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Enhanced External Counterpulsation Improves Exercise Tolerance, Reduces Exercise-Induced Myocardial Ischemia and Improves Left Ventricular Diastolic Filling in Patients With Coronary Artery Disease

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OBJECTIVES We examined whether enhanced external counterpulsation (EECP) improves myocardial ischemia, exercise tolerance and cardiac function in patients with coronary artery disease (CAD).

BACKGROUND Enhanced external counterpulsation reduces angina and improves exercise tolerance in patients with CAD. Some objective improvements of ischemia by EECP have been reported, but they should be confirmed further. Detailed hemodynamic effects of EECP have been less well documented.

METHODS Enhanced external counterpulsation was performed for a total of 35 h in patients with stable CAD ($n = 12$) who showed evidence of exercise-induced myocardial ischemia despite conventional medical or surgical therapies. All patients had significant stenotic lesions in major coronary arteries.

RESULTS Enhanced external counterpulsation improved all exercise test parameters ($p < 0.05$): exercise duration, time to 1-mm ST segment depression, rate-pressure product at peak exercise and rate-pressure product at 1-mm ST segment depression. Moreover, the prevalence of exercise-induced reversible perfusion defects by thallium scintigraphy decreased after treatment ($p < 0.01$). Enhanced external counterpulsation did not alter systolic function but improved diastolic filling, left ventricular (LV) end-diastolic pressure ($p < 0.05$) by cardiac catheterization and LV peak filling rate end-diastolic volume/s ($p < 0.01$) and time to peak filling rate ($p < 0.05$) by radionuclide scintigraphy. These hemodynamic improvements were associated with decreased plasma brain natriuretic peptides levels after EECP ($p < 0.05$).

CONCLUSIONS Thus, EECP treatment improves exercise tolerance and reduced myocardial ischemia by thallium scintigraphy in association with improved LV diastolic filling in patients with stable CAD. (J Am Coll Cardiol 2001;37:93–9) © 2001 by the American College of Cardiology

Conventional treatments for patients with symptomatic coronary artery disease (CAD) include medication, coronary angioplasty and coronary artery bypass grafting. These conventional treatments have made it possible to successfully treat such patients (1–5). However, a number of patients still do not adequately respond to such treatments, and some patients are not candidates for coronary angioplasty or coronary artery bypass grafting for several reasons.

Enhanced external counterpulsation (EECP) may be an alternative nonpharmacologic therapy for patients with symptomatic CAD. Enhanced external counterpulsation involves sequential inflation and deflation of compressive cuffs wrapped around the lower extremities. The cuffs are sequentially inflated from calf to thigh to buttocks proximally during diastole with rapid deflation of all cuffs at the beginning of systole. These sequential events may theoretically result in increased diastolic aortic pressure and cardiac output and decreased cardiac afterload (6,7). Recently, it has been shown that EECP is effective in relieving angina and improving exercise tolerance in patients with chronic angina pectoris (8–10). Moreover, the beneficial effects of EECP have been shown to last for long-term periods (11,12). Some objective improvements of ischemia by EECP have been reported (8–10), but they need to be confirmed. And detailed evaluations of hemodynamics have not been reported. Accordingly, this study was designed to uncover objective evidence of improvement of myocardial ischemia by thallium scintigraphy and to obtain detailed hemodynamic and humoral data. We found that EECP reduces myocardial ischemia and improves diastolic filling in patients with CAD.

METHODS

Study patients. Patients with stable CAD with documented ischemia were considered for inclusion in this study. According to the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) (10), the following patients were excluded from this study: patients who had congestive heart failure, valvular heart disease, myocardial

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Abbreviations and Acronyms

ANP	= atrial natriuretic peptide
BNP	= brain natriuretic peptide
CAD	= coronary artery disease
EECP	= enhanced external counterpulsation
LV	= left ventricular
LVEDP	= left ventricular end-diastolic pressures
MUST-EECP	= Multicenter Study of Enhanced External Counterpulsation
PER	= peak ejection rate
PFR	= peak filling rate
RPP	= rate-pressure product

infarction in the preceding three months, unstable angina, left main stenosis greater than 50%, systemic hypertension >180/100 mm Hg, permanent pacemaker, atrial fibrillation or ventricular premature beats that would interfere with EECP triggering, peripheral vascular occlusive disease, deep vein thrombosis, phlebitis and hemorrhagic diathesis. Some patients did not give consent for the study. Finally, 12 patients were enrolled in the study. Patients' characteristics are shown in Table 1. They were 51 to 78 years old. Eight patients had effort angina, and four had silent myocardial ischemia. They had significant stenotic lesions greater than 75% in at least one major coronary artery by coronary angiography. Seven patients had undergone prior coronary angioplasty, and two patients had undergone prior coronary artery bypass grafting, but residual stenosis was present in these patients. Standard medications including long-acting nitrates, calcium channel blockers, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and aspirin remained unchanged for the duration of the study. None of the patients had received warfarin. The ethics committee at the Kurume University School of Medicine approved these studies, and informed consent for the study was obtained from all patients.

Study protocol. This study consisted of two phases. The first phase of the study was a control period lasting 38 ± 9 days. During the control period, the patients were engaged in sedentary or mild activity in the hospital and were not treated with EECP. Medical history checks, physical examinations and exercise stress tests were performed as baseline evaluation. The baseline exercise stress test used a standard Bruce protocol with continuous monitoring of symptoms, electrocardiogram and heart rate. Systolic blood pressure was periodically measured at 1-min intervals at rest, during exercise and during the initial 5 min of the recovery period. Measurements were made by digital palpation of the brachial artery using a mercury sphygmomanometer. The exercise test was terminated when there was ischemic ST segment depression >2 mm, significant arrhythmias, moderate chest pain, significant hypotension, exercise fatigue, shortness of breath or achievement of 100% of the maximal predicted heart rate. Then, exercise duration, exercise tolerance, time to 1-mm ST segment depression, rate-pressure product (RPP) at peak exercise and RPP at 1-mm ST segment depression were measured. Personnel who had no knowledge of the study design performed the exercise stress test.

The second phase of the study was the EECP treatment period, for which patients were hospitalized. During the second phase, we assessed the effects of EECP treatment. All patients underwent 35 h of EECP each lasting 1 h; treatment could be given once or twice per day. The treatment period was 36 ± 6 days. Before and after treatment, clinical examinations (including the exercise stress test) exercise thallium-201 scintigraphy, gated blood pool cardiac scintigraphy and cardiac catheterization (including left ventricular [LV] and selective coronary angiography) were performed. Collateral vessels were graded according to the Rentrop classification: 0 = no filling of any collateral vessels, 1 = filling of side branches of the artery

Table 1. Patient Characteristics

Patient #	Gender	Age (yrs)	Diagnosis	Residual Vessel Disease	Previous MI, PTCA and CABG	Coronary Risk Factors	Cordiovascular Medications
1	F	67	SMI	1-VD (LCx)	MI, PTCA	HL, HT, DM	N, CA, BB, ACEI, ASA
2	M	51	EA	1-VD (LAD)	MI	HL, HT, CS	N, CA, BB, ACEI, ASA
3	F	68	EA	1-VD (LAD)	PTCA	HL, HT, DM	N, BB, ACEI, ASA
4	F	62	EA	2-VD (LAD, LCx)	PTCA	HL, HT, DM	N, CA, BB, ASA
5	M	61	EA	2-VD (LAD, LCx)	PTCA, CABG	HL, DM	N, CA, BB, ASA
6	M	74	SMI	2-VD (LAD, RCA)	MI, PTCA		N, CA, ACEI, ASA
7	M	72	EA	1-VD (RCA)		HT	N, CA, ASA
8	M	70	SMI	1-VD (LAD)		HL, HT, DM	CA, BB, ASA
9	M	78	SMI	2-VD (LAD, LCx)	MI, PTCA	CS	N, BB, ACEI, ASA
10	M	70	EA	3-VD (LAD, LCx, RCA)		HL, HT	N, BB, ASA
11	M	59	EA	2-VD (LAD, RCA)	MI	HL, HT, CS	N, BB, ACEI, ASA
12	M	71	EA	3-VD (LAD, LCx, RCA)	MI, PTCA, CABG	HT	N, CA, BB, ACEI, ASA
Mean		67					
SD		7					

ACEI = angiotensin-converting enzyme inhibitors; ASA = aspirin; BB = beta-blockers; CA = calcium antagonists; CABG = coronary artery bypass grafting; CS = current smokers; DM = diabetes; EA = effort angina; F = female; HL = hyperlipidemia; HT = hypertension; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = male; MI = myocardial infarction; N = nitrates; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; SD = standard deviation; SMI = silent myocardial ischemia; VD = vessel disease.

perfused by collateral vessels without visualization of the epicardial segment, 2 = partial filling of the epicardial artery by collateral vessels and 3 = complete filling of the epicardial artery by collateral vessels. The reproducibility of this grading system has previously been validated (13). The collateral score was calculated by totaling the Rentrop score of each patient. Peripheral venous blood was drawn for determination of the plasma concentration of atrial natriuretic peptides (ANP) and brain natriuretic peptides (BNP) before and after treatment. Observers blinded to patient identities performed these clinical evaluations.

EECP. Enhanced external counterpulsation equipment (Vasomedical Inc., Westbury, New York) used in this study consisted of an air compressor, a console, a treatment table and two sets of three cuffs. After these cuffs were wrapped around the patient's legs, compressed air pressure was applied via the cuffs to the lower extremities in a sequence synchronized with the cardiac cycle. The diastolic augmentation pressure was progressively increased by increasing external compression. In this study, the pressure applied to the cuffs during EECP was set at 300 mm Hg. Blood pressure changes were continuously monitored by finger plethysmography. To assess the hemodynamic effect of EECP, the diastolic to systolic pressure ratio was calculated. In this study, the mean diastolic to systolic pressure ratio was 1.1 ± 0.4, showing effective diastolic augmentation. There were no major complications during EECP treatment in any of the patients. No other therapeutic interventions were performed during the study.

Exercise thallium single-photon emission computed tomography. Exercise thallium scintigraphy was performed at the same cardiac workload (RPP) before and after EECP treatment to provide a comparison of test results. After an overnight fast, thallium scintigraphy was performed by means of a multistage, symptom-limited bicycle ergometer exercise test with continuous monitoring of symptoms, electrocardiogram and heart rate. Systolic blood pressure was periodically measured at 1-min intervals at rest, during exercise and during the initial 5 min of the recovery period. At peak exercise, patients received 3 mCi of thallium-201 intravenously, and exercise was continued for an additional period of 60 s to allow adequate circulation of the isotope.

Thallium imaging began within 10 min of completion of exercise and was repeated after 4 h. The studies were performed using a rotating gamma camera with a wide field of vision equipped with a low energy, medium resolution, high sensitivity and parallel hole collimator (RC-1500I, Hitachi, Tokyo) centered on the 70-KeV photopeak with a 10% window. The camera was rotated over a 180° arc in an elliptical orbit about the patient's anterior thorax from the 45° right anterior oblique to the 45° left posterior oblique position. Thirty-two images were obtained in a 64 × 64 matrix for 30 s. For image reconstruction, thallium images were processed on an image-analyzing system (RW 3000, Hitachi, Tokyo). Then, reconstruction was performed using a Butterworth filter with a cutoff frequency of 0.25 cycles/pixel and an order of 8. No attenuation or scatter correction was employed.

The initial and delayed tomographic images were interpreted by two experienced observers who had no knowledge of this study design. For each study, the observers evaluated two short axis slices (basal and midventricular) and one midventricular long axis slice. The basal and midventricular short axis slices were divided into six segments each. In the vertical long axis slice, one apical segment was chosen. Then, a total of 13 segments per patient were evaluated in this study. The degree of radiotracer uptake for each of the 13 segments was semiquantitatively assessed using a five point scoring system based on our previous method (14). Regional thallium uptake was graded from 0 to 4, in increments of 1 with a score of 4 signifying normal activity and a score of 0 signifying absent activity. Perfusion abnormalities were defined as fixed or reversible perfusion defects. Scores for each segment were averaged; no change from the exercise to the redistribution study was considered a fixed perfusion defect, and a change of 1 or more from the exercise to the redistribution study was considered as a reversible perfusion defect.

Gated blood pool cardiac scintigraphy. Radionuclide angiography was performed in the supine position using red blood cells labeled in vivo with 15 to 20 mCi of technetium-99m as previously described (15–17). Imaging was accomplished using a conventional camera equipped with a high-sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. Computer-based electrocardiogram gating, using the list-mode data acquisition system, constructed the cardiac image sequence spanning the average cardiac cycle. High temporal resolution of LV time-activity curves was generated from the cardiac image sequence after background correction. Extrasystolic and postextrasystolic cycles were excluded, and the diastolic portion of the time-activity curve was constructed by combined forward gating and reverse gating from the R wave. The time-activity curve represents a measure of relative LV volume changes with time.

The LV fraction was determined by computer analysis of the time-activity curve (15–18). Left ventricular peak ejection rate (PER) and peak filling rate (PFR) were computed by fitting third-order polynomial functions to the systolic ejection and rapid diastolic filling portions of the time-activity curves using a least-squares technique. Both PER and PFR were computed in LV counts per second, normalized for the number of counts at end-diastole and expressed as end-diastolic counts per second (end-diastolic volume/s). The time to PER was measured from end-diastole (maximum volume on the time-activity curve). The time to PFR was measured from end-systole (minimum volume on the time-activity curve).

Table 2. Exercise Stress Test

		EECP Treatment	
	Baseline	**Before**	**After**
Exercise duration, s	321 ± 79	334 ± 90	416 ± 101*†
Exercise tolerance, METs	5.9 ± 0.9	5.9 ± 1.2	7.1 ± 1.2*†
Time to 1-mm ST segment depression, s	260 ± 80	266 ± 106	320 ± 95*†
RPP at peak exercise	20,900 ± 4,300	21,100 ± 3,500	22,400 ± 3,700*†
RPP at 1-mm ST segment depression	16,100 ± 2,600	16,000 ± 2,300	18,500 ± 2,600*†

Data are expressed as mean ± SD. *$p < 0.05$ vs baseline; †$p < 0.05$ vs. before EECP treatment.
EECP = enhanced external counterpulsation; MET = metabolic equivalent of the task; RPP = rate-pressure product.

Measurements of plasma levels of ANP and BNP. To examine plasma levels of ANP and BNP before and after EECP treatment, blood was sampled from the cubital vein in all patients and collected into chilled siliconized tubes containing EDTA (1 mg/mL) and aprotinin (1,000 KIU/mL). The blood was immediately placed on ice and centrifuged at 4°C. The plasma was frozen and stored at −70°C until assay. The plasma levels of ANP were measured using a highly sensitive immunoradiometric assay (Shionoria ANP kit, Osaka, Japan) as previously reported (19). This assay system used two monoclonal antibodies against a-human ANP, one recognizing a carboxyterminal sequence and the other the ring structure of ANP, and measured a-human ANP by sandwiching it between the two antibodies without extraction of plasma. The minimal detectable quantity of a-human ANP was 5 pg/mL. The intraassay and interassay coefficients of variation were 5.5% and 7.1%, respectively. The cross-reactivity with human BNP was less than 0.001% on a molar basis. The plasma levels of BNP were also measured using a highly sensitive immunoradiometric assay (Shionoria BNP kits, Osaka, Japan) as previously reported (19). This assay system used two monoclonal antibodies against human BNP, one recognizing a carboxyterminal sequence and the other the ring structure of BNP, and measured human BNP by sandwiching it between the two antibodies without extraction of plasma. The minimal detectable quantity of a-human ANP was 2 pg/mL. The intraassay and interassay coefficients of variation were 5.3% and 5.9%, respectively. The cross-reactivity with a-human ANP was less than 0.001% on a molar basis.

Statistical analysis. Values are presented as means ± standard deviation or percentages. Statistical comparisons between groups were performed by the paired Student *t*-test. Multiple comparisons were analyzed by repeated measures analysis of variance with a post hoc Scheffé F test. The relationship between two parameters was analyzed by a linear regression analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Exercise stress test before and after EECP treatment. Table 2 shows exercise test findings at baseline and before and after EECP treatment. Exercise test parameters at baseline and before treatment did not differ in terms of the exercise duration, exercise tolerance, time to 1-mm ST segment depression, RPP at peak exercise and RPP at 1-mm ST segment depression. However, these parameters significantly improved after treatment as compared with those at baseline ($p < 0.05$) or before treatment ($p < 0.05$).

Myocardial perfusion abnormalities before and after EECP treatment. Before EECP treatment, normal and abnormal perfusions were identified in 78 (50%) and 78 (50%) of the 156 study segments, respectively (Table 3). Of the perfusion abnormalities, fixed and reversible perfusion defects were observed in 24 (15%) and 54 segments (35%), respectively. After EECP treatment, the prevalence of normal perfusion (67%) significantly increased ($p < 0.01$), and the prevalence of reversible perfusion defects (21%) significantly decreased ($p < 0.01$). The prevalence of fixed perfusion defects did not change significantly. Figure 1 shows the representative LV polar maps of thallium-201 uptake before and after EECP treatment in one patient.

Hemodynamics and collateral vessels before and after EECP treatment. Table 4 shows hemodynamic parameters before and after EECP treatment. Left ventricular end-diastolic pressures (LVEDP) significantly decreased after treatment ($p < 0.05$). However, other parameters did not change in terms of the heart rate, mean pulmonary capillary wedge pressure, mean pulmonary artery pressure, mean right atrial pressure, mean aortic pressure, cardiac index, LV ejection fraction, LV end-systolic and end-diastolic volume indexes and pulmonary and systemic vascular resistance indexes. Furthermore, the Rentrop score as an index of angiographic collateral vessels did not change after treatment.

Table 3. Prevalence and Type of Perfusion Abnormalities Before and After EECP Treatment

	EECP Treatment	
	Before (n = 156)	**After (n = 156)**
Normal perfusion imagings (%)	78 (50)	104 (67)*
Abnormal perfusion imagings (%)	78 (50)	52 (33)*
Fixed perfusion defects (%)	24 (15)	20 (13)
Reversible perfusion defects (%)	54 (35)	32 (21)*

*$p < 0.01$ vs. before EECP treatment.
EECP = enhanced external counterpulsation.

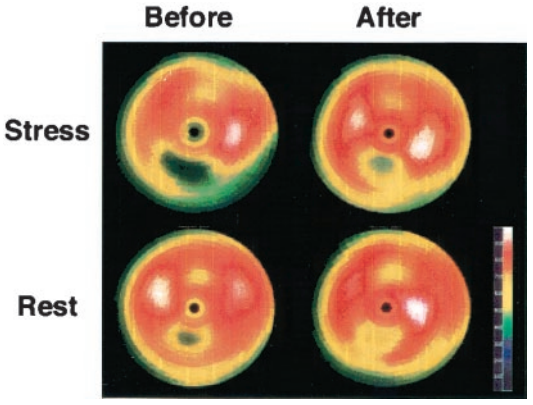

Figure 1. Representative left ventricular polar maps of thallium-201 uptake from a female patient before and after enhanced external counterpulsation treatment. Note that the exercise-induced perfusion defect in an inferior lesion before enhanced external counterpulsation was not apparent after treatment, indicating improved myocardial perfusion.

Gated blood pool cardiac scintigraphy before and after EECP treatment. Heart rate (from 64 ± 8 to 60 ± 6 beats/min, p = NS) and LV ejection fraction (from 66 ± 11 to 64 ± 12%, p = NS) did not change after EECP treatment. In the parameters of systolic ejection, either PER (from 3.0 ± 0.5 to 3.0 ± 0.4 end-diastolic volume/s, p = NS) or time to PER (from 172 ± 38 to 174 ± 34 ms, p = NS) did not change after treatment. However, in the parameters of diastolic filling (Fig. 2), PFR significantly increased, and time to PFR significantly decreased after treatment.

Table 4. Hemodynamics and Collateral Vessels

	EECP Treatment	
	Before	**After**
Hemodynamics		
Heart rate, beats/min	66 ± 8	63 ± 7
Mean pulmonary capillary wedge pressure, mm Hg	7 ± 2	8 ± 3
Mean pulmonary artery pressure, mm Hg	13 ± 3	14 ± 3
Mean right atrial pressure, mm Hg	4 ± 1	5 ± 2
Left ventricular end-diastolic pressure, mm Hg	12 ± 3	9 ± 4*
Mean aortic pressure, mm Hg	94 ± 10	91 ± 12
Cardiac index, l/min/m^2	2.4 ± 0.3	2.3 ± 0.4
Left ventricular ejection fraction, %	61 ± 15	62 ± 13
Left ventricular end-systolic volume index, ml/m^2	38 ± 19	36 ± 18
Left ventricular end-diastolic volume index, ml/m^2	95 ± 22	90 ± 17
Pulmonary vascular resistance index, dynes s cm^{-5} m^2	223 ± 90	235 ± 58
Systemic vascular resistance index, dynes s cm^{-5} m^2	3,056 ± 624	3,086 ± 668
Collateral vessels (assessed by Rentrop score)	1.5 ± 1.0	1.6 ± 1.0

Data are expressed as mean ± SD. *p < 0.05 vs. before EECP treatment.
EECP = enhanced external counterpulsation.

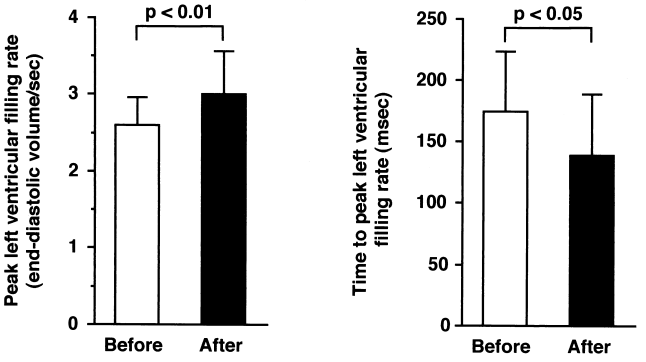

Figure 2. Left ventricular diastolic filling before and after enhanced external counterpulsation treatment. Note that peak filling rate significantly increased **(left panel)** and time to peak filling rate significantly decreased **(right panel)**, indicating an improvement of left ventricular diastolic filling by enhanced external counterpulsation treatment.

Humoral factors before and after EECP treatment. Table 5 shows the plasma levels of ANP and BNP before and after EECP treatment. The plasma level of ANP did not change, but the plasma level of BNP significantly decreased after treatment (p < 0.05). Plasma BNP levels were positively correlated with LVEDP (r = 0.44, p < 0.05) and negatively correlated with PFR (r = −0.47, p < 0.02). However, plasma BNP levels were not correlated with other hemodynamic parameters.

Adverse effects. Enhanced external counterpulsation treatment was well-tolerated. Although some patients developed minor skin eruption (contact dermatitis), it was cured by topical steroid cream. No other complications occurred, and all patients finished this study.

DISCUSSION

In this study, we demonstrated that EECP improved exercise tolerance. Objective evidence of reduced ischemia was demonstrated by thallium scintigraphy. Furthermore, EECP decreased LVEDP, increased PFR and decreased time to PFR in association with decreased plasma levels of BNP. Our findings suggest that the benefits of EECP are associated with improvement of LV diastolic filling.

Effects of EECP treatment on exercise tolerance and myocardial ischemia. Although EECP improved exercise tolerance, warm-up and placebo effects should be always considered. The warm-up or training effect was not likely because the exercise tolerance was not altered during the control period. However, it was significantly improved after

Table 5. Plasma Levels of ANP and BNP Before and After EECP Treatment

	EECP Treatment	
	Before	**After**
ANP, pg/ml	36 ± 22	30 ± 27
BNP, pg/ml	65 ± 33	56 ± 33*

Data are expressed as mean ± SD. *p < 0.05 vs. before EECP treatment group.
ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; EECP = enhanced external counterpulsation.

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EECP treatment. Although we did not have a control group, the MUST-EECP trial demonstrated improved exercise tolerance only in the active EECP group but not in the inactive EECP group (10). The improved exercise tolerance was not due to changes in therapeutic modalities because medications were fixed, and no other interventions were performed during this study period. Taken together, it is suggested that the improved exercise tolerance is related to the EECP treatment.

The increased exercise tolerance may be due to a peripheral training effect but not treatment per se because most study patients were limited by nonanginal symptoms such as shortness of breath or leg fatigue during exercise testing. To address this issue, we measured RPP at peak exercise and RPP at 1-mm ST segment depression before and after EECP treatment. These indexes significantly increased after EECP treatment (Table 2), suggesting the increased ischemic threshold by the augmented myocardial oxygen supply. In order to address this issue further and to obtain objective evidence of improved myocardial perfusion after EECP, we examined myocardial perfusion abnormalities before and after EECP treatment using exercise thallium scintigraphy (Table 3). In our study, exercise thallium scintigraphy was repeated at the same cardiac workload (RPP) as the initial study before EECP treatment. Hence, the degree of myocardial oxygen demand before and after treatment was comparable. Consequently, the prevalence of reversible perfusion defects decreased and the prevalence of normal perfusion increased after EECP treatment, whereas the prevalence of fixed perfusion defects did not change. Thus, our data suggest that improved exercise tolerance is related to reduced myocardial ischemia after EECP.

Effects of EECP treatment on cardiac function. The relation of EECP to systolic or diastolic function has not been investigated previously. In this study, we assessed LV systolic and diastolic function by two methods. One was cardiac catheterization and the other was noninvasive radionuclide angiography. Ejection fraction was not altered by either method, and systolic indexes, such as PER and time to PER, did not change by radionuclide angiography. Thus, cardiac systolic function did not change after EECP treatment. However, LVEDP decreased and diastolic indexes such as PFR and time to PFR were significantly improved after treatment (Fig. 2). Although both PFR and time to PFR used in this study are affected by heart rate, blood pressure, LV ejection fraction and absolute LV volume (15–18), the LV volume indexes obtained by cardiac catheterization and the other parameters were not changed by EECP, suggesting that PFR and time to PFR did improve. Brain natriuretic peptide is a sensitive measure of cardiac function (19–21). Plasma BNP levels rise in heart failure (19). Brain natriuretic peptide is mainly secreted from the left ventricle in response to ventricular wall stress or stretch (19). In this study, plasma BNP levels decreased after EECP, and they were positively correlated with LVEDP and negatively correlated with PFR, suggesting that EECP improved diastolic filling, which led to decreases in plasma BNP levels. The improved diastolic filling associated with decreased BNP was not due to volume loss because body weight was similar before and after EECP (64 ± 9 vs. 64 ± 8 kg) and was not due to peripheral effects because calculated systemic vascular resistance was not changed after EECP. Thus, this study demonstrates for the first time that EECP can improve LV diastolic filling.

Possible mechanisms underlying the effects of EECP treatment. There are some possible mechanisms underlying the beneficial effects of EECP on exercise-induced myocardial ischemia. Impaired diastolic filling is often a manifestation of ischemia (15,16). Conversely, elevated LVEDP increases myocardial oxygen demand (22) and decreases driving pressure for coronary filling (23,24), which cause myocardial ischemia in the presence of coronary artery stenosis. In this study, EECP improved diastolic filling and reduced myocardial ischemia, suggesting that the improved ischemia is related to improved diastolic filling although we did not directly measure LVEDP during exercise. We cannot conclude from this study whether the improved diastolic filling is the cause or consequence of ischemia. It is postulated that EECP may open or enhance the development of collateral channels because intraaortic balloon pumping augments coronary collateral blood flow velocity (25). In this study, angiographically visible collateral vessels did not develop after EECP treatment. However, it is still possible that EECP may have enhanced the development of small coronary vessels that cannot be detected by coronary angiography. This possibility needs to be further investigated. Taken together, the present findings suggest that EECP reduces exercise-induced myocardial ischemia in association with improved LV diastolic filling in patients with CAD. The beneficial effects of EECP treatment may result from the complex interrelationship of several potential effects of EECP.

Study limitations. This study has some limitations. First, only patients with stable CAD were enrolled. Thus, it should be investigated whether EECP is effective and safe for patients with unstable CAD. Second, because patients were hospitalized during the study period, no patient had an attack of angina. Thus, we could not assess the efficacy of EECP on the angina symptom. Finally, this study examined only the immediate effect of EECP treatment. Further study is ongoing in our patients to assess the long-term effects of EECP. In this regard, Lawson et al. (26) recently reported that the majority of patients (64%) with CAD remained alive and without major adverse cardiovascular events and without the need for revascularization five years after EECP treatment, indicating that EECP treatment may be an effective long-term therapy for patients with CAD.

Conclusions. Enhanced external counterpulsation improved exercise tolerance, reduced myocardial ischemia and improved diastolic filling in patients with stable CAD. Although EECP is not first line treatment for patients with

CAD, EECP may be appropriate for patients who are not candidates for revascularization but who continue to have myocardial ischemia.

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REFERENCES

1. Parisi AF, Folland ED, Hartigan P, for the Veterans Affairs ACME Investigators. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. N Engl J Med 1992;326:10–6.
2. Bourassa MG, Pepine CJ, Forman SA, et al., for the ACIP Investigators. Asymptomatic cardiac ischemia pilot (ACIP) study: effects of coronary angioplasty and coronary artery bypass graft surgery on recurrent angina and ischemia. J Am Coll Cardiol 1995;26:606–14.
3. Rita-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second randomized intervention treatment of angina (RITA-2) trial. Lancet 1997;350:461–8.
4. Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the bypass angioplasty revascularization investigation (BARI) randomized trial. Circulation 1997;96:2162–70.
5. Thadani U. Treatment of stable angina. Curr Opin Cardiol 1999;14: 349–58.
6. Zheng ZS, Yu LQ, Cai SR, et al. New sequential external counterpulsation for the treatment of acute myocardial infarction. Artif Organs 1984;8:470–7.
7. Soroff HS, Hui J, Giron F. Current status of external counterpulsation. Crit Care Clin 1986;2:277–95.
8. Lawson WE, Hui JCK, Soroff HS, et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am J Cardiol 1992;70:859–62.
9. Lawson WE, Hui JCK, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology 1996;87:271–5.
10. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;33:1833–40.
11. Lawson WE, Hui JCK, Zheng ZS, et al. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am J Cardiol 1995;75:840–1.
12. Arora RR, Chou TM, Jain D, et al. Results of the multicenter enhanced external counterpulsation (MUST-EECP) outcomes study: quality of life benefits sustained twelve months after treatment (abstr). J Am Coll Cardiol 1999;33:339A.
13. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587–92.
14. Yoshida N, Ikeda H, Wada T, et al. Exercise-induced abnormal blood pressure responses are related to subendocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol 1998;32:1938–42.
15. Bonow RO, Bacharach SL, Green MV, et al. Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation 1981;64:315–23.
16. Bonow RO, Kent KM, Rosing DR, Lipson LC, Bacharach SL, Greem MV. Improved left ventricular diastolic filling in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. Circulation 1982;66:1159–67.
17. Bonow RO, Dilsizian V, Rosing DR, Maron BJ, Bacharach SL, Green MV. Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects. Circulation 1985;72: 853–64.
18. Rocco TP, Dilsizian V, Fischman AJ, Strauss HW. Evaluation of ventricular function in patients with coronary artery disease. J Nucl Med 1989;30:1149–65.
19. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994;90:195–203.
20. Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans: evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991;87:1402–12.
21. Morita E, Yasue H, Yoshimura M, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation 1993;88:82–91.
22. Schwid HA, Buffington CW, Strum DP. Computer simulation of the hemodynamic determinants of myocardial oxygen supply and demand. J Cardiothorac Anesth 1990;4:5–18.
23. Brutsaert DL, Housmans PR, Goethals MA. Dual control of relaxation: its role in the ventricular function in the mammalian heart. Circ Res 1980;47:637–52.
24. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation 1984;69:190–6.
25. Flynn MS, Kern MJ, Donohue TJ, Aguirre FV, Bach RG, Caracciolo EA. Alterations of coronary collateral blood flow velocity during intraaortic balloon pumping. Am J Cardiol 1993;71:1451–5.
26. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study. Clin Cardiol 2000;23:254–8.

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