

## CLINICAL STUDIES

## Myocardial Ischemia

# The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes

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- OBJECTIVES** The purpose of this study was to assess safety and efficacy of enhanced external counterpulsation (EECP).
- BACKGROUND** Case series have shown that EECP can improve exercise tolerance, symptoms and myocardial perfusion in stable angina pectoris.
- METHODS** A multicenter, prospective, randomized, blinded, controlled trial was conducted in seven university hospitals in 139 outpatients with angina, documented coronary artery disease (CAD) and positive exercise treadmill test. Patients were given 35 h of active counterpulsation (active CP) or inactive counterpulsation (inactive CP) over a four- to seven-week period. Outcome measures were exercise duration and time to  $\geq 1$ -mm ST-segment depression, average daily anginal attack count and nitroglycerin usage.
- RESULTS** Exercise duration increased in both groups, but the between-group difference was not significant ( $p > 0.3$ ). Time to  $\geq 1$ -mm ST-segment depression increased significantly from baseline in active CP compared with inactive CP ( $p = 0.01$ ). More active-CP patients saw a decrease and fewer experienced an increase in angina episodes as compared with inactive-CP patients ( $p < 0.05$ ). Nitroglycerin usage decreased in active CP but did not change in the inactive-CP group. The between-group difference was not significant ( $p > 0.7$ ).
- CONCLUSIONS** Enhanced external counterpulsation reduces angina and extends time to exercise-induced ischemia in patients with symptomatic CAD. Treatment was relatively well tolerated and free of limiting side effects in most patients. (J Am Coll Cardiol 1999;33:1833-40) © 1999 by the American College of Cardiology

Current treatment for angina, including drug therapy (1) with nitrates, beta-adrenergic blocking agents and calcium channel blocking agents either as single agents or in combination, or revascularization by either percutaneous transluminal coronary angioplasty (2) or coronary artery bypass

grafting (CABG) (3), can be effective in a significant number of patients. However, side effects of medications, coronary vasculature not amenable to either initial or repeat revascularization or diminishing treatment benefit may occur over time.

The search for more therapeutic options for patients with chronic angina has yielded a wide range of new treatment modalities in various stages of clinical evaluation, including transmyocardial laser revascularization (4), minimally invasive bypass surgery (5), spinal cord stimulation (6), transcatheter electrical nerve stimulation (7) and external counterpulsation (CP) (8).

In the U.S., experience with enhanced external CP (EECP), a modified version of external CP, is based on a series of case studies (9,10) in which EECP was successful in relieving angina, improving exercise tolerance and reducing reversible perfusion defects in radionuclide scans. Despite the use of external CP in its various designs over the

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#### Abbreviations and Acronyms

CABG	=	coronary artery bypass grafting
CAD	=	coronary artery disease
CP	=	counterpulsation
EECP	=	enhanced external counterpulsation
ETT	=	exercise treadmill test
MI	=	myocardial infarction
MUST	=	multicenter study
NO	=	nitric oxide
NTG	=	nitroglycerin

past 30 years (11), no controlled trial has been conducted to determine whether the procedure is effective and safe for reducing angina pectoris in patients with coronary artery disease (CAD).

## METHODS

**Objectives.** The multicenter study (MUST)-EECP trial was a randomized, placebo (sham) controlled, multicenter trial designed to evaluate EECP in patients with angina and documented CAD. Treatment effect was determined by comparing changes in exercise treadmill test (ETT) parameters (exercise duration, time to  $\geq 1$ -mm ST-segment depression), symptoms (frequency of anginal episodes and nitroglycerin [NTG] usage between groups).

**Subjects.** The MUST-EECP trial was conducted at seven medical centers in the U.S. (see Appendix). Approximately 500 patients with chronic stable angina were considered for inclusion, of whom 139 were randomized between May 1995 and May 1997. Main reasons for nonenrollment included failure to satisfy inclusion/exclusion criteria, and patient refusal. To be eligible, patients had to meet the following criteria: 1) be between 21 and 81 years of age; 2) have symptoms consistent with Canadian Cardiovascular Society Classification angina levels I, II or III; 3) have documented evidence of CAD and 4) have an ETT positive for ischemia.

Evidence of CAD required at least one of the three following criteria: one or more angiographically proved stenosis  $>70\%$  in at least one major coronary artery; history of myocardial infarction (MI) documented by characteristic creatine kinase elevation and development of Q waves on the electrocardiogram or positive nuclear exercise stress test for MI or ischemia.

Prospective subjects were excluded if they had the following: MI or CABG in the preceding three months, cardiac catheterization in the preceding two weeks, unstable angina, overt congestive heart failure or a left ventricular ejection fraction  $\leq 30\%$ , significant valvular heart disease, blood pressure  $>180/100$  mm Hg, permanent pacemaker or implantable defibrillator, nonbypassed left main stenosis greater than 50%, severe symptomatic peripheral vascular disease, history of varicosities, deep vein thrombosis, phle-

bitis or stasis ulcer, bleeding diathesis, warfarin use with International Normalized Ratio  $>2.0$ , atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering or baseline electrocardiographic abnormalities that would interfere with interpretation of exercise electrocardiogram. Also excluded were pregnant women, women of childbearing potential, subjects unable to undergo treadmill testing and subjects enrolled in a cardiac rehabilitation program or in another research program.

The study was approved by the Institutional Review Boards at participating institutions and conducted in accordance with the Declaration of Helsinki. Enrollment was conditional upon subjects giving written informed consent.

**Study organization.** The study was coordinated centrally by a Core Laboratory. When an eligible patient was identified at a study center, his or her characteristics were communicated to the Study Coordinator at the Core Laboratory where all eligibility criteria were reviewed. Eligible subjects were assigned at random to receive either active CP or placebo delivered as sham therapy in the form of inactive CP as described below. Treatment allocation was based on random codes generated in blocks of 10, with whole blocks assigned to one center, to ensure that patients were assigned equally to each treatment group at each center (12). The same number of random codes was assigned to each treatment group. Assignment was transmitted only to personnel administering EECP at each study center. Study personnel involved in collecting and processing data at the study centers and at the Core Laboratory remained blinded for the duration of the study. To prevent study subjects from recognizing any observable differences between sham and active treatment, appointments were scheduled so as to minimize any opportunities for study subjects in one group to discuss their experience either with other patients undergoing EECP or with MUST-EECP subjects in the other group. The Study Coordinator at the Core Laboratory was notified of adverse experiences and reported them to an independent data and safety monitoring committee.

**Study design.** Before randomization, medical history, physical examination and a baseline ETT were performed. The baseline ETT used a standard or a modified Bruce protocol and was performed within four weeks of treatment initiation. All medications (except on-demand NTG) remained unchanged for the duration of the study. Once randomized, patients underwent 35 h of either active CP or inactive CP. Treatment sessions, each lasting 1 h, could be given once or twice per day. At each treatment session, vital signs were recorded, lower extremities were examined for areas of redness or ecchymosis, adverse experiences were reported and study subjects reported the number of anginal episodes experienced and NTG tablets taken during the preceding 24-h period. An adverse reaction was defined as the development of any new symptom or complaint from the time of randomization. Within one week after completion of 35 treatment sessions, a posttreatment ETT was

performed. Baseline and posttreatment ETT were performed by personnel not aware whether the patient was in the active-CP or the inactive-CP group.

**Enhanced external counterpulsation.** Enhanced external counterpulsation equipment was supplied by the manufacturer, Vasomedical (Westbury, New York). The equipment consists of an air compressor, a console, a treatment table and two sets of three cuffs. Before a treatment session, these cuffs are wrapped around the patient's legs, one set on each leg. Using compressed air, pressure is applied via the cuffs to the patient's lower extremities in a sequence synchronized with the cardiac cycle. In early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs to propel blood back to the heart. This results in an increase of arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation). At end-diastole, air is released instantaneously from all the cuffs to remove the externally applied pressure, allowing the compressed vessels to reconfirm, thereby reducing vascular impedance. The pressures that can be applied to the cuffs range from 0 to 350 mm Hg. In MUST-EECP, the pressure applied to the cuffs was 300 mm Hg in the active-CP group and 75 mm Hg in the control group, enough to preserve the appearance and feel of an EECP application, but insufficient to alter measurably the patient's blood pressure. Blood pressure changes are monitored by finger plethysmography. To assess the hemodynamic effect of EECP, two ratios are computed electronically, using the systolic and diastolic peak pressures or the area under the systolic and diastolic curves. Ratios greater than one correspond to diastolic values greater than systolic values. In MUST-EECP, the means of patients' diastolic to systolic pressure and area under the curve ratios achieved were  $1.41 \pm 0.51$  (mean  $\pm$  SD) and  $1.59 \pm 0.6$ , respectively, in active CP, showing effective diastolic augmentation. Changes in these parameters were undetectable in inactive CP, confirming the lack of hemodynamic effect in the latter group. All other aspects of treatment delivery were the same in both groups.

**End points.** Tracings of each ETT from each study center were sent to the Core Laboratory where exercise duration (s) and time to  $\geq 1$ -mm ST-segment depression (s) were recorded by personnel unaware of the treatment assignment of each patient and whether the ETT was baseline or posttreatment. Exercise duration was defined as elapsed time from the initiation of exercise to the beginning of the recovery period. Time to ST-segment depression was defined as the elapsed time from initiation of exercise to the occurrence of horizontal or down-sloping ST-segment depression  $\geq 1$  mm, 80 ms after the J point, persisting for at least three consecutive beats.

The average frequency of angina episodes per day (angina counts) was computed by dividing the total number of angina episodes reported at three successive treatment sessions by the number of days in which the sessions took

place. Whenever two sessions were conducted on the same day, only angina episodes reported for the first session were used, because the second session covered the same 24-h period as the first session of that day. The first three sessions (i.e., sessions 1 to 3) were considered as the baseline period. In addition, the difference in angina counts between baseline and at end-treatment were calculated as percentage change for each patient in the active- and inactive-CP groups and were classified into the following categories: 50%+ improvement, 25% to 49% improvement, 0 to 24% improvement, 1% to 25% worsening, 26% to 50% worsening, 51% to 100% worsening and  $>100\%$  worsening. Patients with no episodes at the first three sessions were considered as having no change (0%) if they also had no episodes at other periods, and were considered as worsening by 100% or more if they had episodes at other periods.

**Statistical analyses.** On the basis of a between-patient standard deviation of 87 s in exercise duration, there was 80% power to detect a 45-s difference in exercise duration between the two study groups using a two-sided test with a 0.05 level of significance. The primary efficacy analyses for ETT parameters were performed on an observed case basis using the intention to treat population. Changes in exercise duration and time to  $\geq 1$ -mm ST-segment depression from baseline to posttreatment ETT were calculated for each subject and compared between treatment groups. An analysis of variance with treatment group as a main effect and treatment site as a blocking factor was then made. The method used for computing angina counts took into account the varying total treatment time among patients many of whom, for the sake of convenience, underwent two treatment sessions daily for at least part of the treatment course (see End Point section). Two analyses of angina counts were performed. An analysis of variance, on rank transformed data by treatment center, was applied to changes in angina counts from baseline to follow-up. Also, the difference between the two treatment groups with respect to percentage change in angina counts was computed for the entire intention to treat population (all randomized patients) and for those patients with  $\geq 34$  sessions (i.e., for patients having completed EECP treatment). The difference between the two treatment groups with respect to the percent change in each parameter was tested using a Cochran-Mantel-Haenszel chi-square test for ordered categories, stratified by treatment center. Results are presented as adjusted means (least-squares), calculated to accommodate any imbalance in the number of patients in each group among treatment centers. This conforms to the analysis of variance model using treatment center as a blocking factor. The analysis of average usage of on-demand NTG tablets per day (NTG count) was conducted in the same manner as for the analysis of angina counts.

**Adverse experiences.** The number of patients reporting adverse events was compared between groups using a

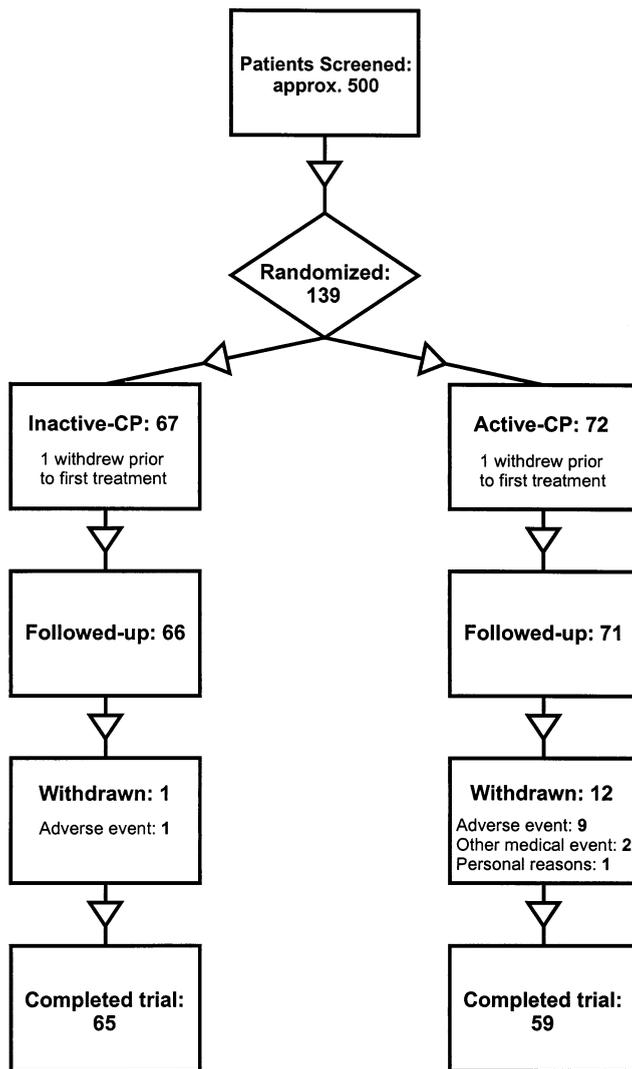


Figure 1. Patient disposition. CP = counterpulsation.

chi-square test. A chi-square test was also used to compare the number of sessions where leg discomfort was reported.

## RESULTS

**Patient enrollment.** One hundred thirty-nine patients were randomized in MUST-EECP. Patient disposition is shown in Figure 1.

Exercise duration data were available for 57 subjects in the active-CP and 58 in the inactive-CP group. Fourteen subjects in active CP were not evaluable for exercise duration: 4 had protocol violations, 7 withdrew because of adverse experiences and 3 dropped out for personal reasons. In the inactive-CP group, 8 subjects were not evaluable for exercise duration. Seven of these had protocol violations, and one dropped out because of an adverse experience. Evaluable data for time to  $\geq 1$ -mm ST-segment depression were available for 56 subjects in each study group. Digoxin

Table 1. Patient Characteristics

	Inactive CP	Active CP	p Values
n	66	71	
Age (mean $\pm$ SD)	62 $\pm$ 9 yr	64 $\pm$ 9 yr	> 0.1
Male	58 (87.9%)	61 (85.9%)	> 0.8
Race			> 0.5
White	49 (74.2%)	55 (77.5%)	
Black	2 (3.0%)	3 (4.2%)	
Hispanic	10 (15.2%)	5 (7.0%)	
Asian	3 (4.5%)	5 (7.0%)	
Other	2 (3.0%)	3 (4.2%)	
CV history			
CCSC			> 0.9
I	17 (25.8%)	19 (26.8%)	
II	34 (51.5%)	35 (49.3%)	
III	15 (22.7%)	17 (23.9%)	
Angina years (mean $\pm$ SD)	4.5 $\pm$ 4.06	8.56 $\pm$ 7.88	< 0.01
Previous MI	27 (40.9%)	40 (56.3%)	< 0.05
Previous CABG	25 (37.9%)	33 (46.5%)	> 0.3
Previous PTCA	22 (33.3%)	27 (38.0%)	> 0.5
Residual vessel disease			> 0.1
0	5 (7.6%)	5 (7.0%)	
1	23 (34.8%)	21 (29.6%)	
2	17 (15.8%)	19 (26.8%)	
3	9 (13.6%)	21 (29.6%)	
No data	12 (18.2%)	5 (7.0%)	
CV medications			> 0.8
Nitrates	54 (81.8%)	56 (78.9%)	
ASA	60 (90.9%)	32 (87.3%)	
CCB	36 (54.5%)	44 (62.0%)	
BB	51 (77.3%)	50 (70.4%)	
Lipid-lowering agents	33 (50.0%)	44 (62.0%)	

Angina years = years since diagnosis; ASA = acetylsalicylic acid taken as an antithrombotic; BB = beta-blocker; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CCSC = Canadian Cardiovascular Society functional classification for angina; CP = counterpulsation; CV = cardiovascular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

use invalidated time to ST-segment depression analysis in one subject in the active-CP group and two in the inactive-CP group.

**Patient characteristics.** The characteristics of the randomized groups were similar, although a higher percentage of patients in the active-CP group had a history of previous MI and suffered from angina for a longer period of time (Table 1). Antianginal treatment was similar for both groups (Table 1). More than 70% of patients in each group had Canadian Cardiovascular Society Classification class II or III and over 70% of each group had undergone prior CABG or angioplasty.

**Efficacy. EXERCISE TREADMILL TEST.** Exercise duration was 426  $\pm$  20 s at baseline and 470  $\pm$  20 s posttreatment in the active-CP group. In the inactive-CP group, exercise

**Table 2.** Exercise Treadmill Test

	Inactive CP				Active CP				Between-Group p Value
	n	Pre-CP	Post-CP	p Value	n	Pre-CP	Post-CP	p Value	
Exercise duration (s)	58	432 ± 22	464 ± 22	< 0.03	57	426 ± 20	470 ± 20	< 0.001	< 0.31
Time to ≥1-mm ST-segment depression (s)	56	326 ± 21	330 ± 20	< 0.74	56	337 ± 18	379 ± 18	< 0.002	= 0.01

Duration in seconds, mean ± SEM.

Pre-CP: baseline, before counterpulsation; Post-CP: follow-up, postcounterpulsation. p values are computed based on adjusted change in duration from baseline to follow-up.

duration was 432 ± 22 s at baseline and 464 ± 22 s posttreatment (Table 2). There was no significant difference between groups in change in exercise duration from baseline to posttreatment (adjusted mean: active CP: 42 ± 11 s vs. inactive CP: 26 ± 12 s; p > 0.3).

Time to ≥1-mm ST-segment depression was 337 ± 18 s at baseline and 379 ± 18 s posttreatment in the active-CP group. In the inactive-CP group, time to ≥1-mm ST-segment depression was 326 ± 21 s at baseline and 330 ± 20 s posttreatment (Table 2). There was a significant difference between groups in the change in time to exercise-induced ischemia from baseline to posttreatment (adjusted mean: active CP: 37 ± 11 s vs. inactive CP: -4 ± 12 s; p = 0.01).

**ANGINA COUNTS.** In the intention to treat analysis, angina counts were 0.76 ± 0.15 at baseline and 0.55 ± 0.27 posttreatment in the active-CP group. In the inactive-CP group, angina counts were 0.76 ± 0.13 at baseline and 0.77 ± 0.2 posttreatment. The difference between groups in the change in angina counts from baseline to posttreatment showed a trend to statistical significance (adjusted mean: active CP: -0.11 ± 0.21 vs. inactive CP: 0.13 ± 0.22; p < 0.09). In patients who completed ≥34 sessions, angina counts were 0.72 ± 0.14 at baseline and 0.57 ± 0.38 posttreatment in the active-CP group. In the inactive-CP group, angina counts were 0.77 ± 0.14 at baseline and 0.76 ± 0.22 posttreatment. The difference between groups in the change in angina counts from baseline was statistically significant (adjusted mean: active CP: -0.033 ± 0.27 vs. inactive CP: 0.15 ± 0.27; p < 0.035). A similar number of patients in each group showed a 0 to 25% level of improvement, but more patients reported a >50% improvement in

angina frequency, and fewer worsened in the active-CP group compared with the inactive-CP group (p < 0.05, Table 3).

**NITROGLYCERIN USAGE.** In the intention to treat analysis, NTG usage was 0.47 ± 0.13 at baseline and 0.19 ± 0.07 posttreatment in the active-CP group. In the inactive-CP group, NTG usage was 0.51 ± 0.15 at baseline and 0.45 ± 0.19 posttreatment. The difference between groups in change in NTG usage from baseline to posttreatment was not significant (adjusted mean: active CP: -0.32 ± 0.12 vs. inactive CP: -0.10 ± 0.12; p > 0.1). In patients who completed ≥34 sessions, NTG usage was 0.39 ± 0.11 at baseline and 0.12 ± 0.04 posttreatment in the active-CP group. In the inactive-CP group, NTG usage was 0.56 ± 0.17 at baseline and 0.43 ± 0.21 posttreatment. The difference between groups in this parameter from baseline to posttreatment was not significant (adjusted mean: active CP: -0.32 ± 0.15 vs. inactive CP: -0.19 ± 0.14; p > 0.1).

**ADVERSE EXPERIENCES.** Both treatment groups, in response to queries, reported a relatively high incidence of adverse events at each treatment session. This is not surprising, because patients were questioned daily by research nurses about any adverse reaction experienced since the previous session. More patients in the active-CP group reported adverse events than in the inactive-CP group: 39 (55%) versus 17 (26%), p < 0.001. Ten of the 25 events reported by the 17 patients in the inactive-CP group were considered device-related, involving either the skin, lower legs or back. Thirty-seven of the 70 events reported by the 39 patients in the active-CP group were considered device-

**Table 3.** Angina Counts

	Median	Improvement			Worsening				P Value
		50+%	25%-49%	0%-24%	1%-25%	26%-50%	51%-100%	100+%	
Intention to treat									
Inactive CP	66	0%	21	3	28	2	2	4	6
Active CP	71	-20%	32	1	33	0	0	2	3
≥34 sessions									
Inactive CP	59	0%	19	2	24	0	2	5	7
Active CP	57	-50%	29	1	23	0	0	0	4

Categories of change are expressed in percent versus baseline. Daily average of self-reported episodes of angina pectoris are computed over three 24-h periods. p values are calculated for between-group differences using a Cochran-Mantel-Haenszel chi-square test for ordered categories stratified by treatment center.

**Table 4.** Adverse Experiences

	Inactive CP	Active CP	p Value
	(n = 66)	(n = 71)	
	n (%)	n (%)	
Patients with AE	17 (25.8)	39 (54.9)	< 0.001
Adverse experiences— non-device related			
Viral syndrome	0	1	> 0.5
Anxiety	0	2	= 0.5
Dizziness	1	3	> 0.5
Tinnitus	0	1	> 0.5
GI disturbances	1	1	> 0.5
Headache	0	1	> 0.5
Blood pressure change	1	1	> 0.5
Epistaxis	0	2	= 0.5
Angina	1	1	> 0.5
Other chest pain	3	7	= 0.3
A/V arrhythmia	3	9	> 0.2
Heart rate change (sinusal)	3	0	= 0.1
Respiratory	2	4	> 0.5
Total	15	33	< 0.005
Adverse experiences— device related			
Paresthesia	1	2	> 0.5
Edema, swelling	0	2	= 0.5
Skin abrasion, bruise, blister	2	13	= 0.005
Pain (legs, back)	7	20	= 0.01
Total	10	37	< 0.001

Some patients reported more than one adverse experience (AE), hence total AE exceed numbers of patients reporting AE. p value: Fisher exact test.

A/V = atrioventricular; CP = counterpulsation; GI = gastrointestinal.

related. The remaining complaints in each group were considered minor and not directly related to treatment (Table 4). Leg discomfort was reported in  $11.6 \pm 22.7\%$  of active-CP sessions and  $4.9 \pm 18.7\%$  of active-CP sessions ( $p = 0.06$ ). Although 47 of the 95 events reported by both groups combined were considered device-related, only five patients withdrew from the study due to leg complaints (e.g., pain, abrasion).

## DISCUSSION

**Effect on exercise treadmill test.** The MUST-EECP trial confirms that EECP can reduce exercise-induced ischemia in patients with symptomatic CAD. The lack of a significant treatment effect on exercise duration despite reduction in other measures of ischemia has been seen in other clinical trials involving antianginal agents (13,14). Training effect or the fact that most study patients were limited by nonanginal symptoms such as fatigue or shortness of breath on the treadmill tests may have produced a fixed exercise duration and account for this observation. Moreover, EECP might be less likely to extend exercise capacity when added to background treatments of antianginal drugs and coronary

revascularization than if such treatments were not in place. There was, however, an increase in time to exercise-induced ischemia, a more objective parameter of treatment effect, in the active-CP group, and the between-group difference was significant.

**Effect on angina counts and NTG usage.** A trend in angina reduction with EECP was seen in the intention to treat analysis and became significant when the analysis included only those subjects completing at least 34 sessions. This observation suggests that a certain number of treatment hours are required to maximize the antianginal benefit of this device (see Mechanisms of Action section). Although NTG usage dropped in the active-CP group, no between-group difference was noted. The wide range of NTG tablets taken by both groups and the common practice of patients with this degree of angina of taking NTG prophylactically, a habit unlikely to be changed over the course of a seven-week study, may explain this finding.

**Mechanisms of action.** The mechanisms underlying the effects of EECP have been under investigation for many years. Acute hemodynamic improvement simulating the effects of intra-aortic balloon CP can be achieved (15), and a multicenter randomized trial in patients with acute MI and heart failure demonstrated that external CP reduced morbidity and mortality (16). The use of this early device to treat angina also suggested benefit (17,18), but variations in treatment protocol produced variable results.

Reasons for continued relief of angina beyond the acute hemodynamic beneficial effects of EECP treatment as described in case series (8-10) are unclear. Increased transmural pressure gradients for the prescribed 35 sessions could open collaterals (19,20). Chronic exposure of the coronary and peripheral arterial bed to the augmented blood flow and increased shear forces produced by EECP could lead to increased endothelial cell production of nitric oxide (NO) and prostacyclin, powerful mediators of vasodilation. Supporting this notion is the recent observation that sustained exercise in dogs increased endothelial NO synthase gene expression and coronary vascular NO production (21). Increased blood flow may regulate the elaboration of a variety of paracrine substances that participate in vascular remodeling and reactivity (22). Consistent with these hypotheses, other strategies targeted to improve endothelial-dependent vasodilation, such as estrogen replacement in postmenopausal women (23) and low density lipoprotein lowering in hypercholesterolemic patients (24), have also been shown to decrease ischemia.

**Clinical implications.** Because coronary disease is a chronic condition, and long-term survival is extended with secondary prevention, practitioners see patients with recurrent angina despite therapy with anti-ischemic agents and coronary revascularization. Most patients enrolled in MUST-EECP fall into this category. In addition, there are many patients who are inoperable, at high risk for operative

complications or postoperative failure, whose coronary anatomy is not readily amenable to invasive procedures or who have comorbid states associated with excessive risk. For such patients, EECP could extend the range of treatment options.

**Limitations.** The design of MUST-EECP has several limitations. The use of a sham method to serve as a placebo control is imperfect but is used often in device- or procedure-related clinical trials (25,26). The fact that some patients in the sham-treated group reported lower leg and skin adverse reactions suggests that sham CP simulated active treatment as intended. Although care was taken to prevent study participants from witnessing other patients receiving EECP, it is possible that some patients in MUST-EECP guessed correctly their form of treatment. Furthermore, it was impossible to blind personnel applying the EECP treatment, leaving open the possibility that the form of treatment could have been suggested inadvertently. Although angina counts and NTG usage were assessed using the subjects' recollection, patients were only asked to recall whether these events had occurred in the 24-h period preceding each treatment session. Most treatments for angina have been the subject of cost-effectiveness analyses and, at the present time, no such data are available for EECP. In addition, MUST-EECP examines only the immediate effect of treatment. Its long-term effects on symptoms and clinical events are not known.

**Conclusions.** The MUST-EECP trial, the first randomized controlled study to evaluate EECP, indicates that enhanced external CP can reduce angina and extend the time to ischemia on ETT in patients with symptomatic CAD. The treatment was relatively well tolerated and free of limiting side effects in most patients.

## APPENDIX

### *MUST-EECP Study Centers*

Columbia-Presbyterian Medical Center, Columbia University (New York, New York); Moffit-Long Hospital, University of California at San Francisco (San Francisco, California); Yale University School of Medicine (New Haven, Connecticut); Beth Israel Deaconess Medical Center, Harvard University (Boston, Massachusetts); Grant/Riverside Methodist Hospitals (Columbus, Ohio); Presbyterian University Hospital, University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania); and Loyola University Medical Center (Maywood, Illinois).

### *MUST-EECP Trial Coordinators*

Columbia-Presbyterian Medical Center: Christine Constantine, RN; Patricia Blowers, RN; Christopher Kaszubski, RN; Patricia Pugni, RN. Moffit-Long Hospital: Kim Prouty, RN; Olga Dimitratos, RN; Xian-Hong Shu, MD. Yale University School of Medicine: Poonamma Chanada, MD; Sanila Rehmatullah, MD; Neil Jairath. Beth Israel

Deaconess Hospital: Carol McKenna, RN; Peggy McGowan-Gump, RN. Grant/Riverside Methodist Hospitals: Karen Manzo, RN. Presbyterian University Hospital, University of Pittsburgh Medical Center: Virginia Schneider, RN; Louanne Tempich, RCVT; Ozlem Soran, MD. Loyola University Medical Center: Ellen Galbraith, RN.

### *MUST-EECP Organization*

**Core laboratory.** Cardiology Division, University Hospital and Medical Center, State University of New York at Stony Brook: Peter F. Cohn, MD (Director); William E. Lawson, MD; Lynn Burger, RN.

**Data and safety monitoring committee.** University of Florida College of Medicine at Gainesville, Florida: Carl J. Pepine, MD (Director); Ronald G. Marks, PhD; Eileen Handberg, RN.

**Database management and analyses.** Anabase International Corp., Stockton, New Jersey.

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