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...
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.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Residual Vessel Disease</th>
<th>Previous MI, PTCA and CABG</th>
<th>Coronary Risk Factors</th>
<th>Cardiovascular Medications</th>
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<tr>
<td>1</td>
<td>F</td>
<td>67</td>
<td>SMI</td>
<td>1-VD (LCx)</td>
<td>MI, PTCA</td>
<td>HL, HT, DM</td>
<td>N, CA, BB, ACEI, ASA</td>
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<td>2</td>
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<tr>
<td>12</td>
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<td>HT</td>
<td>N, CA, BB, ACEI, ASA</td>
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<tr>
<td>Mean</td>
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<td></td>
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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.

**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.
perfused by collateral vessels without visualisation 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).
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 5 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 2. Exercise Stress Test

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

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.

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

<table>
<thead>
<tr>
<th></th>
<th>Before (n = 156)</th>
<th>After (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal perfusion imagings (%)</td>
<td>78 (50)</td>
<td>104 (67)*</td>
</tr>
<tr>
<td>Abnormal perfusion imagings (%)</td>
<td>78 (50)</td>
<td>52 (33)*</td>
</tr>
<tr>
<td>Fixed perfusion defects (%)</td>
<td>24 (15)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Reversible perfusion defects (%)</td>
<td>54 (35)</td>
<td>32 (21)*</td>
</tr>
</tbody>
</table>

*p < 0.01 vs. before EECP treatment. EECP = enhanced external counterpulsation.
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 5.** Plasma Levels of ANP and BNP Before and After EECP Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before (pg/ml)</th>
<th>After (pg/ml)</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>ANP</td>
<td>36 ± 22</td>
<td>30 ± 27</td>
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</tr>
<tr>
<td>BNP</td>
<td>65 ± 33</td>
<td>56 ± 33</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. *p < 0.05 vs. before EECP treatment group.

**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 EECP treatment.
Effects of EECP on Diastolic Filling

Enhanced external counterpulsation improves 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