Imaging and Diagnostic Testing

The effects of enhanced external counterpulsation on myocardial perfusion in patients with stable angina: A multicenter radionuclide study

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Background Enhanced external counterpulsation (EECP) reduces angina and extends time to exercise-induced ischemia in patients with symptomatic coronary disease. One- and two-center studies and a retrospective case series reported that EECP improves myocardial perfusion in stable angina pectoris. We sought to critically evaluate and quantify the effect of EECP on myocardial perfusion.

Methods In 6 US university hospitals, EECP was performed for 35 hours in patients with class II to IV angina who had exercise-induced myocardial ischemia. Symptom-limited quantitative gated technetium Tc 99m sestamibi single photon emission computed tomography exercise perfusion imaging was performed at baseline and 1 month post-EECP. Sestamibi was injected at the same heart rate in both stress tests. Single photon emission computed tomography images were read at a blinded core laboratory.

Results Thirty-seven patients were enrolled, 34 of whom completed pre- and post-EECP stress testing. The mean age was 61 $\pm$ 10 years, 81% were male, 78% had prior revascularization, and 68% had 3-vessel disease. The mean angina class decreased from 2.7 $\pm$ 0.7 at baseline to 1.7 $\pm$ 0.7 after EECP ($P < .001$). Exercise duration increased from 9.1 $\pm$ 3.7 minutes at baseline to 10.2 $\pm$ 3.6 minutes post-EECP ($P = .03$). The average percentage of tracer uptake, magnitude of reversibility, average thickening fraction, and the left ventricular ejection fraction remained unchanged after EECP.

Conclusions We confirm previous report that EECP reduces angina and improves exercise capacity. There were no significant changes in mean defect magnitude, amount of reversibility, thickening fraction, and ejection fraction measured using myocardial quantitative single photon emission computed tomography imaging when compared at identical pre- and post-EECP heart rates. (Am Heart J 2005;150:1066-73.)

The current standard treatment of stable angina pectoris includes lifestyle modification, antiplatelet and antianginal pharmacologic therapy, and percutaneous and/or surgical coronary revascularization.[1] Enhanced external counterpulsation (EECP) is a noninvasive counterpulsation treatment of angina that uses the sequential inflation of lower extremity pneumatic cuffs to reduce left ventricular afterload and augment coronary perfusion pressure.[2] Enhanced external counterpulsation has been shown to improve angina and time to ST-segment depression during exercise stress testing in patients with refractory angina.[3,4] Enhanced external counterpulsation results in immediate and sustained antianginal benefits,[5,6] with improvement in angina class and quality of life.[7,8] The exact mechanisms by which EECP exerts its beneficial effects are unknown, but one of its effects is believed to be the development and recruitment of coronary collateral vessels.

One single-center study,[9] one 2-center study,[10] one retrospective single-center study,[11] and one retrospective multicenter study,[12] each using a variety of stress protocols and imaging techniques, have reported

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improvements in the extent of myocardial ischemia that is detected by radionuclide myocardial stress scintigraphy. Another single-center study reported an increase in myocardial perfusion at rest and with pharmacologic stress using positron emission tomography.[13] The purpose of this study was to use the blinded analysis of radionuclide imaging at a single core laboratory to assess changes in the scintigraphic extent of exercise-induced myocardial ischemia in patients undergoing EECP for angina.

Methods

Study patients

Patients with Canadian Cardiovascular Society Classification (CCSC) class II to IV angina pectoris or angina equivalent occurring on average at least twice per week were considered for inclusion in this study. Patients were required to have a diagnosis of coronary artery disease by (1) angiographic evidence of ≥70% diameter stenosis in at least 1 major coronary artery or a documented history of myocardial infarction, and (2) scintigraphic evidence of a reversible perfusion defect on baseline exercise myocardial perfusion imaging with technetium Tc 99m sestamibi testing confirmed by the core laboratory, with blinding before enrollment. Eligible patients also were required to exercise at least 3 minutes on the Cornell treadmill protocol, but ST-segment depression was not a requirement for study entry.

Patients were excluded from this study if they had prior EECP treatment; acute coronary syndrome or myocardial infarction within the past 6 weeks; nonbypassed left main coronary artery disease with a luminal stenosis of ≥50%; cardiac catheterization within the past 2 weeks; arrhythmia that would significantly interfere with EECP cuff inflation and deflation timing; clinically apparent heart failure; left ventricular ejection fraction (LVEF) ≤30%; severe valvular heart disease; triggering of an implantable cardiac defibrillator within the past 6 months; history of aortic aneurysm, deep venous thrombosis, phlebitis, stasis ulcer, or pulmonary embolism; bleeding diathesis; warfarin use with international normalized ratio >2.0; uncontrolled systemic hypertension (defined as ≥180/110 mm Hg); or electrocardiographic findings of ventricular pacing, left bundle-branch block, or ST-segment depression >1 mm at rest. Also excluded were pregnant women, subjects unable to undergo treadmill testing, and subjects enrolled in another research program within the past month.

The study was approved by the institutional review boards at the 6 participating institutions and was conducted in accordance with the Declaration of Helsinki. Enrollment was conditional upon subjects giving a written informed consent.

Enhanced external counterpulsation

Enhanced external counterpulsation (Vasomedical, Inc, Westbury, NY) was administered as a 1-hour daily session, 5 d/wk, over a 7-week period, for a total of 35 hours. Patients were instructed to continue their usual medications. Adjustments in antianginal medications were determined by the patients' physicians during the course of the study, and any changes were documented. No other interventions were performed during the study period.

Clinical and quality of life end points

Before EECP and 1 month after the completion of EECP, patients had a focused history and physical examination. Canadian Cardiovascular Society Classification of anginal status, quality of life using the Medical Outcomes Survey 36-Item Short-Form Health Survey (SF-36) and Seattle Angina questionnaires, medication use (including nitroglycerin use), and interim adverse clinical events were recorded.

Exercise treadmill test end points

Symptom-limited exercise treadmill tests were performed using the Cornell protocol.[14] Three and four weeks before EECP, 2 exercise tests were performed at 1-week intervals to reduce the effect of learning on initial treadmill performance, with the second test used as baseline. Original copies of all exercise tests and investigator data sheets were examined by a single physician in the core exercise laboratory, who was blinded to the scintigraphic data. ST-segment depression was made at a point 60 milliseconds after the J junction from averaged or incrementally updated complexes.[15] Test outcome was defined from ST depression (STD) beyond baseline and the slope of the ST segment. A positive test result was defined as ≥1.0 mm of additional horizontal or downsloping STD, and a negative test result was defined as <1.0 mm of additional STD; a test response with ≥1.0 mm of additional upsloping STD was defined as equivocal.[16] Time to 1.0-mm ST-segment depression was noted. To calculate the Duke treadmill score,[17] exercise duration on the Cornell protocol was converted to equivalent Bruce protocol duration at a corresponding workload.[14] Heart rate recovery was calculated as the difference in heart rate at peak exercise and at 1 minute of recovery.[18]

Myocardial scintigraphic end points

Quantitative gated technetium Tc 99m sestamibi single photon emission computed tomography (SPECT) exercise perfusion imaging studies performed by participating centers were given coded identification, and the raw data files were sent electronically to the Radionuclide Core Laboratory for processing. The studies were reconstructed into standard short-axis, vertical long-axis, and horizontal long-axis images. Planar projection images were formed into a cine-loop display to evaluate motion and attenuation artifact. The perfusion studies were processed quantitatively to show the relative percentage of tracer uptake in each of 14 myocardial segments.[19,20] The gated studies were processed quantitatively to show thickening fractions estimated from relative count changes in end-diastolic and end-systolic frames. Thickening fractions were calculated and displayed in the same 14 segments used for perfusion measurements.[19] Global LVEF was measured from the regional thickening fractions.[20]

Quantitative values for perfusion images were compared with a sex-specific normal database, and values were flagged at 2 SDs outside the normal database. Differences between rest and stress tracer uptake were flagged as indicating reversibility if the difference was >1 SD, based on the measured SD of the difference of the 2 measurements. Quantitative values for thickening fractions were flagged at 2 SDs outside the normal database.

The images were sent electronically to Anabase International Corporation, where they were incorporated into a secure Web-based image interpretation system. The coded images were

Table I. Demographic factors at baseline (n = 34)

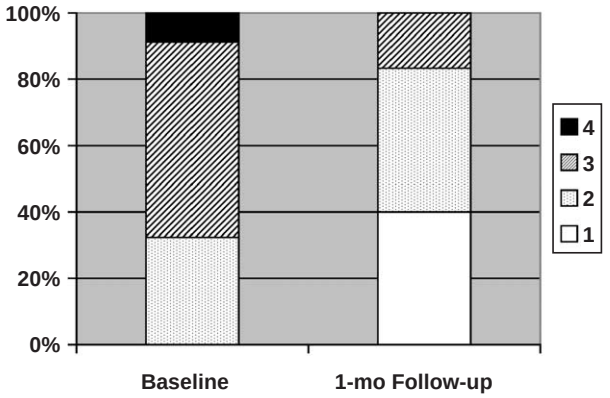
Age ± SD	61 ± 10 y
Male	81%
Body mass index	28.7 ± 6.3 kg/m^2
Hyperlipidemia	92%
Diabetes mellitus	49%

Table II. Baseline coronary disease factors

Prior myocardial infarction	70%
Multivessel disease	92%
2-Vessel	24%
3-Vessel	68%
Prior PCI	54%
Prior CABG	66%
Prior myocardial laser revascularization	9%
Angina class	
I	0%
II	38%
III	47%
IV	14%
Angina ± SD	10 ± 13 episodes per week

PCI, Percutaneous coronary intervention; *CABG*, coronary artery bypass graft.

Figure 1



Angina class at baseline and 1 month after EECP.

Table III. Quality of life outcomes 1 month after EECP

	Improvement (%)	*P*
SF-36 questionnaire		
General health perceptions	52	.002
Physical limitations	70	<.001
Emotional limitations	4	.057
Social functioning	73	<.001
Bodily pain	68	<.001
Mental health	18	.02
Vitality	97	<.001
Seattle Angina Questionnaire		
Exertional capacity	84	.003
Anginal stability	74	<.001
Anginal frequency	75	<.001
Treatment satisfaction	26	<.001
Disease perception	108	<.001

randomized and were posted for online interactive interpretation. A single experienced nuclear cardiologist categorized each segment using drop-down menus.

The interpreter selected "target segments." These abnormal segments had significant viability, with at least partial reversibility. These were segments that could be expected to show improvement if the intervention increased perfusion to the corresponding segment. Segments with severe fixed defects were excluded. The blinded interpreter did not know whether the study was pre- or post-EECP in an unpaired manner. In the primary data analysis, only the target segments chosen for the pretreatment study were used, and these same segments on the post-EECP study were evaluated for possible change. Quantitative perfusion measurements and thickening fractions were used to detect possible changes in the target segments.

Statistical analysis

Data compilation and analysis were provided by Anabase International Corporation. Data are presented as percentages for categorical variables or as mean values and SDs for continuous variables. The paired Student *t* test was used to test whether changes from baseline to the 1-month follow-up were significant. Two-tailed *P* values <.05 were considered significant. This study had an 89% power to detect a post-EECP 10% increase in the percentage of tracer uptake in target segments during exercise.

Results

Patient characteristics

Of the 37 patients enrolled, 34 patients had completed baseline and post-EECP stress testing and formed the basis for the following results. Demographic data are shown in Table I. All patients have undergone prior coronary angiography. Extent of coronary artery disease, prior coronary revascularization, and baseline angina class are shown in Table II.

Safety, clinical, and quality of life end points

Of the 37 patients enrolled, 1 patient stopped EECP and was hospitalized for unstable angina and pulmonary edema that occurred during EECP therapy. A second patient was hospitalized for crescendo angina that did not occur during the EECP sessions. After diagnostic coronary angiography without revascularization, the patient resumed and completed EECP therapy. The following minor adverse events occurred in 7 other patients: crescendo angina not during the 1-hour EECP sessions (n = 2), ventricular bigeminy (n = 1), and lower extremity discomfort (n = 4). All 34 patients in this

Table IV. Exercise treadmill test results

	Total population (N = 34)			Angina at entry (n = 24)			No angina at entry (n = 10)		
	Entry	Exit	P	Entry	Exit	P	Entry	Exit	P
Exercise duration (Cornell; min)	9.1 ± 3.7	10.2 ± 3.6	.03	8.6 ± 3.4	10.1 ± 3.3	.03	10.4 ± 4.3	10.7 ± 4.5	.71
Time to angina (min; n = 24)	5.4 ± 3.0	7.5 ± 3.2	.05	5.4 ± 3.0	7.5 ± 3.2	.05	–	–	–
Angina-free exercise (min)	6.9 ± 4.1	9.4 ± 4.0	<.01	5.4 ± 3.0	8.9 ± 3.7	<.01	10.4 ± 4.3	10.7 ± 4.5	.71
Change in STD (μV)	75.8 ± 69.2	84.4 ± 90.1	.53	79.1 ± 73.0	78.9 ± 91.7	1.0	68.0 ± 62.5	97.0 ± 89.6	.27
Time to 1.0-mm STD (min)	8.2 ± 5.2	8.3 ± 3.7	.10	8.2 ± 5.1	7.7 ± 2.3	.2	8.3 ± 6.5	9.3 ± 5.4	.50
HR recovery	12.4 ± 10	11.7 ± 8.1	.60	11.5 ± 8.8	12.1 ± 6.9	.7	14.5 ± 13.2	10.7 ± 10.7	.14
Duke treadmill score	−3.7 ± 6.1	−1.1 ± 6.7	.04	−6.5 ± 4.6	−2.4 ± 7.4	.01	2.7 ± 4.0	1.7 ± 3.7	.40

analysis completed 35 hours of EECP. There were no changes in medication noted during the study period. No cardiac cointerventions occurred, such as hospitalization or coronary revascularization.

Comparing CCSC angina class from baseline to 1-month post-EECP, angina class improved significantly ($P < .001$) (Figure 1). Fifty-four percent of patients had a decrease of 1 CCSC angina class, 26% had a decrease of 2 CCSC classes, 20% had no change in angina class, and none had an increase in angina class. Quality of life determined by the SF-36 questionnaire showed a significant improvement in general health perception, bodily pain, mental health, vitality, and physical limitations (Table III). Quality of life by the Seattle Angina Questionnaire showed significant improvements in exertional capacity, anginal stability and frequency, treatment satisfaction, and disease perception.

Exercise treadmill testing

Angina occurred during entry exercise in 24 (71%) of 34 patients, including 18 (55%) of 34 patients in whom angina was the test end point (Table IV). Of these 24 subjects, EECP resulted in a 46% reduction in the occurrence of angina with exercise; 13 patients continued to have angina as the exercise end point, and 11 patients did not have angina at exit stress testing. Ten patients did not have angina during exercise either at entry or at exit. Consistent with the limited effort tolerance, low heart rates achieved, and high prevalence of β-blockade in this population, mean STD at entry was 0.76 mm.

For the total group, EECP was associated with an overall mean 12% increase in effort duration by the Cornell protocol (Table IV). Improvement in effort capacity was greater among the patients who had angina during entry exercise testing, in whom reduced angina resulted in a mean 65% increase in angina-free exercise time. However, improved exercise time after EECP was not simply a consequence of the absence of angina in some patients during maximal exit exercise testing. Among the 13 patients with angina at both entry and exit, time to angina increased by a mean 42% ($P < .05$). The 10 patients without angina at entry or at exit had no significant increase in effort duration during EECP.

For the total group, mean STD and heart rate recovery were similar before and after EECP. For the total group and in patients with entry angina, the Duke treadmill score was significantly decreased (improved) because of increased effort duration and reduction in angina after EECP. Angina is a powerful contributing factor to the Duke score. There was no change in Duke score in the 13 patients who had angina on both entry and exit testing, despite significantly increased effort duration, or in the 10 patients who did not have angina on entry exercise testing.

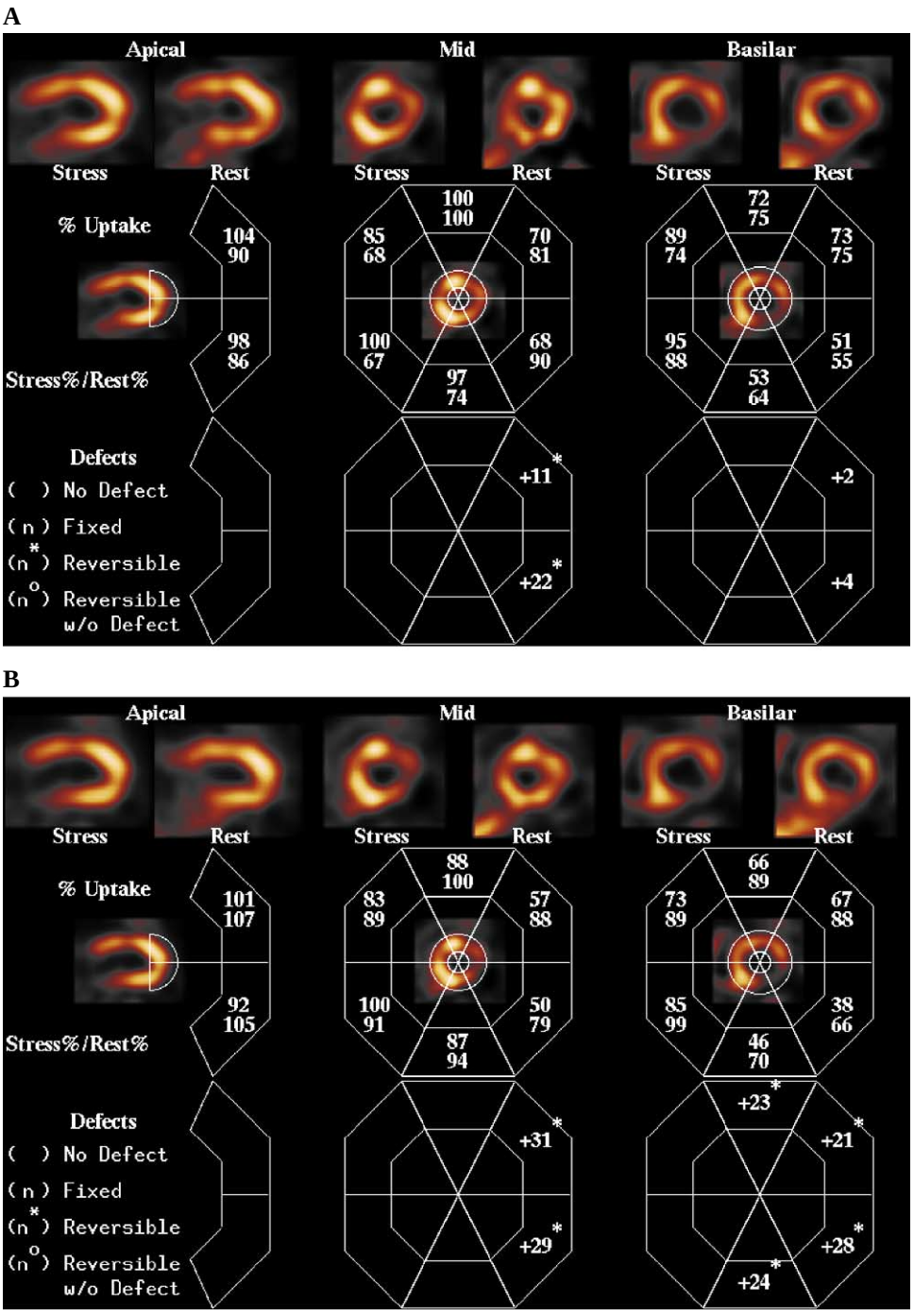
Myocardial scintigraphic outcomes

The average percentage of tracer uptake of target segments at baseline versus 1 month post-EECP at rest was 73.9 ± 10.7 versus 72.6 ± 9.9 ($P = .17$) and, after exercise, was 63.4 ± 11.6 versus 62.9 ± 13.3 ($P = .66$), respectively (Figure 2). The magnitude of reversibility (rest-stress) was 10.5 ± 6.4 at baseline compared with 9.6 ± 7.9 at follow-up ($P = .51$). Average thickening fractions in the target segments were 27.3% ± 11.4% at baseline versus 27.6% ± 13.5% at follow-up ($P = .87$). Left ventricular ejection fraction was 55.3% ± 8.8% at baseline versus 54.1% ± 9.2% at follow-up ($P = .56$). Comparing ischemic area in the anterior versus non-anterior walls, there were no changes at baseline or post-EECP in the radionuclide findings.

Discussion

In this study, we confirmed that EECP significantly improved exercise tolerance, reduced angina, and

Figure 2



Representative quantitative SPECT imaging before (A) and 1 month after (B) EECP. Sestamibi imaging is shown for the apical, mid, and basilar left ventricular segments at stress and rest in the top row. The middle row shows the average percentage of uptake (stress over rest) to these corresponding segments. The bottom row quantitates the percentage of uptake for fixed and reversible defects.

improved quality of life. Similar to prior studies of exercise testing,[3,9,10,12] patients had a significant increase in exercise duration. However, this study did not demonstrate a change in the magnitude of inducible myocardial ischemia, regional wall thickening, or ejection fraction using a blinded interpretation of exercise radionuclide scintigraphic stress testing.

Angina class and quality of life

In this patient cohort, there was a high incidence of severe angina with multivessel disease. Similar to the results of the randomized EECP multicenter study[3] and the International EECP Patient Registry,[21,22] there was a significant reduction in angina class after EECP. Moreover, there were significant improvements in quality of life, similar to the findings reported previously.[5-8]

Exercise tolerance test

The increase in exercise time after EECP is similar to the findings in the multicenter study of EECP (MUST-EECP).[3] Post-EECP treadmill testing had a 46% reduction in angina during testing and a 75% increase in angina-free exercise time. The improved exercise tolerance was not due to changes in therapeutic modalities but because medications were unchanged and no other cointerventions were performed during the study period. Despite the use of 2 baseline pre-EECP exercise treadmill tests, changes in exercise performance still could be attributable to training and placebo effects.

Myocardial perfusion by quantitative gated technetium Tc 99m sestamibi SPECT exercise perfusion imaging

There are 5 important design features used in the present study: (1) use of 2 exercise treadmill tests performed 3 and 4 weeks before beginning EECP, (2) use of an identical nuclear imaging technique and quantitative formatting at all 6 testing sites, (3) only subjects with a significant perfusion defect that was significantly reversible (as determined by the core laboratory) were enrolled, (4) injection of sestamibi at the identical heart rate during baseline and post-EECP exercise treadmill tests, and (5) the scintigraphic images were read by an experienced nuclear cardiologist at the Radionuclide Core Laboratory who was blinded to patient identification, study location, and whether the study was pre- or post-EECP. Using these rigorous techniques, the blinded readings of quantitative gated technetium Tc 99m sestamibi myocardial perfusion imaging showed no difference after 35 hours of EECP in myocardial tracer uptake at rest or stress, magnitude of reversibility, average thickening fractions, or ejection fraction. This study was adequately powered (recalculated at 89%) to detect a 10% improvement in the percentage of tracer uptake in target segments during exercise.

The scintigraphic findings from this study differ from those of previous studies in literature. Lawson et al[11] performed a retrospective study of 50 patients undergoing EECP for symptomatic coronary disease who had an exercise-induced reversible radionuclide perfusion defect. Patients underwent repeat stress testing within 1 week after completing 35 hours of EECP. Radionuclide images were evaluated by 2 independent readers blinded to patient identities. The isotope and imaging protocol(s) used were not specified. The authors reported that the perfusion defects completely resolved in 58%, partially resolved in 22%, and were unchanged in 20%. The finding that 80% of the perfusion defects resolved completely or partially after EECP may have been subject to bias in this retrospective study. Whether the readers were blinded to pre- versus post-EECP images was not stated.

The other retrospective study assessing the effects of EECP on radionuclide coronary perfusion reported the results of 175 patients from 7 international sites.[12] Exercise testing within 1 month before EECP and 6 months post-EECP was performed, using either technetium Tc 99m sestamibi or thallium 201 with either SPECT or planar imaging. The post-EECP stress test protocol varied, with maximal cardiac workloads in 3 sites and identical workload in 4 sites. Radionuclide images were read by 2 independent blinded physicians. Stys et al[12] reported that 70% of the subjects had a significant improvement in the radionuclide extent of ischemia on post-EECP testing.

Urano et al[9] conducted a single-center study of 12 angina patients undergoing bicycle exercise thallium scintigraphy pre- and post-EECP. The thallium images were read by 2 blinded readers. The investigators reported no change in the fixed defects but a 41% reduction in the incidence of reversible perfusion defects. Tartaglia et al[10] conducted a 2-center, prospective study in which 25 patients with angina performed symptom-limited exercise SPECT testing pre- and post-EECP. The radionuclide perfusion scores showed a significant 15% relative reduction in ischemic segments after EECP.

These prior studies had $\geq$1 of the following design limitations: retrospective study design, inadequate blinding of scintigraphic readers, single- to double-study center design, and/or nonquantitative interpretation of the myocardial perfusion scans. All these studies used qualitative measures when comparing the scintigraphic images to report whether the perfusion defects improved (partially or completely), worsened, or remained unchanged. The reading of paired images, as opposed to images blinded to patient and timing in the study, may lead to additional biases during image interpretation.

Mechanisms of action of EECP

We found that the significant improvements in exercise tolerance, angina class, and quality of life were not associated with improvement in the scintigraphic

extent of myocardial ischemia on radionuclide perfusion imaging. These findings question whether the clinical benefits of EECP are attributable to the development and recruitment of coronary collateral vessels. If coronary collaterals contributed to symptomatic improvement, myocardial perfusion at rest and during stress would have been expected to improve. Moreover, our findings do not support the hypothesis that coronary collaterals are recruited to the ischemic zones, the nonischemic territories, or both.

Our findings support the hypothesis that EECP induces a "training effect," resulting in a decreased peripheral vascular resistance and a decreased heart rate response to exercise.[23] Exercise training reduces the resting heart rate, double product (heart rate × blood pressure), and myocardial oxygen consumption at any given level of exercise.[24] Exercise training has been shown to improve endothelium-dependent vasodilation in patients with prior myocardial infarction.[25] Enhanced external counterpulsation has been reported to have other beneficial effects on endothelial function such as increasing nitric oxide levels and decreasing endothelin 1 levels.[13] It is reported that these changes persist after the completion of the 35-hour EECP treatment course. Soran et al[26] reported improvements in peak oxygen uptake and exercise capacity in a small group of patients with heart failure, after EECP. These results suggest that the efficiency of peripheral oxygen uptake is increased after EECP. It remains unclear whether EECP directly results in physiological effects that are mimicking a training effect and/or facilitates improved exercise capacity, thus increasing the patient's ability to train with less severe angina.

Study limitations

Several limitations are inherent in any pilot study. First, this study enrolled a small number of patients. This study, however, still had an 89% power to detect the primary end point of a 10% increase in percentage of tracer uptake in target segments during exercise. Second, there was no control group in this nonrandomized study. The patients' baseline testing results served as a comparator for the repeat studies 1 month after EECP. Third, a global increase in myocardial perfusion may not be detected with quantitative gated technetium Tc 99m sestamibi SPECT exercise perfusion imaging. If EECP resulted in improved coronary and/or peripheral endothelial function, SPECT imaging may not demonstrate these physiological changes. Although this technique may detect relative segmental changes in myocardial perfusion, invasive coronary flow measures,[27] magnetic resonance imaging of coronary sinus flow,[28] or positron emission tomography[13] are superior techniques that can detect absolute changes in coronary blood flow. Thus, this scintigraphic technique may not detect global changes in myocardial perfusion or coronary artery blood flow because of changes in endothelial function. Fourth, the findings of this study cannot be generalized to patients with LVEF ≤30% or left bundle-branch block, and those unable to undergo exercise treadmill testing because these patients were excluded from study entry.

Conclusions

This study provided corroborative evidence that EECP significantly improved exercise tolerance, angina class, and quality of life in patients with symptomatic chronic ischemic heart disease with reversible myocardial perfusion defects on radionuclide imaging. Symptom-limited quantitative gated technetium Tc 99m sestamibi SPECT exercise perfusion imaging did not show improvement in myocardial perfusion at rest or during exercise, and did not show a change in ejection fraction. A training effect with improved coronary endothelial function appears a potential explanation for the mechanism of the benefit of EECP.

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Appendix A

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Appendix B

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