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Exercise Capability and Myocardial Perfusion in Chronic Angina Patients Treated with Enhanced External Counterpulsation

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Summary

Background: Enhanced external counterpulsation (EECP) has been shown to improve treadmill times and myocardial perfusion. However, improvement in perfusion defects has been demonstrated only in patients exercised to the same cardiac workload on the post-EECP as the pre-EECP stress test.

Hypothesis: This study was to determine the effect of EECP on exercise capacity and myocardial perfusion by comparing results of maximal exercise radionuclide testing pre- and post-EECP treatment.

Methods: This prospective study included 25 patients with angina who had performed maximal symptom-limited exercise tolerance tests (ETT) with Bruce protocol and radionuclide perfusion single-photon emission computed tomography (SPECT) study prior to and at completion of EECP treatment.

Results: After 35 h of EECP, 23 patients (93%) improved by at least one functional angina class. There is a significant improvement in their total treadmill times (357 ± 93 to 449 ± 97 s, $p < 0.001$). There was a significant change in their peak double products, from 18,891 ± 3,939 pre-EECP to 20,464 ± 4,305 post-EECP ETT ($p < 0.03$). Pre EECP, 16 patients had ST-segment depression on their initial ETT. After EECP, 13 of these patients (80%) either no longer had ST depression or had a significant increase in their time to ST depression (229 ± 52 to 315 ± 60 s, $p < 0.001$). The radionuclide perfusion scores also showed a significant reduction in ischemic segments (16.36 ± 10.52 to 14 ± 10.9, $p < 0.05$).

Conclusions: Patients treated with EECP demonstrated a reduction in angina symptoms, improvement in exercise capacity, increase in time to ST-segment depression, and decrease in perfusion defects despite performing at a higher workload.

Key words: external counterpulsation, angina, radionuclide perfusion, ST depression

Introduction

Enhanced external counterpulsation (EECP) is a noninvasive treatment for angina pectoris that employs the sequential inflation of lower extremity pneumatic cuffs to reduce left ventricular overload, increase venous return to the heart, and augment diastolic aortic pressure, which, in turn, increases coronary flow. Although the technique has been in use for more than 30 years, a new improved model (Vasomedical, Inc., Westbury, N.Y., USA) has only been available since 1995.[1] After 35 consecutive hours of EECP treatment with this device, improved exercise tolerance and sustained improvements in exercise-induced reversible defects have been reported in the majority of patients.[2,3] The mechanism of action is presumably that of development of collateral channels and/or enhanced collateral flow.[4] It has also been reported to reduce psychological distress and to improve quality of life.[5,6] A recent multicenter placebo-controlled double-blinded study showed a significant increase in the time to ST-segment depression;[7] however, this study did not include radionuclide perfusion scanning. In earlier published studies, patients underwent radionuclide perfusion scanning in conjunction with exercise stress test (ETT) exercise to the same heart rate × blood pressure product (same double product), introducing the possibility that improvement in peripheral muscle function and reduced myocardial oxygen demands, rather than increased collateral flow, might be the principal mechanism of reduction in the exercise-induced reversible defects. Our approach was to perform a symptom-limited maximal ETT with radionuclide perfusion before and after treatment to determine

Dr. Hui is an employee and member of the Board of Directors of Vasomedical, Inc., a company that manufactures and markets the EECP device described in this paper. Dr. Tartaglia owned stock in Vasomedical at the time this paper was written; he no longer does.

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whether perfusion defects can be improved with EECP despite performing at a higher workload.

Materials and Methods

We prospectively studied 25 patients from two centers, with angiographically proven coronary artery disease, defined as >70% diameter stenosis in one or more major coronary arteries or having undergone coronary artery bypass graft (CABG). These patients were not candidates for percutaneous transluminal coronary angioplasty (PTCA)/stent or CABG surgery, or refused CABG (two patients). All patients had Canadian Cardiovascular Society (CCS) class II or higher angina pectoris, and were able to perform ETT according to the Bruce protocol. Patient cardiovascular profiles are shown in Table I. All patients were on adequate medical therapy for angina. Sixteen patients (64%) had had prior CABG, and 8 (34%) had had prior PTCA. Patients were excluded if they were unable to exercise on treadmill, had a myocardial infarction within prior 6 weeks, or had unstable angina, uncontrolled hypertension, severe valvular heart disease, or malignant ventricular arrhythmia. All medications were continued during both pre- and post-EECP stress tests. The protocol was reviewed by the institutional review board in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. All 25 patients completed the protocol without serious adverse effects. Angina was assessed on site by CCS classification prior to and at the completion of the protocol. A significant change on the electrocardiogram was considered 1 mm of ST-segment depression or greater horizontal or downsloping for >0.8 mm from the J point for at least three consecutive beats, as interpreted by two cardiologists blinded to the patient's identity and protocol sequence. The patients exercised until they stopped due to angina, dyspnea, or fatigue.

TABLE I Patient baseline clinical and angiographic characteristics

Number of patients	25
Age (years)	68 ± 9
Male gender (%)	23 (92)
Race	
Caucasian (%)	22 (88)
Black (%)	2 (8)
Hispanic (%)	1 (4)
Hypertension (%)	10 (40)
Diabetes (%)	5 (20)
Smoker (%)	14 (56)
EF	49 ± 7.5
Coronary arteries with >70% stenosis	
Single-vessel (%)	3 (12)
Double-vessel (%)	1 (4)
Triple-vessel (%)	21 (84)
Prior CABG (%)	16 (64)
Prior PTCA (%)	8 (32)
CV medication	
Nitrates (%)	22 (88)
Beta blockers (%)	20 (80)
Calcium-channel (%)	13 (52)
Aspirin (%)	24 (96)
Coumadin (%)	3 (12)
Lipid-lowering agents (%)	24 (96)
Canadian Cardiovascular Society class	
Class II (%)	10 (40)
Class III (%)	14 (56)
Class IV (%)	1 (4)

Abbreviations: EF = ejection fraction, CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty, CV = cardiovascular.

Single-photon emission computed tomography (SPECT) acquisition began 60 to 90 min after injection of the radiopharmaceutical. All images were acquired using a standard dual- or single-headed SPECT camera equipped with a low-energy, high-resolution collimator. All centers used technetium-99m (^{99m}Tc)-sestamibi; 9 to 15.7 mCi was injected for the same-day protocol and 22 to 30 mCi for the separate-day protocol. Twenty-five sections/projections for rest and stress images were obtained over a 180° semicircular arc. All images were stored in a 64 × 64 × 16 matrix. Filtered back projection was performed using a low pass Butterworth filter with a frequency cutoff of 0.66 cycles/pixel and order of 5 for reconstruction of the transit axial slices to a thickness of 6.6 mm. No preprocessing filtration or attenuation correction was used. Two experienced nuclear cardiologists at a core laboratory, blinded to patient identity, stress protocol, or sequence of study, interpreted all images, and agreement was by consensus. Images were scored by dividing the myocardium into 17 segments. Each segment was scored on a scale from 0 to 4 (0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease, and 4 = complete absence of photon activity). The summed stress and rest scores were determined by adding the scores from all 17 segments. An image defect was considered present if, by consensus, a discrete region of absent or decreased activity was seen. The defect was anatomically located using the 17-segment model. A defect present in both stress and rest perfusion images was considered a scar; a defect present only during exercise was considered reversible ischemia. Either partial or complete resolution of the defect qualified as reversible ischemia.

Enhanced external counterpulsation was performed in a standard fashion, as described elsewhere.[7] In brief, the EECP system consists of a compressor, a console, a treatment table, and three sets of cuffs. Prior to treatment, the cuffs are wrapped around the patient's calves and the lower and upper thighs, including the buttocks. The compressor delivers air pressure via the cuffs to the patient's lower extremities, synchronized sequentially to the cardiac cycle. At the beginning of diastole, pressure is applied from the calves and thighs to produce a retrograde flow to the root of the aorta. Increase in arterial pressure during diastole increases coronary perfusion pressure and blood flow. At end diastole, the air is rapidly released, allowing the compressed vessels to rebound and greatly reduce vascular impedance. The pressure that had to be applied to the cuffs ranged from 250 to 300 mmHg. The mean of the patient's diastolic to systolic peak pressure ratio was 1.02 ± 0.4 (mean ±

standard deviation [SD]), and the ratio of the area under the diastolic to systolic curves was 1.21 ± 0.23. There were no changes in medication throughout the course of the study.

Statistical analysis was preformed using the chi-square test to examine the differences in sestamibi stress and rest nuclear perfusion scores before and after EECP. Exercise duration, exercise time, heart rate, blood pressure, double product, and angina class before and after EECP were analyzed using a paired, two-tailed Student's *t*-test. The stress and rest perfusion scores were analyzed with the hypothesized mean difference of zero (*t*-test: paired two sample for mean). The subgroup of patients with ST-segment depression was analyzed separately for change in exercise time using a paired, two-tailed Student's *t*-test. Statistical significance was achieved at the 5% level ($p < 0.05$).

Results

At baseline, 88% of the 25 patients were on nitrates, 80% on beta blockers, 52% on calcium-channel blockers, 96% on aspirin, 12% on coumadin, and 96% on lipid-lowering agents. There was no change in medication over the course of the study, and medications were maintained at the same levels (Table I).

Most patients (21/25) had a reduction in at least one angina class (84%); 3 of 25 had a reduction of two angina classes (12%), and 1 of 25 had no significant change in angina class (4%). The majority (23/25) had improved treadmill times (94%), and 16 of 25 (64%) had improved nuclear scores on the stress study despite having achieved a higher workload on the post-EECP ETT (see Figs. 1 and 2). There were 16 of 25 patients with ST-segment depression on the pre-EECP ETT. Post EECP, 3 patients had no ST-segment depression on their ETT and 10 patients had a significant delay in their time to ST-segment depression (Fig. 3). Peak double products increased from 18,891 ± 3,939 on the pre-EECP ETT to 20,464 ± 4,305 on the post-EECP ETT ($p < 0.03$). The peak heart rate increased from 118 ± 15 to 125 ± 18 beats/min ($p < 0.06$, NS). Peak systolic blood pressure increased from 159 ± 25 to 163 ± 22 mmHg ($p < 0.68$, NS); and peak diastolic blood pressure remained unchanged, from 82 ± 10 to 81 ± 7 mmHg ($p < 0.68$, NS).

Sixteen of 25 patients (64%) had improved nuclear scores on the post-EECP stress SPECT scans. The average radionuclide stress perfusion score pre EECP was 16.36 and decreased to 14.12 post EECP ($p < 0.05$). All patients' nuclear scans had defects that correlated with an anatomical occlusion in the corresponding coronary artery or in the bypass graft to the distribution of that artery.

Discussion

A limitation of this study was that there was no placebo control group; instead, each patient served as his or her own control. In addition, the stress tests were not performed blinded and it was not possible to eliminate an exercise training effect on the patient. The number of patients in the study is small, and until other studies confirm the findings of this study it must be interpreted with caution. Finally, the study was limited to patients who are capable of exercising on a treadmill according to a Bruce protocol, and the findings are not necessarily applicable to all patients with chronic stable angina.

Enhanced external counterpulsation improved exercise capacity in a group of patients with chronic stable angina, of whom 80% had undergone prior revascularization procedures.

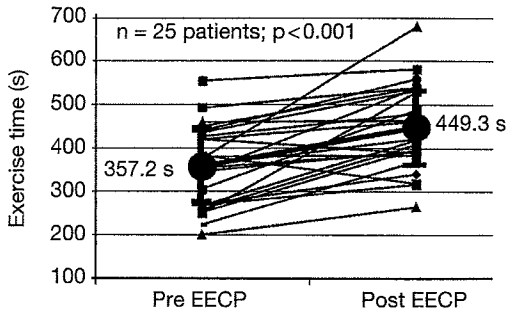

FIG. 1 Improvement of exercise treatment treadmill time pre- and post-enhanced external counterpulsation (EECP) treatment.

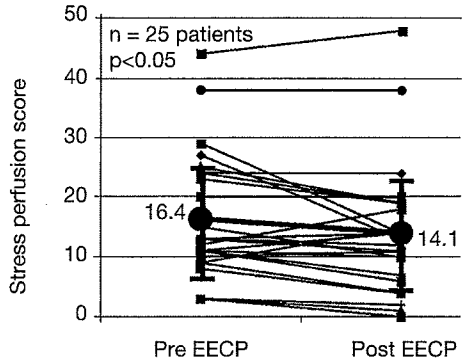

FIG. 2 Decrease of stress radionuclide perfusion score pre- and post-enhanced external counterpulsation (EECP) treatment.

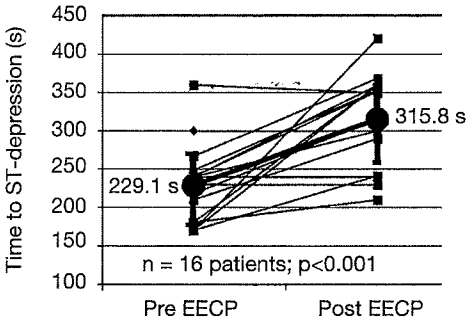

FIG. 3 Change in exercise time to ST-segment depression pre- and post-enhanced external counterpulsation (EECP) treatment.

Although the reduction in reversible perfusion defects was less than that reported in other studies,[2, 5, 8] the prior studies performed nuclide imaging to the same heart rate/blood pressure in the post- as in the pre-EECP ETT, a condition that may not provide sufficient stress to induce perfusion defects. A recent seven-center study including 175 patients reported the effects of EECP on radionuclide perfusion: four centers performed post-EECP stress to the same level as pre-EECP, showing improved perfusion distribution in 87% of patients; three centers performed maximal stress post EECP with 54% improvement.[10] In the present study, we performed maximal exercise stress testing post EECP, giving a higher level of stress and using an objective scoring method to analyze the radionuclide perfusion images. However, 64% of our patients improved their perfusion score, a result somewhere between the groups that exercise to the same stress level and to the maximal level. The differences may come from the different methods of analyzing the perfusion images. In addition, the patients in the cited reference who performed maximum exercise had no significant change in double product, whereas the current study shows a significant increase.

The mechanism of EECP remains largely unproven. The hemodynamic effects of EECP have been well described.[11] The aortic pressure gradient is believed to stimulate recruitment of collateral vessels as shown in earlier animal models, and recent work has demonstrated improved microcirculation in regions of myocardial infarction, increasing capillary density in infarcted regions by 30%.[12] Enhanced external counterpulsation has been reported to have other beneficial effects, such as an increase in nitric oxide levels[13, 14] and a decrease in plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP),[15, 16] possibly mediated by an increase in shear stress. Development of collaterals may be mediated by increased shear stress, which, in turn, may release angiogenic factors.

Improvement in treadmill times and the reduction in reversible defects on the post-EECP ETT and SPECT perfusion imaging is probably due to recruitment of collateral flow. In the present study, the double products and exercise duration increase significantly post EECP, eliminating the postulated peripheral "training" effect reported earlier.[5] Therefore, we conclude that patients who can attain higher workloads on post-EECP stress tests and still demonstrate reduction in perfusion defects are showing increased collateral development.

Conclusion

In patients with chronic stable angina, at least one mechanism by which EECP appears to be effective is by improving coronary flow, presumably by enhanced collateral circulation. Even though the majority of patients in the present study had high rates of failed prior revascularization, EECP was still effective in reducing angina symptoms, improving exercise capacity, increasing the time to ST-segment depressions, and significantly decreasing exercise-induced reversible perfusion defects.

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