Efficacy of Enhanced External Counterpulsation in the Treatment of Angina Pectoris

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Eighteen patients with chronic angina despite surgical and medical therapy were treated with an improved system of enhanced external counterpulsation (EECP) (1 hour daily for a total of 36 hours). Patients underwent a baseline treadmill thallium-201 stress test. After EECP treatment, a thallium stress test was repeated for the same exercise duration. One week after treatment, patients also underwent a maximal stress test. All patients improved in anginal symptoms and generally decreased antianginal medications, with 16 obtaining complete relief from angina. Pre- and post-thallium stress testing performed for the same duration showed complete resolution of ischemic defects in 12 patients (67%), reduction in the area of ischemia in 2 (11%), and no change in 4 (22%). Thus, a decrease in myocardial ischemia was observed in 14 patients (78%; $p < 0.01$). The exercise duration of maximal stress testing after EECP significantly improved from 8.14 ± 0.71 to 9.72 ± 0.77 minutes ($p < 0.005$), although the double product did not change significantly. Analysis of these 2 tests in the subgroup of 14 patients with improvement in thallium studies showed significant increases in both exercise duration (8.58 ± 0.66 to 10.44 ± 0.59 minutes; $p < 0.001$) and double product (21,827 ± 2,044 to 24,842 ± 1,707 mm Hg · beats/min; $p < 0.01$).

The improvement in reperfusion defects and increase in exercise duration are reflections of improved perfusion to ischemic regions of the myocardium. EECP uses additional thigh balloons and sequenced balloon inflation, effecting a significant increase in diastolic augmentation over previously available methods. It appears to be a safe and effective therapy for selected patients with chronic angina.

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External counterpulsation is a noninvasive treatment that has been demonstrated to improve survival in patients with cardiogenic shock after myocardial infarction[1] and to significantly reduce the mortality rate during the acute period after myocardial infarction.[2] Its physiologic effects are accomplished by increasing myocardial oxygen supply through increasing diastolic perfusion pressure and by reducing cardiac work load through decreasing left ventricular afterload. The efficacy of external counterpulsation in producing sustained benefits in patients with angina is unknown. The purpose of this study was to determine whether an improved system of enhanced external counterpulsation (EECP) alleviates the symptoms of patients with chronic angina and produces a sustained increase in the perfusion of the ischemic myocardium. Specifically, we assessed whether the hemodynamic changes produced by EECP would result in a sustained reduction of exertional ischemia and angina, and in an improved exercise tolerance. Thallium imaging was used to demonstrate exertional myocardial ischemia before treatment with EECP and to test for its presence after EECP. The change in functional status after EECP was assessed by symptom-limited stress testing.

METHODS

Patients: Patients with chronic, stable angina, despite medical and surgical therapy, and evidence of exertional ischemia by thallium-201 perfusion imaging were considered for inclusion in the study. Exclusion criteria were: clinical congestive heart failure, aortic insufficiency, myocardial infarction within the previous 3 months, significant ventricular ectopic activity or atrial fibrillation, nonischemic cardiomyopathy, severe occlusive peripheral vascular disease, recurrent deep vein thrombophlebitis, systemic hypertension (>180/110 mm Hg) and a bleeding diathesis.

Protocol: Patients were instructed to continue their usual medications. A baseline treadmill thallium-201 study was performed in all patients, using the standard Bruce protocol (test 1). The exercise was terminated because of symptoms such as chest pain, fatigue, dyspnea and claudication. The double product was calculated as the product of heart rate and systolic blood pressure obtained at peak exercise. Two minutes before cessation of exercise, 2.5 mCi of thallium-201 were injected intravenously and planar imaging was performed in the left anterior oblique, left lateral and anterior projections. Three hours later, redistribution images were obtained using the same projections. Reversible defects were considered indicative of myocardial ischemia, whereas fixed defects were considered to indicate myocardial infarction. Reinjection imaging was not performed. All thalli-

um scans were interpreted by 2 experienced observers who did not know of the patient's participation in the study.

Patients were treated with EECP 1 hour daily for a total of 36 hours (Figure 1). All patients were monitored hemodynamically and clinically during EECP treatment. The diastolic augmentation pressures were progressively increased by increasing the external compression. The maximal external pressure used to maximize the diastolic/systolic pressure ratio (diastolic augmentation) was 280 mm Hg. Blood pressure waveforms were continuously monitored by finger plethysmography. Adjustments in anginal medications were determined by patients and their physicians during the course of the study. No other interventions were performed during the study.

After completing the course of EECP therapy, a thallium-201 stress test (with usual medications continued) was performed for the same exercise duration as at baseline to provide comparison of test results (test 2). Furthermore, ≤1 week after EECP treatment, a maximal stress test was performed to exercise tolerance (test 3).

Statistical analysis: Statistical analysis was performed using the chi-square test to examine differences in thallium perfusion images before and after EECP.

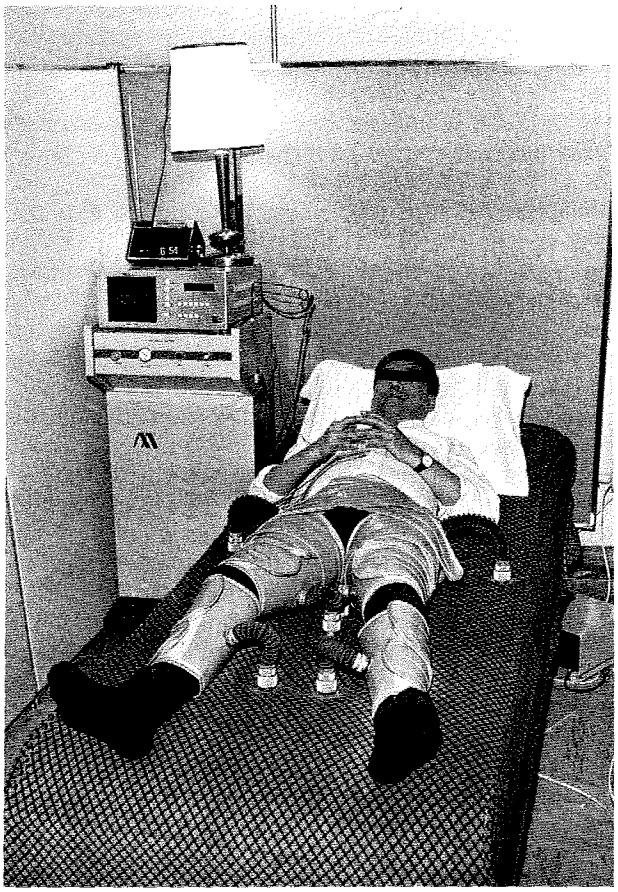

FIGURE 1. Enhanced external counterpulsation system consists of 3 sets of balloons wrapped around calves, and lower and upper thighs (including buttocks), which are inflated sequentially during diastole. Inflation is triggered by R wave. Control and display units are shown on *left*.

Exercise parameters (exercise time, heart rate, blood pressure and double product) from both the thallium stress tests before and after EECP were compared using a paired, 2-tailed Student's *t* test (tests 1 and 2). Furthermore, the same exercise parameters from the thallium stress test before EECP (test 1) and the maximal stress test after EECP (test 3) were compared and evaluated for statistically significant differences, using a paired, 2-tailed Student's *t* test. The subgroup of patients with improvement in thallium scans after EECP were analyzed separately for changes in exercise duration and double product, using a paired, 2-tailed Student's *t* test. Statistical significance was achieved at the 5% level ($p < 0.05$).

RESULTS

Seventeen men and 1 woman entered the study. All patients were receiving standard medical therapy with nitrates, β blockers or calcium antagonists. Before entry in the study, all patients experienced incapacitating angina despite medical therapy. Medication dosage and frequency remained unchanged or were adjusted downward in all patients during the study period. Eight patients underwent 19 prior attempts at revascularization by either angioplasty or bypass surgery. Seven patients had experienced a total of 14 myocardial infarctions and 2 patients had only abnormal thallium tests.

All 18 patients had substantial improvements in anginal symptoms after EECP; 16 had complete relief from angina during the usual activities of daily living. Thallium-201 stress testing (performed for the same exercise duration before and after EECP treatment) showed complete resolution of ischemic defects in 12 patients (67%), a decrease in the area of ischemia in 2 (11%), and no change in 4 (22%). Thus, 14 patients had a reduction in myocardial ischemia as assessed by thallium-201 imaging ($p < 0.01$). There were no significant differences in exercise duration and double product on the thallium stress tests before and after EECP (8.14 ± 0.71 vs 8.16 ± 0.76 minutes, and $22{,}062 \pm 1{,}664$ vs $20{,}532 \pm 1{,}156$ mm Hg · beats/min, respectively).

In comparing maximal stress test results after EECP with those before EECP (tests 1 and 3), there was a significant increase in exercise duration (8.14 ± 0.71 to 9.72 ± 0.77 minutes, $p < 0.005$; Figure 2) and no significant change in double product ($22{,}062 \pm 1{,}664$ to $22{,}816 \pm 1{,}653$ mm Hg · beats/min; Figure 3).

Subgroup analysis of the 14 patients with improvement in thallium scans after EECP showed increases in both exercise duration (8.58 ± 0.66 to 10.44 ± 0.59 minutes, $p < 0.001$; Figure 4) and double product ($21{,}827 \pm 2{,}044$ to $24{,}842 \pm 1{,}707$ mm Hg · beats/min, $p < 0.01$; Figure 5) in maximal stress testing after EECP.

DISCUSSION

In this study, EECP was performed by compressing the vascular beds within the muscles of the legs and thighs, including the buttocks, in a sequential manner, progressing from the calves to the lower and then upper thighs. The compression is accomplished by introducing air into 3 sets of balloons wrapped around the calves,

and lower and upper thighs. The timing of the compression is controlled by the patient's electrocardiogram, so that increased blood flow and pressure will reach the coronary vessels during diastole at the time of lowest intramyocardial tension. Furthermore, the compression of the venous bed of the lower extremities increases venous return and cardiac output. The external pressure is then released during systole, causing systolic unloading and decreasing cardiac work load.

The 36-hour treatment course is performed for 1 hour daily over a period of approximately 7 weeks. The expectation that this will produce long-term benefit for patients with angina pectoris is based on the hypothesis

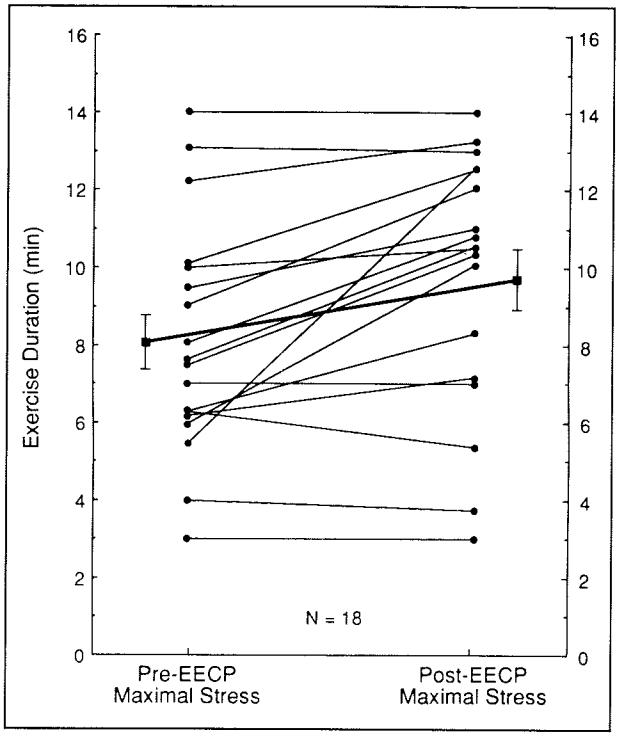

FIGURE 2. Maximal stress test duration before and after enhanced external counterpulsation (EECP). Mean durations ± 1 SEM are significantly different (p <0.005).

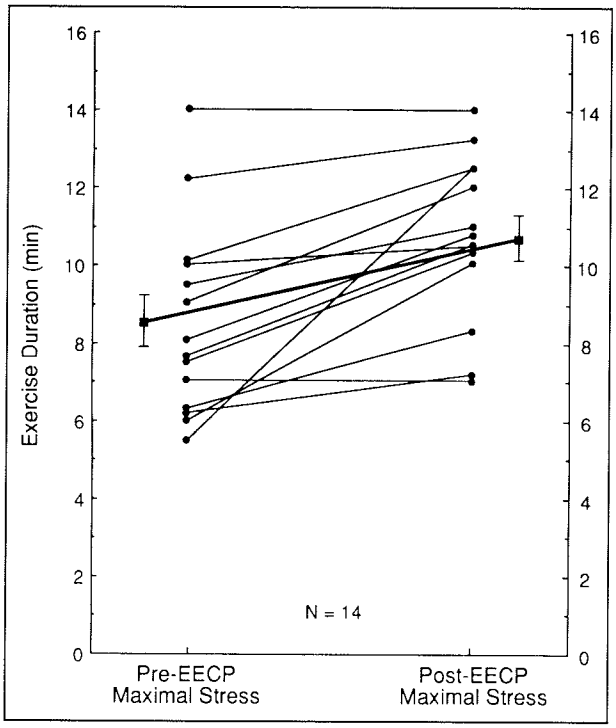

FIGURE 4. Maximal stress test duration before and after enhanced external counterpulsation (EECP) in subgroup of 14 patients with improved thallium perfusion. Mean durations ± 1 SEM are significantly different (p <0.001).

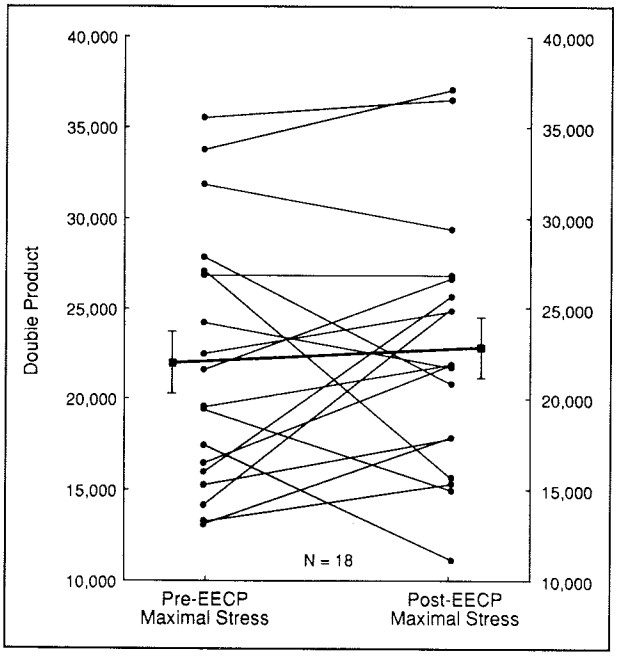

FIGURE 3. Double product (peak exercise heart rate × systolic pressure) before and after enhanced external counterpulsation (EECP). Mean double products ± 1 SEM are not significantly different.

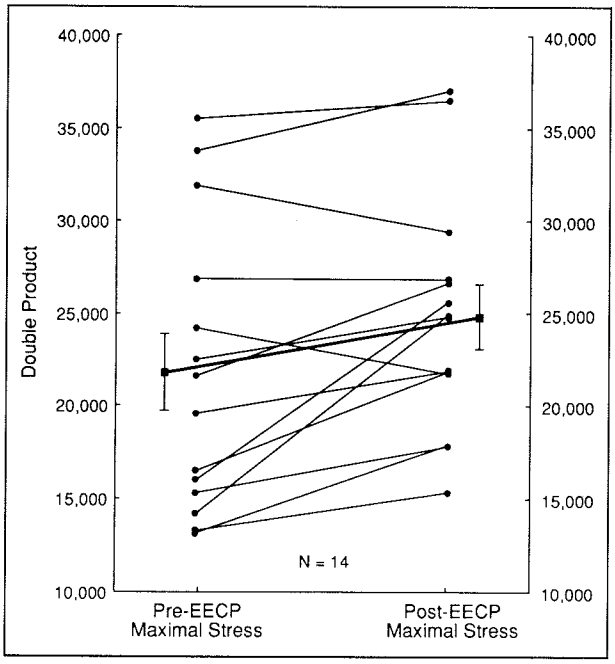

FIGURE 5. Double product before and after enhanced external counterpulsation (EECP) in subgroup of 14 patients with improvement in thallium reperfusion scans. Mean double products ± 1 SEM are significantly different (p <0.01).

that the repeated and pulsed increases in diastolic pressure enhance or stimulate the opening of collateral channels in the coronary vascular system, increasing perfusion of ischemic areas. Initial theoretical considerations suggest that ≥1 coronary vessel must be patent proximally to transmit the increased diastolic pressure and flow to the coronary vascular bed.

The use of counterpulsation in the treatment of patients with angina due to coronary artery disease was previously evaluated with mixed results.[3] However, a much less effective system for producing external counterpulsation was used in previous studies, in which compression was limited to the upper legs and lower thighs. Furthermore, water was used as the compressing medium.[2,4,5] The pioneering work of Zheng et al[6] created a greatly improved system for producing sequential external counterpulsation. This new system is capable of significantly augmenting the diastolic pressure by 46%, which is much greater than the previous system could accomplish.

In the present study, EECP was effective in improving exertional thallium perfusion defects in 14 of 18 patients with angina that was refractory to medical therapy. All 4 patients without improvement by thallium perfusion scintigraphy after EECP had either 3-vessel or diffuse coronary artery disease. The extensive nature of these patients' disease may have limited the effectiveness of EECP therapy.

The observed improvement in thallium perfusion after EECP for the same exercise duration was not caused by an alteration in the double product or heart rate. These determinants of myocardial oxygen demand did not significantly change in the thallium-201 stress tests after EECP. Because myocardial oxygen demand was unaltered by EECP treatment, the improvement in reperfusion defects is presumably a reflection of improved myocardial perfusion (increased supply), rather than a result of a peripheral training effect.

Patients with improved thallium scans demonstrated (not unexpectedly) an improvement in cardiac performance on maximal stress testing after EECP; they increased their exercise time by a mean of 1.46 minutes and simultaneously achieved an increase in double product by a mean of 3,015 mm Hg · beats/min.

The mechanism of the improvement remains speculative. Whereas some of the increase in exercise time could be due to a training effect, this could not explain the thallium finding. One possible explanation is that EECP may open or enhance the development of collateral channels. This may also explain the relative lack of efficacy in patients with severe and diffuse 3-vessel coronary artery disease. At least one open conduit may be necessary to enable transmission of the force and flow necessary to achieve this effect. Angiography and distal occluded pressures (not performed in our study patients) would be necessary to confirm collateral enhancement as a potential mechanism.

In a group of 200 patients with angina, Zheng et al[6] demonstrated prolonged symptomatic improvement in 97% of EECP-treated patients compared with 72% of medically treated control patients. Exercise tolerance was also found to be consistently improved. Similarly, Banas et al[3] found consistent improvement in symptoms in a small group of patients with frequent and disabling angina treated with external counterpulsation. Coronary angiography performed before and 4 to 8 weeks after counterpulsation in 11 patients showed increased vascularity in 5, equivocal changes in 4, and no visible changes in 2. The absence of visual macrocollaterals does not exclude improved coronary perfusion or rule out an improvement in myocardial function. Patency of ≥1 major epicardial vessel was necessary for the occurrence of clinical benefit in this study. Despite the potential benefits shown in these and other studies, external counterpulsation has been little used as a therapeutic modality in this country.[4]

In the present study, patients were used as their own controls. Whereas coronary artery disease is largely unpredictable in its course, regression would not be expected to occur over 6 to 7 weeks in this group of patients whose angina had been disabling or progressive over a period of months and years. The enrolled patients did not undergo any simultaneous therapy such as diet, lipid reduction, weight loss or smoking cessation. Antianginal medications were decreased in dosage or remained the same over the course of the study in all patients. The study cohort was predominantly male, and therefore definitive conclusions regarding efficacy in women should await future studies.

EECP was well-tolerated by all patients enrolled in the study. No patient withdrew after enrollment, and there were no complications of EECP therapy. Further studies are ongoing in this patient cohort to evaluate the long-term, sustained efficacy of EECP.

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