Enhanced External Counterpulsation Treatment Improves Arterial Wall Properties and Wave Reflection Characteristics in Patients With Refractory Angina

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OBJECTIVES To determine if arterial properties and wave reflection characteristics are favorably altered after enhanced external counterpulsation (EECP) treatment in patients with refractory angina.

BACKGROUND Early return of reflected waves from the lower body, resulting from increased arterial stiffness, augments central aortic pressure and increases left ventricular (LV) afterload and myocardial oxygen demand. EECP acutely enhances coronary perfusion (supply) and reduces LV afterload (demand). However, the mechanisms responsible for the sustained beneficial effects of EECP treatment are unclear.

METHODS Radial artery pressure waveforms were recorded by applanation tonometry and central aortic pressure waveforms generated using a mathematical transfer function in 20 patients with stable refractory angina. Data were collected before and after 34 1-h EECP sessions. Augmentation index (AI_a) and timing of the reflected pressure wave were calculated from the aortic waveform.

RESULTS EECP treatment caused a decline in AI_a and an increase in reflected wave travel time. These modifications in wave reflection characteristics caused a decrease in aortic systolic pressure and wasted LV pressure energy. The average number of angina episodes and Canadian Cardiovascular Society (CCS) class, both decreased in concordance with the physiologic changes due to EECP treatment.

CONCLUSIONS EECP treatment reduces arterial stiffness and improves wave reflection characteristics in patients with refractory angina. These changes decrease LV afterload and myocardial oxygen demand and reduce the number of angina episodes, therefore enabling patients to participate in continuous exercise programs which in turn may provide long-term benefits and sustained improved quality of life. (J Am Coll Cardiol 2006;48:1208–14) © 2006 by the American College of Cardiology Foundation

The clinical benefits of enhanced external counterpulsation (EECP) therapy in chronic stable refractory angina patients who fail to respond to conventional treatment, such as percutaneous coronary intervention or bypass surgery combined with aggressive antiangina medication, include reductions in myocardial ischemia, angina episodes, and nitrate use (1) and improvement in exercise tolerance (1–3), erectile function (4), and quality of life (5,6). Furthermore, the most recent report from the International EECP Patient Registry

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showed that EECP treatment decreased angina episodes and improved quality of life in patients with severe left ventricular (LV) dysfunction (ejection fraction ≤35%) (7). These beneficial effects occur early and are sustained in many patients up to 5 years (6–9).

The mechanisms responsible for both short-term and long-term clinical benefits are not completely clear. It is common knowledge that EECP enhances coronary artery blood flow and myocardial perfusion acutely during cuff inflation in diastole and reduces LV and aortic systolic pressure (i.e., afterload) during deflation in systole (10), but whether there is a sustained or chronic increase in coronary perfusion and/or decrease in LV afterload after EECP treatment is unknown. Improvement in both coronary (11) and peripheral artery endothelial function has been demonstrated in patients for up to 1 month after EECP treatment (12). Furthermore, recent studies have demonstrated improvement in endothelium-dependent vasorelaxation in the carotid arteries of hypercholesterolemic pigs after 8 weeks of EECP treatment (13). Such studies imply both a cardiac and a peripheral effect and suggest that improvement after EECP treatment may be associated with both improved myocardial perfusion and decreased cardiac afterload (3). Because myocardial ischemia results from an imbalance between myocardial oxygen supply (coronary blood flow) and demand (LV work), some investigators believe the benefits of EECP treatment are supply side related. Whereas most previous EECP treatment studies have focused on improvement in collateral function and increased coronary blood flow (supply), the present study focuses on improvement in peripheral arterial function and decreased myocardial oxygen demand.

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Abbreviations and Acronyms

AI_a = augmentation index
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
Δt_p = round trip travel time of the pressure wave from the heart to the periphery and back
$\Delta t_p/2$ = one-way travel time of the reflected pressure wave from the periphery to the heart
Δt_r = systolic duration of the reflected wave
EECP = enhanced external counterpulsation
LV = left ventricular
NO = nitric oxide
TTI = tension-time index

The aim of this study was to determine if arterial properties and wave reflection characteristics, determinates of LV afterload and myocardial oxygen demand, are improved after EECP treatment in patients with chronic stable angina refractory to conventional medical and revasculization treatment.

METHODS

Patients. Twenty-three consecutive patients with chronic stable angina referred for EECP treatment were enrolled in the study. The study was approved by the Institutional Review Board of the University of Florida, and written informed consent was obtained from all patients. Patients characteristically exhibited multiple cardiovascular risk factors (Table 1), had several prior cardiac events and interventions, including coronary artery bypass grafting and percutaneous coronary interventions, and were considered unsuitable for further coronary revascularization. The patients were referred for EECP treatment because they had a chronic condition characterized by the presence of angina for more than 3 months caused by myocardial ischemia in the presence of angiographic multivessel coronary artery disease (CAD) that could not be controlled by a combination of medical therapy, angioplasty/stent, and/or coronary bypass surgery. Exclusion criteria included lower extremity skin disorder, unstable angina, aortic aneurysm, aortic insufficiency, markedly irregular heart rhythm, hypertrophic cardiomyopathy, overt cardiac failure, severe uncontrolled hypertension (systolic pressure >170 mm Hg or diastolic pressure >100 mm Hg), or severe peripheral vascular disease. Patients were instructed to abstain from eating, smoking, and drinking caffeinated beverages at least 2 h before each EECP session and to continue taking their regular medications and maintain their usual diet and physical activity throughout the study. All patients underwent a standard round of 35 1-h daily sessions of EECP over a period of 7 to 8 weeks using cuff inflation pressures ranging from 200 to 300 mm Hg. EECP equipment (Vasomedical, Westbury, New York) has been described previously (1). Crude assessment of acute diastolic pressure augmentation during EECP was monitored using conventional finger plethysmography. For each patient, all EECP sessions were scheduled at the same time of day in order to minimize the possible effects of circadian variability of vascular reactivity. Patients were interviewed before each session to obtain information on severity and number of angina episodes, amount of nitroglycerin used, and general cardiovascular function. Severity of angina was assessed using the Canadian Cardiovascular Society (CCS) grading system (14).

Table 1. Baseline Patient Characteristics (n = 20) and Cardiovascular Drug Regimen

Patients in Cohort	Percentage/n
Male	80/16
Age >65 yrs	35/7
Body mass index >25<30	35/7
Body mass index >30	40/8
Left ventricular ejection fraction <35%	25/5
Prior myocardial infarction	30/6
Multivessel coronary artery disease	100/20
Prior percutaneous coronary intervention	60/12
Prior coronary artery bypass graft	70/14
More than 1 prior revascularization	15/3
Unsuitable for revascularization	30/6
Stent	50/10
Diabetes	35/7
Hypertension	50/10
Hyperlipidemia	55/11
Present smoker	15/3
Family history of coronary artery disease	75/15
Aspirin	70/14
Plavix	60/12
Lipid-lowering agent	90/18
Diuretic	40/8
Angiotensin-converting enzyme inhibitor	60/12
Angiotensin-receptor blocker	15/3
Calcium-channel antagonist	40/8
Beta-blocker	70/14
Long-acting nitrate	80/16
Digoxin	20/4

Peripheral cuff blood pressure. Brachial systolic, diastolic, and pulse blood pressure measurements were made in the left arm using a validated automatic oscillometric blood pressure monitor (Omron R3; Omron Healthcare, Kyoto, Japan) with the patient lying supine. Three measurements were taken at least 2 min apart with the latter two averaged and used in data analysis.

Pulse waveform analysis. Assessment of arterial wall properties and wave reflection characteristics was performed noninvasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Radial artery pressure waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Texas). After 20 sequential waveforms had been acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic pressure waveform (15–19). Indexes of LV afterload and myocardial oxygen demand were derived from the pressure waveform using the technique of pulse wave analysis (20–23). The merging point of incident and reflected waves (the inflection point, P_i) is identified on the pressure waveform in Figure 1. ($P_i - P_d$) is the amplitude of the incident wave (unaugmented pressure) created by ven-

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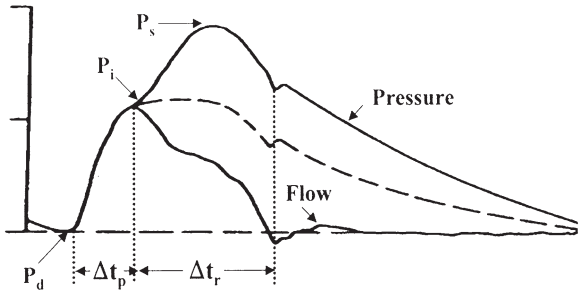

Figure 1. The early part of the ascending aortic pressure wave, with amplitude ($P_i - P_d$), is generated by the left ventricular (LV) ejection (flow) wave. This forward-traveling pressure wave is dependent upon central (elastic) arterial stiffness and pulse wave velocity (PWV) and is not influenced by wave reflections. The later part of the pressure wave, with amplitude ($P_s - P_i$), is generated by the reflected wave arriving from the lower body during systole and adding to the forward pressure wave. This wave is dependent upon the elastic properties of the entire arterial tree and PWV. Pulse pressure = ($P_i - P_d$) + ($P_s - P_i$) = ($P_s - P_d$), and augmentation index (AI_a) = ($P_s - P_i$)/($P_s - P_d$). AI_a is dependent on the elastic properties of the entire arterial tree, transmission velocity of the reflected wave, and distance to the major reflecting site. Δt_p is inversely related to arterial stiffness and is the round-trip travel time of the pressure wave from the heart to the periphery and back; Δt_r is the systolic duration of the reflected wave. Wasted LV pressure energy ($2.09\ \Delta t_r[P_s - P_i]$) and tension-time-index (area under the systolic portion of the pressure wave) are measures of myocardial oxygen demand. The broken curve is the pressure or flow wave without reflections.

tricular ejection, and ($P_s - P_i$) is the amplitude of the reflected wave from the lower body (augmented pressure).

Unaugmented pressure is related to central elastic artery stiffness and is not influenced by reflected waves. In general, acute changes in elastic artery stiffness occur passively (i.e., with a change in distending pressure), whereas chronic changes occur over time (i.e., primarily with changes in arterial wall thickness and collagen and elastin content) (15,20). The aortic augmentation index (AI_a) is defined as reflected wave amplitude divided by pulse pressure ($P_s - P_d$) and expressed as a percentage (24). Smaller values of AI_a indicate decreased wave reflection intensity and delayed return of the reflected wave from the lower body as a result of decreased arterial stiffness (and pulse wave velocity) and vice versa. Reflected wave amplitude and AI_a are dependent upon the elastic properties of the entire arterial tree (elastic and muscular arteries), transmission velocity of the reflected wave, and distance to the major reflecting site (15). Acute reduction in AI_a is due, primarily, to relaxation of smooth muscle cells in the lower body causing vasodilation and a decrease in pulse wave velocity. In addition, because AI_a is influenced by heart rate, an index normalized for heart rate of 75 beats/min (AI_a @75) was also collected (25).

The time, Δt_p, from the beginning upstroke of the synthesized aortic systolic pressure waveform to the upstroke of the reflected wave (inflection point, P_i) is the round-trip travel time of the pressure wave to and from the major reflecting site in the lower body (24), and the time, Δt_r, from the inflection point to the incisura (or dicrotic notch), is systolic duration of the reflected wave (23). $\Delta t_p + \Delta t_r$ represents LV ejection duration, and both segments correlate strongly with arterial pulse wave velocity and vessel wall stiffness (14). Decreased pulse wave velocity leads to a longer Δt_p and a shorter Δt_r and indicates delayed return of the reflected wave from the periphery to the heart (20,24).

When the reflected wave returns during systole, as seen in Figure 1, the aortic pressure is augmented and, therefore, the LV must generate enough energy to overcome this added boost in pressure and opposition to emptying. This energy is wasted, because it does not contribute to blood flow production, and can be estimated as $\Delta t_r(P_s - P_i)\pi/2$ (24). Furthermore, wasted energy is also deleterious to the circulation, because it causes a reduction in ejected volume during blood flow deceleration. Tension-time index (TTI) was obtained as the area under the systolic portion of the aortic pressure wave, and the double-product was calculated as the product of peak aortic systolic pressure and heart rate. These three variables are closely related to myocardial oxygen demand (26).

Only high-quality recordings, defined as an in-device quality index of >80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection, were included in the analysis.

All measurements were performed by the same person (W. Nichols) with the patient in the supine position in a quiet temperature-controlled room after a brief rest period of at least 5 min. Data were collected and analyzed at the first and 35th visits before beginning EECP.

Statistics. Data are presented as mean value and standard deviation for continuous variables. Comparisons between the baseline (before the first session) hemodynamic variable values and those after EECP treatment (before the 35th session) were assessed using a paired 2-tailed Student *t* test for paired observations. A p value of <0.05 was considered to be significant.

RESULTS

Three patients (13%) did not complete the entire EECP treatment, which lasted for 7 to 8 weeks, and were excluded from analysis. One had treatment discontinued because of chronic lower back pain, the second had a cardiac catheterization after 7 treatment sessions and did not return to finish the treatment program, and the third developed atrial fibrillation during the course of treatment and therefore measurements of central pressure could not be obtained. Twenty CAD patients (16 men and 4 women, age range 48 to 70 years) with chronic stable refractory angina completed the EECP treatment program.

Table 1 describes the baseline characteristics and drug regimen of the patients. More than a third of them were older than 65 years, and the majority were men (80%) and overweight (75%). They had a long history of CAD, and most had multiple cardiac catheterizations and coronary interventions and were not candidates for further revascu-

larization therapy when they entered the EECP treatment program. All patients were taking at least 2 antianginal drugs, and the majority (60%) were taking 3. The patients did not change their daily medication or physical activity during the 7 to 8 weeks of the study. Seven patients in the study were diabetic with indices (elevated AI_a and reduced Δt_p) indicating increased arterial stiffness. Although these diabetic patients benefited from EECP treatment, the observed changes in arterial stiffness and wave reflections were not as great as those in the nondiabetic group. Only 3 of the patients were current smokers; therefore, comparison with nonsmokers would not be worthwhile.

The other baseline patient characteristics and response of the different variables to EECP treatment are shown in Table 2. The 20 patients completed the entire course of EECP treatment with no major adverse cardiovascular events.

Components of peripheral and central blood pressure. Pulse pressure (peripheral and central), and to a lesser degree systolic pressure, is dependent upon heart rate, ejection duration, peak flow, and arterial stiffness, whereas mean pressure is dependent upon arteriolar caliber and peripheral resistance; diastolic pressure is inversely related to arterial stiffness (20). In the present study, heart rate and ejection duration did not change with EECP treatment (Table 2). Compared with baseline, all orthodox components of both peripheral and central blood pressure decreased significantly. An example of the measured radial artery pressure wave and the synthesized central aortic pressure wave obtained in 1 of the patients before and after EECP treatment is shown in Figure 2. For the entire group, both brachial systolic and pulse pressure decreased (both $p < 0.001$). Central aortic systolic and pulse pressure were both significantly less (both $p < 0.001$) than brachial systolic (average 12 mm Hg) and pulse pressure (average 13 mm Hg) at baseline, and both decreased (both $p < 0.001$) with EECP treatment. Mean and diastolic pressure also decreased (both $p < 0.001$). Unaugmented pressure, ($P_i - P_d$), decreased ($p < 0.01$), indicating a decrease in central aortic stiffness with EECP treatment.

Table 2. Patient Variables (Mean ± SD) Before (Pre) and After (Post) Enhanced External Counterpulsation (EECP)

	Pre-EECP	Post-EECP	p
Age (yrs)	61 ± 7.1	62 ± 7.3	NS
Height (cm)	175 ± 7.3	174 ± 7.1	NS
BMI (kg/m^2)	30.4 ± 5.4	30.7 ± 5.5	NS
HR (beats/min)	62 ± 9.5	61 ± 9.7	NS
Brachial SP (mm Hg)	132 ± 18	121 ± 18	0.001
Brachial PP (mm Hg)	61 ± 15	54 ± 16	0.001
Aortic SP (mm Hg)	120 ± 18	108 ± 18	0.001
Aortic PP (mm Hg)	48 ± 14	41 ± 16	0.001
DP (mm Hg)	71 ± 8.9	67 ± 6.2	0.01
MP (mm Hg)	92 ± 13	84 ± 9.5	0.001
Ejection duration (ms)	325 ± 28	322 ± 39	NS
($P_i - P_d$) (mm Hg)	35 ± 9.0	32 ± 9.7	0.01
($P_s - P_i$) (mm Hg)	13 ± 7.1	8.7 ± 6.8	0.001
AI_a @75 beats/min (%)	18 ± 9.6	12 ± 8.4	0.01
Δt_r (ms)	182 ± 33	168 ± 41	0.01
Cross product (mm Hg × beats/min)	7,183 ± 1,633	6,326 ± 1,359	0.001
CCS class	3.2 ± 0.4	1.2 ± 0.6	0.001
Angina episodes/wk	7.1 ± 6.0	1.1 ± 0.2	0.02
Diastolic/systolic augmentation ratio	0.9 ± 0.24	1.3 ± 0.28	0.001

AI_a = augmentation index; BMI = body mass index; CCS = Canadian Cardiovascular Society; DP = diastolic pressure; Δt_r = systolic duration of reflected wave; HR = heart rate; MP = mean pressure; PP = pulse pressure; SP = systolic pressure.

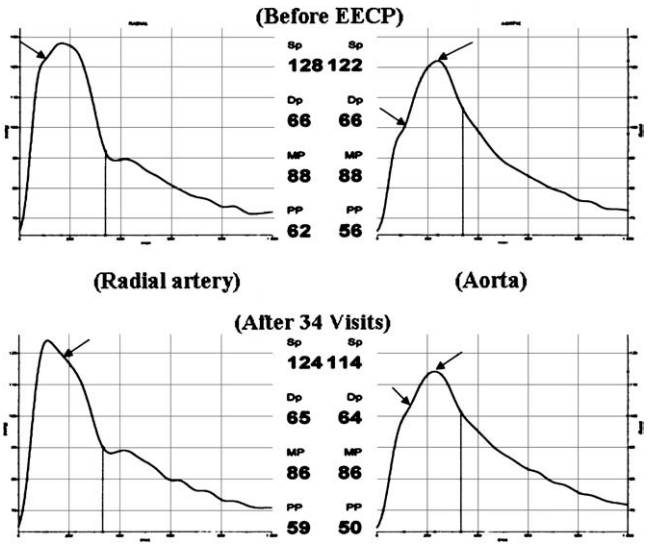

Figure 2. Noninvasive recordings of radial artery pressures waves **(left)** and synthesized aortic pressure waves **(right)** before and after EECP treatment in a 58-year-old woman with stable refractory angina. **Arrows** on the radial pressure wave denote the beginning of the reflected wave, and those on the aortic pressure wave denote the beginning and peak of the reflected wave.

Wave reflections. Associated with the fall in arterial blood pressure was an improvement in wave reflection characteristics. Compared with baseline, reflected wave amplitude, ($P_s - P_i$), decreased ($p < 0.001$) with EECP treatment, causing a significant decrease in central aortic augmentation index (AI_a) ($p < 0.001$) (Fig. 3) and AI_a referenced to a heart of 75 beats/min ($p < 0.01$), indicating a reduction in total arterial stiffness (i.e., elastic and muscular artery stiffness) (15,20). The reduced arterial stiffness caused a decrease in transmission velocity and increase in travel time ($\Delta t_p/2$) of the reflected wave ($p < 0.001$) from the lower body to the heart and a decrease in reflected wave systolic duration (Δt_r) ($p < 0.01$).

Indexes of myocardial oxygen demand. The improvement in arterial wall properties and wave reflection characteristics indicate a significant reduction in LV afterload. These afterload changes were associated with improvement in indexes of myocardial oxygen demand. The reduction in wave reflection amplitude with EECP treatment and the associated decrease in wave reflection duration caused a decline in LV wasted energy (Fig. 4) ($p < 0.001$). Also, compared with baseline, both TTI (Fig. 4) and the cross product decreased with EECP treatment (both $p < 0.001$) (Table 2).

Functional class and angina. Thirty-four EECP sessions led to an improvement by 1 CCS class in 2 patients (10%),

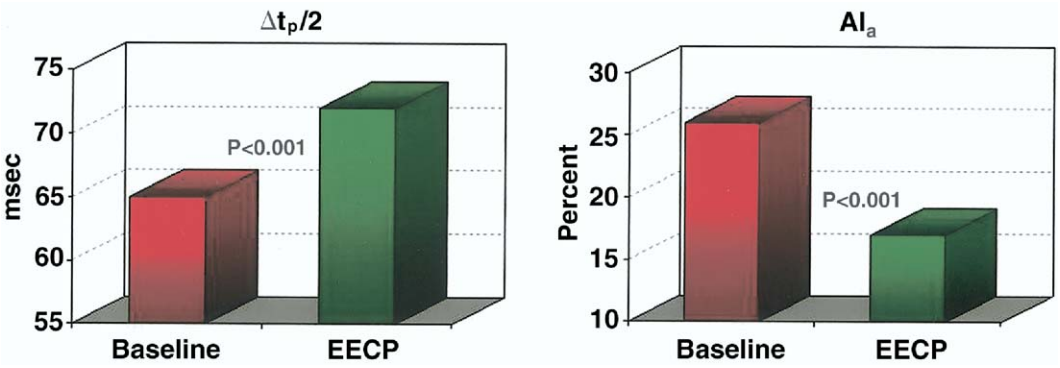

Figure 3. Effects of enhanced external counterpulsation (EECP) treatment on indices of estimated arterial pulse wave velocity and arterial stiffness. EECP caused an increase in travel time of the reflected wave, $\Delta t_p/2$, from 68 ± 8.0 ms to 74 ± 6.6 ms ($p < 0.001$) and a decrease in augmentation index (AI_a) from 27 ± 10% to 19 ± 10% ($p < 0.001$).

by 2 classes in 17 patients (85%), and by 3 classes in 1 patient (5.0%). Average CCS class ($p < 0.001$) and the number of angina episodes per week decreased ($p < 0.02$) in the entire group with EECP treatment (Table 2).

DISCUSSION

Previous studies have shown that coronary artery disease (CAD), myocardial ischemia, and refractory angina are associated with increased total arterial stiffness, reduced endothelial function, and decreased nitric oxide (NO) availability (15,20,27–30). Stiffness of elastic arteries is primarily related to collagen-elastin content and vessel wall thickness, whereas muscular artery stiffness is primarily related to smooth muscle tone and NO bioavailability (16). Vasodilator drugs have little direct effect on elastic arteries but can markedly lower systolic pressure and ventricular afterload by decreasing muscular artery stiffness, pulse wave velocity, and wave reflection amplitude (15,20). Increased arterial stiffness causes the reflected pressure wave to arrive at the heart during ejection and augments systolic blood pressure, which places an extra workload on the heart. These changes in arterial properties and wave reflection characteristics cause a deleterious mismatch between the heart and arterial system. In the present study, we investigated the hemodynamic response to EECP treatment in patients with stable refractory angina using applanation tonometry and pulse wave analysis. The main novel finding of the study was that EECP treatment reduces estimated arterial stiffness and improves ventricular-vascular coupling. These alterations in arterial properties caused a significant fall in aortic augmentation index (AI_a), probably by peripheral vasodilation and reduction in arterial pulse wave velocity possibly resulting from increased NO release and improved endothelial function. This afterload reduction may improve cardiovascular function and reduce angina through a decrease in myocardial oxygen demand.

Our results are in disagreement with those from a similar study published recently showing that EECP treatment did not alter arterial stiffness and aortic augmentation index (31), although there was a significant reduction in peripheral arterial blood pressure, which is, in general, related to smooth muscle relaxation. Those authors concluded from their results that the beneficial effects of EECP treatment are exerted solely through central cardiac effects, including increased coronary collateral vessel development and coronary endothelial function rather than through a concomitant improvement in central or peripheral arterial function. The reason for the conflicting results between the two studies is not immediately clear. However, there are at least 3 possibilities. 1) The authors did not state if baseline and treatment measurements were collected at the same time of day. In our study all measurements were collected at the same time of day to minimize the possible effects of

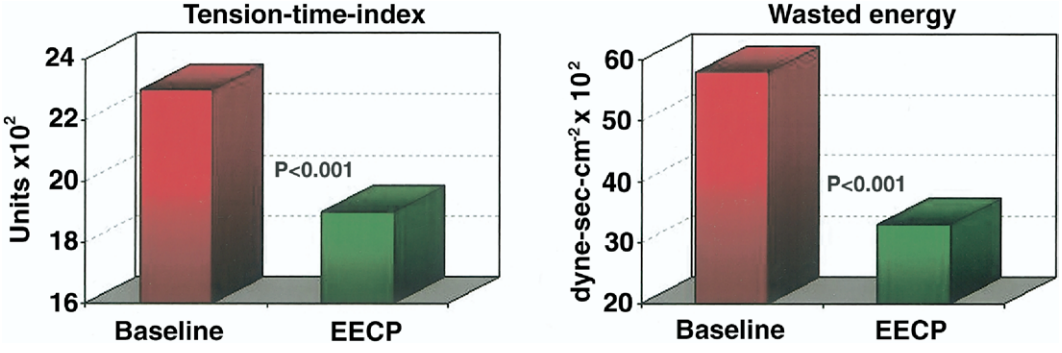

Figure 4. Effects of enhanced external counterpulsation (EECP) treatment on indices of estimated myocardial oxygen demand. EECP caused a decrease in tension-time index (TTI) from 23 ± 5.1 × 10^2 units to 19 ± 3.9 × 10^2 units ($p < 0.001$) and a decrease in wasted LV energy from 56 ± 16 × 10^2 dyne-s-cm^{-2} to 36 ± 13 × 10^2 dyne-s-cm^{-2} ($p < 0.001$).

circadian variability on vascular reactivity. 2) Baseline or treatment measurements could have been collected shortly after a meal, drinking caffeinated beverages, or smoking, all of which influence arterial properties, wave reflection characteristics, and endothelial function (32–34). The patients in our study abstained from eating, smoking, and drinking caffeinated beverages for at least 2 h before data collection. 3) A quality index (i.e., the accuracy of measurement of the pulse) was not presented in their study. A low-quality index (e.g., <50%) may introduce errors in both the measured and the synthesized pressure waveforms. In our study we only accepted high-quality pressure recordings for analysis, defined as an in-device quality index of >80%.

Estimated arterial stiffness. Total systemic arterial (i.e., elastic + muscular arteries) stiffness was estimated from measurements of pressure wave travel time (Δt_p) and aortic augmentation index (AI_a) obtained from the synthesized central aortic pressure wave. Δt_p is inversely related (35) and AI_a is directly related (15) to arterial pulse wave velocity. Furthermore, central aortic (elastic artery) stiffness was estimated from measurements of unaugmented pressure ($P_i - P_d$), which is directly related to central aortic pulse wave velocity (15). EECP treatment caused a significant reduction in both AI_a and ($P_i - P_d$) and an increase in reflected wave travel time ($\Delta t_p/2$). The fall in AI_a and increase in Δt_p are probably due to reduced smooth muscle tone of peripheral conduit arteries, especially those of the lower body, and the decrease in ($P_i - P_d$) is likely due indirectly to the fall in mean arterial pressure and peripheral resistance or directly to a decrease in collagen content.

As suggested previously by Lawson et al. (3), EECP treatment appears to exert a "training" effect. Indeed, the results from the present study with EECP treatment are similar to those reported by others as a result of exercise training (36,37) produced by running, which increases blood flow and wall shear stress in the muscular arteries of the legs. This chronic maneuver increases release of NO from endothelial cells and thus causes vasodilation, with a resulting decrease in arterial pressure and AI_a and a delayed return of the reflected wave from the lower body to the heart (37). Increased NO release in coronary arteries with EECP treatment has been attributed to improvement in coronary flow reserve and endothelial function, which was associated with an increase in myocardial perfusion and exercise tolerance (11). Furthermore, other studies have demonstrated an increase in NO release, improvement in peripheral endothelial function, and smooth muscle vasorelaxation with EECP treatment (4,12,13).

Possible mechanisms for decreased arterial stiffness. Under basal conditions, NO is continually released from endothelial cells and serves to relax smooth muscle cells and maintain arterial patency and distensibility. A variety of mechanical forces, such as arterial wall shear stress and cyclic strain, stimulate NO release, causing vasodilation (38,39). The diastolic inflation/systolic deflation sequence of EECP augments aortic pressure throughout most of diastole and therefore increases diastolic blood flow and shear stress in coronary arteries and arteries in the arms. Coincident with these changes is an increase in diastolic (backward) and systolic (forward) blood flow and shear stress in arteries of the legs. Previous studies in dogs have shown that shear stress resulting from both antegrade and retrograde flow causes NO release (38). EECP treatment and associated increase in shear stress could possibly improve the morphology and function of arterial endothelial cells and increase NO release. Because it mimics physical training, long-term EECP treatment has similar effects on arteries as regular aerobic exercise. For example, aerobic exercise causes cyclic strain on leg arteries as a result on intermittent skeletal muscle contraction and relaxation, which is similar to the inflation/deflation sequence of EECP. Also, both aerobic exercise and EECP increase arterial blood flow and wall shear stress in arteries of the legs and heart and thus improve endothelial function. These modifications in arterial wall properties decrease arterial stiffness and improve wave reflection characteristics, which reduce myocardial ischemia and angina.

In summary, it appears that EECP treatment, like aerobic exercise, improves endothelial function by up-regulating the expression of NO synthase to a higher level in the endothelium in response to increased endothelial shear stress caused by higher blood flow and cyclic strain caused by the inflation/deflation sequence of the pneumatic cuffs on the legs. The improvement in endothelial function may be responsible for increased coronary blood flow and sustained reduction in central aortic pressure augmentation and reduced smooth muscle tone in and wave reflection from peripheral conduit arteries. The acute hemodynamic benefit of EECP is easy to comprehend and is similar to that of intra-aortic balloon counterpulsation, but the sustained benefit of EECP treatment is not so easy to comprehend. However, because the procedure does provide passive exercise to the legs it may be similar to the sustained benefits resulting from chronic exercise programs that tend to make patients feel better and improve their exercise performance. Patients who undergo EECP treatment have not, in general, been able to exercise before EECP treatment owing to angina, but after treatment most are less limited by angina, thus allowing them to participate in continuing exercise programs which they then can maintain. This ability to exercise at a higher level after EECP treatment may contribute to the sustained beneficial action of the procedure.

Study limitations. There are some major limitations to this study. 1) This was an open-label study and did not have a parallel control or placebo group. The use of a sham method to serve as a placebo control in this type of study is imperfect but was used previously in the MUST-EECP (Multicenter Study of EECP), a multicenter, prospective, randomized, blinded, and controlled trial by Arora et al. (1). Those authors pointed out that it is almost impossible to design a procedure that blinds the patients and personnel applying EECP treatment. Therefore, almost all EECP studies are performed without a control group. In the study by Arora et al. (1), exercise duration and time to ST-segment depression

increased and angina episodes and nitroglycerin use decreased in the active group (300 mm Hg cuff pressure) but not in the inactive sham group (75 mm Hg cuff pressure). 2) This was a short-term study that only examined the immediate effects of EECP treatment. The long-term effects of EECP treatment on arterial stiffness and wave reflection characteristics and clinical improvement in symptoms were not determined.

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