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EXCERPTA MEDICA

Effects of Enhanced External Counterpulsation on Stress Radionuclide Coronary Perfusion and Exercise Capacity in Chronic Stable Angina Pectoris

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Enhanced external counterpulsation (EECP) is an effective noninvasive treatment for patients with coronary artery disease (CAD). EECP has been demonstrated to improve anginal class and time to ST-segment depression during exercise stress testing. This study assesses the efficacy of EECP in improving stress-induced myocardial ischemia using radionuclide perfusion treadmill stress tests (RPSTs). The international study group enrolled patients from 7 centers with chronic stable angina pectoris and a baseline ischemic pre-EECP RPST. Patients' demographic and clinical characteristics were recorded. A baseline pre-EECP maximal RPST was performed within 1 month before EECP treatment. The results were compared with a follow-up RPST performed within 6 months of completion of a 35-hour course of EECP. Four centers performed post-EECP RPST to the same level of exercise as pre-EECP, whereas 3 centers performed maximal RPST post-EECP. The study enrolled 175 patients (155 men and 20 women). Improvement in angina, defined by ≥1 Canadian Cardiovascular Society angina class change, was reported in 85% of patients. In the centers performing the same level of exercise, 81 of 97 patients (83%) had significant improvement in RPST perfusion images. Patients who underwent maximal RPST revealed improvement in exercise duration (6.61 ± 1.88 pre-EECP vs 7.41 ± 2.03 minutes post-EECP, p <0.0001); 42 of the 78 patients (54%) in this group showed significant improvement in RPST perfusion images. Thus, EECP was effective in improving stress myocardial perfusion in patients with chronic stable angina at both comparable (baseline) and at maximal exercise levels. ©2002 by Excerpta Medica, Inc.

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Enhanced external counterpulsation (EECP) is an effective noninvasive treatment for coronary artery disease (CAD). EECP utilizes 3 sets of pneumatic cuffs applied to the lower extremities that inflate sequentially during diastole to provide diastolic augmentation, presystolic unloading, increased venous return, and cardiac output. EECP has been demonstrated to improve anginal class and time to ST-segment depression during exercise stress testing. The efficacy of EECP in producing sustained benefits over a long-term period after treatment has also been reported.[1,2] It has been hypothesized that the benefit of EECP in improving angina and exercise tolerance is secondary to development or recruitment of collaterals that enhance myocardial perfusion in areas with compromised blood flow.[3–6] Its role in modification of the neurohumoral derangements and endothelial dysfunction associated with cardiovascular disorders is an active area of investigation.[7–11] This international study was designed to assess the efficacy of EECP in improving exertional ischemia in chronic stable angina using radionuclide perfusion treadmill stress tests (RPSTs) and the impact of different patient characteristics (sex, age, extent of CAD, and history of coronary interventions) on effectiveness of the treatment. Pre-RPST was used to demonstrate exertional myocardial ischemia before treatment and was compared with post-EECP RPST as an objective means of assessing response to EECP treatment. In centers performing maximal RPST, exercise tolerance pre- and post-EECP was also compared.

METHODS

The international study group enrolled patients from 7 centers with chronic stable angina and a baseline ischemic pre-EECP RPST over a period of 7 years. Exclusion criteria were: congestive heart failure, aortic insufficiency, myocardial infarction within the previous 3 months, significant ventricular ectopic

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TABLE 1 Prevalence of Cardiovascular Risk Factors and Morbidities in the Study Population

Patient Characteristics	Prevalence (%)
Hypertension	56%
Diabetes	21%
Elevated cholesterol	71%
Smoking	22%
Peripheral vascular disease	9%
History of myocardial infarction	51%
History of heart failure	8%
Previous percutaneous coronary intervention	75%
Previous coronary bypass surgery	41%

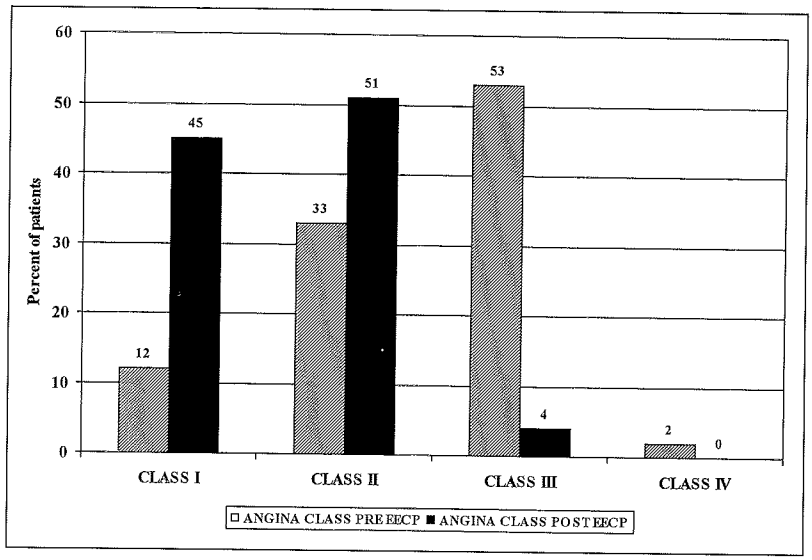

FIGURE 1. Comparison of CCS angina class before and after EECP treatment.

activity or atrial fibrillation, nonischemic cardiomyopathy, severe occlusive peripheral vascular disease, recurrent or active deep vein thrombophlebitis, uncontrolled systemic hypertension (blood pressure >180/110 mm Hg), and clinically significant bleeding diathesis (patients treated with aspirin, clopidogrel, or warfarin were included). Patients' age, sex, extent of CAD, and history of myocardial infarction, coronary angioplasty, or bypass surgery were recorded.

Patients were instructed to continue their usual medications. Canadian Cardiovascular Society (CCS) angina class was determined before and after completion of a 35-hour course of EECP therapy. A baseline pre-EECP maximal RPST was performed within 1 month before EECP treatment using a Bruce protocol with technetium-99m sestamibi or thallium-201 isotopes and single-photon emission computed tomography or planar imaging. The results were compared with a follow-up RPST, using the same technique, within 6 months of completion of a 35-hour course of EECP. Four centers performed post-EECP RPST to the same level of exercise as pre-EECP, whereas 3 centers performed RPST post-EECP to a maximal cardiac workload. The pre- and post-EECP RPSTs were read in a blinded fashion by 2 independent physicians for location, size, and severity of perfusion defects. Improvement was determined by a decrease in the size or number of reversible perfusion defects; deterioration was considered to be an increase in the size or number of perfusion defects. Patients in whom the original perfusion defects remained unchanged or in whom improved perfusion in initial defects were balanced by decreased perfusion in other areas were read as unchanged.

Patients were treated with EECP 1 hour daily for a total of 35 hours. All patients were monitored clinically and hemodynamically, by oximetry and electrocardiographic monitoring, during EECP treatment. The diastolic augmentation pressures were progressively increased by increasing the external compression. The maximal external compression used to maximize the diastolic/systolic pressure ratio (diastolic augmentation) was 225 to 275 mm Hg. Blood pressure waveforms were continuously monitored by finger plethysmography. Adjustment in anginal medications were determined by patients and their physicians during the course of the study and any changes were documented. No other interventions were performed during the study.

The analysis of demographic characteristics and determination of their relation to perfusion improvement were performed with testing for statistical significance using the chi-square test; statistical significance was set at $p < 0.05$. The pre- and post-EECP exercise parameters were compared and evaluated for statistically significant differences using a paired 2-tailed Student's *t* test.

RESULTS

The study enrolled 175 consecutive patients with follow-up (155 men and 20 women, mean age 61 ± 9.5 years). Patients characteristically exhibited multiple risk factors for cardiovascular diseases, had had prior cardiac events and interventions, and were considered refractory to medical therapy and unsuitable for further revascularization (Table 1).

Overall, 85% of patients reported improvement in angina of ≥1 CCS angina class, and 15% reported improvement by ≥2 CCS angina classes (Figure 1).

In centers performing the same level of exercise pre- and post-EECP, 81 of 97 patients (83%) had significant improvement in RPST perfusion defects; 16 patients had no improvement. None of the patients had worsening of the RPST.

Patients who underwent maximal RPST revealed improvement in exercise duration (6.61 ± 1.88 pre-EECP vs 7.41 ± 2.03 minutes post-EECP, $p < 0.0001$) with no significant change in double product (20,389 ± 5,100 vs 20,408 ± 5,572). In this group, 42 of 78

TABLE 2 Comparison of Exercise Parameters Between Patient Groups With Same Pre- and Postenhanced External Counterpulsation (EECP) Level of Exercise Versus Maximal Post-EECP Level of Exercise

	Exercise Time Pre-EECP	Exercise Time Post-EECP	Double Product Pre-EECP	Double Product Post-EECP
Same pre- and post-EECP level of exercise (n = 97)	7.46 ± 2.85	7.62 ± 3.01	20,816 ± 5,411	19,786 ± 4,939*
Maximal post-EECP level of exercise (n = 78)	6.61 ± 1.88	7.41 ± 2.03†	20,389 ± 5,100	20,408 ± 5,572

*$p < 0.05$; †$p < 0.0001$.

patients (54%) showed improvement in RPST defects, 33 (42%) patients had unchanged RPSTs, and 3 (4%) patients revealed worsening of RPSTs (Table 2).

Patients with a history of angioplasty had a higher rate of improvement in RPST compared with those who had no history of percutaneous revascularization (74% vs 48%, $p < 0.025$). There were no significant differences in the percentage of patients improving with EECP treatment by other patient characteristics. EECP was well tolerated by patients enrolled in the study.

DISCUSSION

Patients in this study, who underwent maximal RPSTs, showed a significant improvement in exercise duration after EECP therapy without significant alteration of the double product. Thus, in these patients, the observed improvement in RPST perfusion was not caused by an alteration in the determinants of myocardial oxygen demand, but was rather a reflection of improved myocardial perfusion (increased supply). This supports the hypothesis that EECP improves myocardial perfusion via collateral recruitment or development (angiogenesis).

The patient group who underwent RPSTs at the same level of exercise showed an even greater improvement in post-EECP RPST perfusion. In contrast to the patients who underwent post-EECP maximal RNSTs, patients who exercised to the same cardiac workload attained a significantly lower double product on post-EECP RPST. The lower double product reflects a decrease in myocardial oxygen demand at the same exercise level and would be expected to decrease the size and number of ischemic defects. This finding has been previously reported post-EECP as analogous to the peripheral vascular conditioning effect seen with exercise, in which improved vasomotor tone decreases the blood pressure response to exercise.[4]

In this study, the patients served as their own controls. An inactive EECP control with double blinding is difficult given the nature of the treatment. Although CAD is unpredictable in its course, regression would not be expected to occur over 6 to 7 weeks in this group of patients, whose angina is disabling or progressive over a period of months and years. The enrolled patients did not undergo any change in or initiation of simultaneous therapy, such as diet, lipid reduction, weight loss or smoking cessation, and the stable medical regimen was maintained.

The study cohort was predominantly male; therefore definitive conclusions regarding efficacy in women should await further studies. The long-term sustained clinical benefit of EECP has been previously reported. Our study analyzed the effect of EECP on coronary perfusion in the early period after treatment. The long-term maintenance of improved coronary perfusion needs further investigations.

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