular ejection fraction was similar in both groups (46% [14%] vs 47% [14%], P = not significant [NS]), as were the proportions with left ventricular ejection fraction <35% (19.8% vs 18.7%, P = NS). Angiotensin-converting enzyme inhibitors (45% vs 33%, $P < .001$), nitrates (84% vs 78%, $P < .01$) and angiotensin II receptor blockers (11% vs 8%, $P < .05$) were prescribed more often in patients with diabetes. There were no significant differences in the proportions taking β-blockers (71%),

Table II. Cardiac events during or within 5 days of the last day of EECP by diabetes status

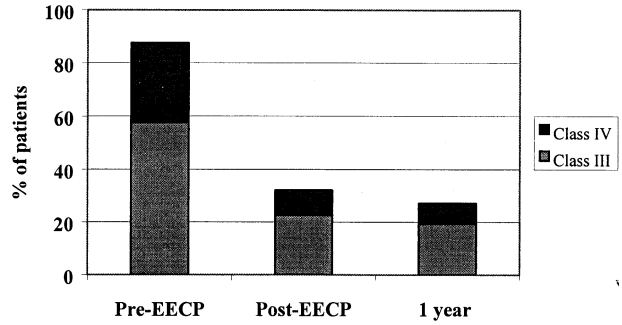
	No diabetes (n = 867)	Diabetes (n = 665)	P
Death (%)	0.5	0.3	NS
CABG (%)	0.3	0	NS
PCI (%)	0.8	0.8	NS
MI (%)	0.2	1.7	<.01
MACE (%)	1.6	2.7	NS
Unstable angina (%)	3.2	3.9	NS
Congestive heart failure (%)	1.3	3.3	<.01

MACE, Major adverse cardiac event (including death, MI, CABG, PCI); *MI*, myocardial infarction.

Table III. Cardiac events at 1-year follow-up by diabetes status

	No diabetes (n = 779)	Diabetes (n = 572)	P
Death (%)	3.9	7.5	<0.01
CABG (%)	3.8	3.6	NS
PCI (%)	6.1	7.7	NS
MI (%)	5.3	7.7	NS
MACE (%)	16.3	22.6	<.01
Unstable angina (%)	15.2	18.8	NS
Congestive heart failure (%)	6.1	12.8	<.001

Figure 1



Patients with diabetes with Canadian Cardiovascular Society angina Class III and IV.

calcium-channel blockers (47% vs 48%), lipid-lowering agents (71% vs 72%), or aspirin (77% vs 76%).

Outcome of initial treatment course

As presented in Table II, mean (SD) EECP therapy duration (DM versus ND, 32.3 [10.7] vs 33.2 [9.9] hours, P = NS) and completion rates (79% vs 82% respectively) were similar in both groups. Reasons for failure to complete a course of treatment included disruption of treatment due to a medical event or voluntary discontinuation of treatment by the patient. Skin breakdown (2.0% vs 0.7%, $P < .01$) and musculoskeletal complaints (1.5% vs 1.2%, P = NS) were infrequent in both groups. In the post-EECP period, myocardial infarction and heart failure occurred more often in the DM group than in the ND group. Post-EECP, angina had decreased by at least 1 Canadian Cardiovascular Society class in the majority of patients (DM versus ND, 69% vs 72%, P = NS).

Events and status at 1 year

One-year follow-up was completed in 86.0% of patients with diabetes (n = 572) and 89.9% of patients without diabetes (n = 779).

Death and episodes of heart failure occurring in the 1-year period after EECP were reported more frequently in the DM group. The incidences of unstable angina and repeat revascularization were similar in both groups (Table III).

Figure 1 shows the proportion of patients with diabetes and symptoms consistent with Canadian Cardiovascular Society angina class III and IV at baseline and during follow-up. There was a statistically significant reduction in angina class ($P < .001$) from pre- to post-EECP. The most frequent angina class was reduced from III to II after EECP and improvement was maintained at 1 year after completion of treatment. Episodes of angina and on-demand sublingual nitroglycerin use were also reduced during the follow-up period (Figure 2). In addition, patients reported significant improvement in quality of life (QoL), with improvement persisting at 1 year (Figure 3). The difference between pre- and post-EECP was statistically significant (health related QoL $P < .001$, overall QoL $P < .001$, and satisfaction with QoL $P < .001$).

Discussion

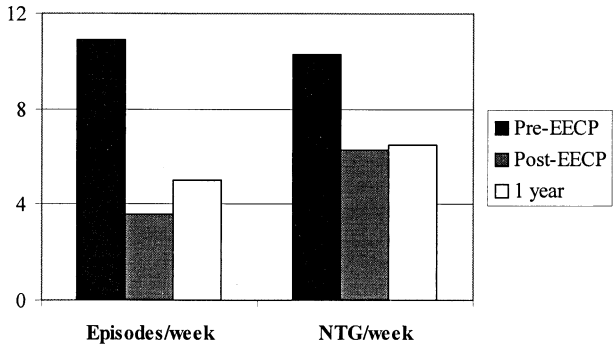
Effect on angina

This large, prospective, observational study suggests that EECP is safe and effective in treating angina in patients with diabetes. This effect was maintained in most patients at 1 year despite a high prevalence of severe symptomatic disease and prior revascularization, and a high proportion of patients who were considered unsuitable for additional standard revascularization procedures. Moreover, reduction in angina was achieved despite more advanced and severe cardiovascular disease in those with DM.

Mechanisms of action

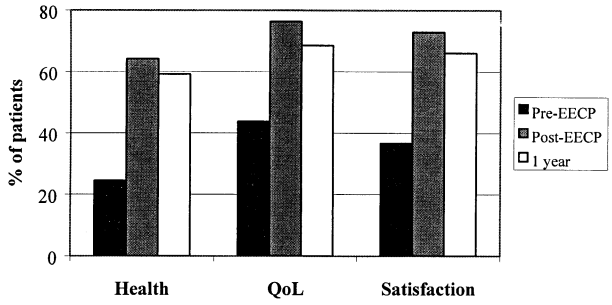
It has recently been demonstrated that EECP unequivocally and significantly increases directly measured coronary flow velocity and pressure accompa-

Figure 2



Angina frequency and nitroglycerin use in patients with diabetes. *NTG*, Sublingual nitroglycerin.

Figure 3



Patients with diabetes reporting good, very good or excellent quality of life. *QoL*, Quality of life.

nied by left ventricular systolic unloading.[27] Objective evidence of improved myocardial perfusion has been documented in patients after EECP,[17–19,28] and this may be due in part to improved collateral circulation,[29,30] perhaps secondary to increased transmyocardial pressure gradients occurring during therapy. Masuda et al have provided indirect evidence of improved collateral circulation by showing that EECP therapy is associated with improved myocardial perfusion by positron emission tomography, improved coronary flow reserve and improvement of time to ST depression during exercise.[18] Improvement in endothelial function was suggested in an early report showing that duration of EECP therapy correlates positively with levels of nitric oxide, and negatively with the vasoconstrictor endothelin-I, and that these biochemical changes persist for 3 months.[31] Augmented blood flow and increased shear stresses in the coronary and peripheral arterial beds could initiate these biochemical changes that could lead to vasodilation and vascular remodeling.[32] Another recent study has shown improved myocardial perfusion and improved left ventricular diastolic filling and decreased cardiac work after EECP.[28]

Table IV. Cumulative 1-year mortality in patients aged ≥55 years enrolled in coronary intervention studies

	IEPR (n = 1297)	NHLBI Dynamic Registry of PCI (n = 3186)	BARI (n = 2863)
No diabetes (%)	4.6	5.2	3
Diabetes (%)	7.7	10.1	6.9
No diabetes + CHF (%)	9.3	14.6	9.4
Diabetes + CHF (%)	11.9	20.3	12.5

IEPR, International EECP Patient Registry; *NHLBI*, National Heart Lung and Blood Institute; *BARI*, Bypass Angioplasty Revascularization Investigation; *CHF*, congestive heart failure.

Cardiac events

Comparison of patients with symptomatic coronary artery disease treated with EECP to patients treated with elective PCI (National Heart, Lung, and Blood Institute Dynamic Registry of Coronary Interventions) has recently been reported.[33] This comparison showed that patients treated with EECP have a higher prevalence of risk factors; and, although PCI was associated with substantially lower rates of 1-year anginal symptoms, 1-year survival and major event rates were comparable in both cohorts. Comparison of patients with diabetes with symptomatic coronary artery disease treated with EECP to patients enrolled in the Dynamic Registry and the Bypass Angioplasty Revascularization Investigation (BARI) has been explored (personal communication, Sheryl Kelsey). Initial evaluation reveals that, although patients with diabetes differ in the 2 registries, there is no evidence that 1-year mortality is increased in patients with diabetes treated with EECP (Table IV).

Clinical implications

Many patients have angina despite aggressive medical therapy and previous revascularization procedures. EECP can extend the range of treatment options for such patients. Although intracoronary stenting[34] and aggressive antiplatelet therapy[35,36] have improved immediate outcome and increased coronary patency rates after percutaneous coronary intervention,[37] the presence of diabetes is usually associated with worse outcomes[2–4,10–13] even with the application of these advances. The same relationship exists for patients undergoing coronary artery bypass surgery[6,7,9,13] and

repeat revascularization procedures.[14,15] The noninvasive nature of EECP therapy makes it an attractive alternative for patients with diabetes, particularly for those who have had previous revascularization procedures.[38]

Limitations

It is possible that some patients have been misclassified with respect to diabetes status and clinical events. However, this is the first study of its kind and clinical outcome is reported in a large number of patients. Angina classification is self-reported and therefore it is likely that there has been some placebo effect, though there is no reason to believe that this would have been different in groups with and without DM.

Conclusions

This study suggests that in patients with diabetes, EECP is safe, well tolerated and associated with improvement in angina, functional status and quality of life. Clinical benefit was maintained in most patients at 1 year. EECP may be useful in select patients with diabetes with severe cardiovascular disease who are considered unsuitable for further coronary intervention.

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