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External Counterpulsation Therapy Improves Endothelial Function in Patients With Refractory Angina Pectoris

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OBJECTIVES The goal of this study was to investigate the influence of short-term external counterpulsation (ECP) therapy on flow-mediated dilation (FMD) in patients with coronary artery disease (CAD).

BACKGROUND In patients with CAD, the vascular endothelium is usually impaired and modification or reversal of endothelial dysfunction may significantly enhance treatment. Although ECP therapy reduces angina and improves exercise tolerance in patients with CAD, its short-term effects on FMD in patients with refractory angina pectoris have not yet been described.

METHODS We prospectively assessed endothelial function in 20 consecutive CAD patients (15 males), mean age 68 ± 11 years, with refractory angina pectoris (Canadian Cardiovascular Society [CCS] angina class III to IV), unsuitable for coronary revascularization, before and after ECP, and compared them with 20 age- and gender-matched controls. Endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin (NTG)-mediated vasodilation were assessed before and after ECP therapy, using high-resolution ultrasound.

RESULTS External counterpulsation therapy resulted in significant improvement in post-intervention FMD (8.2 ± 2.1%, $p = 0.01$), compared with controls (3.1 ± 2.2%, $p = 0.78$). There was no significant effect of treatment on NTG-induced vasodilation between ECP and controls (10.7 ± 2.8% vs. 10.2 ± 2.4%, $p = 0.85$). External counterpulsation significantly improved anginal symptoms assessed by reduction in mean sublingual daily nitrate consumption, compared with controls (4.2 ± 2.7 nitrate tablets vs. 0.4 ± 0.5 nitrate tablets, $p < 0.001$ and 4.5 ± 2.3 nitrate tablets vs. 4.4 ± 2.6 nitrate tablets, $p = 0.87$, respectively) and in mean CCS angina class compared with controls (3.5 ± 0.5 vs. 1.9 ± 0.3, $p < 0.0001$ and 3.3 ± 0.6 vs. 3.5 ± 0.5, $p = 0.89$, respectively).

CONCLUSIONS External counterpulsation significantly improved vascular endothelial function in CAD patients with refractory angina pectoris, thereby suggesting that improved anginal symptoms may be the result of such a mechanism. (J Am Coll Cardiol 2003;42:2090–5) © 2003 by the American College of Cardiology Foundation

Patients with symptomatic coronary artery disease (CAD) are usually treated with conventional drug therapy including nitrates, beta-receptor blocking agents, and calcium channel blockers (1), or coronary revascularization when appropriate, either by percutaneous transluminal coronary intervention (PCI) (2) or coronary artery bypass grafting (CABG) (2–6). However, a number of patients do not respond satisfactorily to such therapy, or are unsuitable candidates for invasive treatment.

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Enhanced external counterpulsation therapy (ECPT) has been studied for over 40 years as a noninvasive method for the treatment of CAD (7). It may be a successful alternative therapy for symptomatic CAD patients who are either unsuitable for coronary revascularization or refractory to conventional pharmacologic treatment or repeat interventions, including CABG and/or PCI (8–14). The exact mechanisms by which ECPT exerts its beneficial effects are unknown, but one of its effects is considered to be the development and recruitment of collateral vessels (15). Recent studies suggest that shear stress induced by ECPT might result in the release of a variety of growth factors and the subsequent stimulation of angiogenesis in coronary beds (16).

It is known that the vascular endothelium plays a key role in circulatory homeostasis through its ability to regulate the vascular milieu by the synthesis and release of biologically active substances, such as endothelium-derived relaxing factor (17,18). The endothelium influences not only vascular tone, but also vascular remodeling, as well as hemostasis and thrombosis through platelet, coagulant, and fibrin effects (19,20). In atherosclerotic arteries, these endothelium functions are impaired and potentiate an adverse pathophysiology through increased vasoconstriction (i.e., paradoxical vasoconstriction) (20,21) and thrombosis (20). It has been suggested that by reducing cardiovascular risk factors, the modification or reversal of endothelial dysfunction may be of significant therapeutic benefit in the treatment of CAD (20,22).

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
ECP = external counterpulsation
ECPT = external counterpulsation therapy
FMD = flow-mediated dilation
NO = nitric oxide
NTG = nitroglycerin
NYHA = New York Heart Association
PCI = percutaneous transluminal coronary intervention
%FMD = diameter percent change caused by endothelium-dependent flow-mediated vasodilation
%NTG = endothelium-independent percent change from baseline in nitroglycerin-mediated vasodilation

Over the past decade, a noninvasive technique has been developed to evaluate endothelium-dependent, brachial artery flow-mediated dilation (FMD) (23–25). This stimulus provokes the endothelium to release nitric oxide (NO) with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function. The advantages of this high-frequency ultrasonographic imaging of the brachial artery are two-fold; it is noninvasive and also facilitates repeated measurements (25).

Because the impact of ECPT on endothelial function has not yet been investigated, we designed a study to test the impact of short-term ECPT on FMD in CAD patients with refractory angina pectoris, unsuitable for coronary revascularization. We hypothesized that ECPT would improve FMD in CAD patients with refractory angina pectoris.

METHODS

Study design and population. Twenty consecutive patients were recruited from a supervised external counterpulsation (ECP) program at the Heart Institute of the Sheba Medical Center and comprised the ECP group. Twenty age- and gender-matched consecutive CAD patients who did not want to participate in the ECP program represented the control group. Study inclusion criteria included men and women age >20 years with CAD documented by prior myocardial infarction, coronary artery bypass surgery, or coronary angiography or angioplasty. Refractory angina pectoris (Canadian Cardiovascular Society [CCS] angina class III or IV), obligatory in all patients and rendering them unsuitable for coronary revascularization (either CABG or PCI), was determined by two criteria (26): objective ischemia producing severe symptoms, and/or exhaustive attempts of all known conventional therapies. Patients with refractory angina (CCS angina class III or IV) had to be either markedly limited or incapable of performing even ordinary physical activity without discomfort. Objective evidence of ischemia, as demonstrated by exercise treadmill testing, stress imaging studies or coronary physiologic studies, continuing symptoms despite maximal tolerated medical therapy, and a consensus on the lack of feasibility of revascularization either by PCI or CABG, was considered to be mandatory. Exclusion criteria included unstable angina, congestive heart failure New York Heart Association (NYHA) functional class >II, aortic regurgitation, valvular heart disease, acute myocardial infarction <3 months, left main stenosis >50%, systemic hypertension >180/110 mm Hg, permanent pacemaker, atrial fibrillation, or ventricular premature beats that would interfere with ECP triggering, clinically evident peripheral vascular disease, deep vein thrombosis, phlebitis and hemorrhagic diathesis, use of anticoagulants, pregnancy, abdominal aortic aneurysm, history of drug or alcohol abuse, chronic liver disease, or refusal to sign the informed consent. The institutional review board approved the study, and all participants signed the written informed consent form.

Patients were instructed to continue taking their regular medications and maintain their usual diet throughout the study. Before and after a full 35-h ECP course of treatment in the ECP group or after a 2-month period in the control group, and after an overnight fast, patients underwent a physical examination, brachial artery reactivity testing, CCS angina class assessment, and were asked to list the number of anginal episodes experienced and the number of nitroglycerin (NTG) tablets taken during the preceding 7 days.

The ECP system. The ECP device (CardioAssist System, Cardiomedics, Inc., Irvine, California) contains a portable control console containing pumps and valves and reusable fabric cuffs that contain inflatable plastic bladders, which are fastened with Velcro around the patient's calves, thighs, and buttocks. During diastole, the cuffs are sequentially inflated first around the calves, then around the thighs, and finally around the buttocks, and are synchronized with the patient's electrocardiogram. Compression of the cuffs during diastole forces blood from the legs and buttocks up to the heart, increasing the flow of blood through the coronary arteries to the heart muscle. The decompression of the cuffs during systole reduces the work effort of the heart. The pressures applied to the cuffs range from 0 to 310 mm Hg. Blood pressure changes are monitored by finger plethysmography.

Duration time for each full ECP course was 35 h, extended over a 7-week period. Individual treatment sessions, operating 5 days a week, lasted 1 h per session. Vital signs were recorded at each treatment session, lower extremities were examined for areas of redness or ecchymosis, adverse experiences were reported, the number of anginal episodes and the number of NTG tablets taken during the preceding 24-h period were registered. An adverse reaction was defined as the development of any new symptom or complaint from the time of the first ECP session.

Vascular function protocol. Endothelial function in the form of endothelium-dependent brachial artery FMD was measured as previously described (24,25,27,28). Briefly, FMD was assessed in the subject's right arm in the

recumbent position in a temperature-controlled room (220°C) after a 10-min equilibration period, by a single ultrasonographer blinded to treatment assignment. Using a 15-6 MHz linear array (15-6L HP) ultrasound (HP SON09-09OS 5500 CV system, Agilent Technologies Inc., Andover, Massachusetts), the brachial artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease, where the clearest image was noted. When a reasonable image was obtained, the surface of the skin was marked, and the arm and the ultrasound probe were kept in the same position by the ultrasonographer throughout the study. An electrocardiogram was monitored continuously, and blood pressure was taken in the left arm every minute throughout the study.

Study phases. ENDOTHELIUM-DEPENDENT FMD. Following a 2-min baseline period, a frozen 3-cm longitudinal image of vessel without color flow was obtained and frozen for 5 s. The image was then unfrozen and switched to a pulse wave Doppler for 5 s at a sweep speed of 50 mm/s. A pneumatic tourniquet placed around the forearm proximal to the target artery was inflated after the baseline phase to a pressure of 50 mm Hg above the subject's systolic blood pressure (or until no blood flow was noticed through the brachial artery by the Doppler probe), and this pressure was held for 5 min. Increased flow was then induced by sudden cuff deflation. A continuous scan was performed at deflation, 60 and 90 s after cuff deflation, with frozen and Doppler measurements recorded at similar intervals to the baseline phase.

NTG-INDUCED (NON-ENDOTHELIUM-DEPENDENT) VASODILATION. Thirteen minutes after cuff deflation, a second 2-min baseline-resting scan was recorded to confirm vessel recovery. After the administration of a sublingual NTG tablet (Nitrostat, 0.4 mg, Parke-Davis, New Jersey), scanning was performed continuously for 5 min.

Data analysis. The ultrasound images were recorded on an S-VHS videotape with an SLV-RS7 videocassette recorder (SONY, California). The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia ("m line") at a fixed distance (29). The mean diameter was calculated from four cardiac cycles synchronized with the R-wave peaks on the electrocardiogram. All measurements were made at end diastole to avoid possible errors resulting from variable arterial compliance (30). The internal diameter was calculated with PC Prosound software (USC, Los Angeles, California) using a Horita Data Translation Image Processing board (DT2862-60Hz; Mission Viejo, California) (24). The diameter percent change caused by endothelium-dependent flow-mediated vasodilation (%FMD) and endothelium-independent percent change from baseline in NTG-mediated vasodilation (%NTG) were expressed as the percent change relative to that at the initial resting scan. The intraobserver variability for repeated measurements is 0.0 ± 0.07 mm in our laboratory.

Table 1. Baseline Characteristics of Study Population

Variable	ECP Group (n = 20)	Control Group (n = 20)
Age (yrs)	68 ± 11	67 ± 12
Body mass index (kg/m^2)	26 ± 4	25 ± 7
CCS angina class IV	15 (75)	14 (70)
CCS angina class III	5 (25)	6 (30)
Systemic hypertension	10 (50)	7 (35)
Diabetes mellitus	7 (35)	8 (40)
Current smoker	0	0
Hypercholesterolemia	15 (75)	16 (80)
Previous myocardial infarction	14 (70)	13 (65)
Previous coronary angioplasty	12 (60)	13 (60)
Previous coronary bypass	10 (50)	11 (55)
Beta-receptor antagonist	14 (70)	13 (65)
Calcium antagonists	9 (45)	7 (35)
Diuretics (lasix)	4 (20)	5 (25)
Aspirin	19 (95)	19 (95)
Long-acting nitrates	16 (80)	17 (85)
ACE inhibitors	13 (65)	12 (60)
Lipid-lowering agents	15 (75)	16 (80)

Values are expressed as mean ± SD or n (%). All p = NS.
ACE = angiotensin-converting enzyme; CCS = Canadian Cardiovascular Society; ECP = external counterpulsation.

Statistical analysis. Group data are expressed as mean ± SD. Differences between clinical characteristics and brachial artery vasodilator responses were evaluated and analyzed by unpaired *t* tests for two-group comparisons, and one-way analysis of variance for multiple-group comparisons. Comparison of biochemical measurements was performed using the unpaired Student *t* test and Wilcoxon signed-rank test. The Wilcoxon-Mann-Whitney *U* test was used to calculate differences over time and to compare the treatment groups. A value of $p < 0.05$ was considered significant.

RESULTS

Our study population was comprised of 40 CAD patients, 20 patients (15 males) in the ECP group and 20 (17 males) in the control group, with a mean age of 68 ± 11 years (range 44 to 82), and mean body mass index of 26 ± 4 kg/m^2 (range 20 to 37 kg/m^2) (Table 1). No significant group differences in baseline characteristics were seen (Table 1). Baseline lipid values were within the National Cholesterol Education Program Adult Treatment Panel III treatment goal. Overall group mean low-density cholesterol at study entry was 91 ± 14 mg/dl (2.35 mmol/l) (range 43 [1.11] mmol/l to 132 [3.41] mmol/l). All patients had refractory angina pectoris, and 75% had CCS angina class IV (Table 1). There were no significant changes in concomitant medication use and no serious adverse effects throughout the study.

Treatment effect on endothelial function. At baseline, the total study population had FMD of 3.0 ± 2.6% and NTG-mediated vasodilation of 10.2 ± 2.4%. There were no significant differences at baseline FMD (Fig. 1) or NTG-mediated dilation between the two groups. External counterpulsation therapy resulted in a significant improvement in post-intervention FMD (8.2 ± 2.1%, p = 0.01 compared

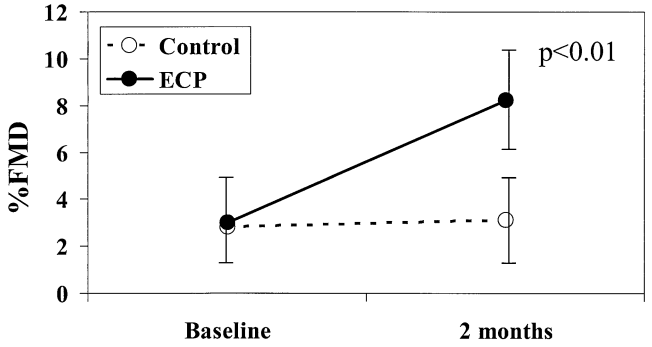

Figure 1. The percent change in endothelium-dependent brachial artery flow-mediated vasodilation (%FMD) from baseline in external counterpulsation (ECP) **(closed circles)** (n = 20) and control **(open circles)** (n = 20) groups at baseline and after two months.

with baseline), a finding not evident in the control group (3.1 ± 2.2%, p = 0.78 compared with baseline) (Fig. 1). At the end of the trial, ΔFMD (post-intervention %FMD − baseline %FMD divided by baseline %FMD) was significantly higher in the ECP group compared with the control (1.7 ± 0.1% vs. 0.1 ± 0.1%, p <0.01, respectively). There was no significant effect of treatment on NTG-induced vasodilation between the ECP and control groups (10.7 ± 2.8% vs. 10.2 ± 2.4%, p = 0.85, respectively).

Treatment effect on symptoms. External counterpulsation treatment significantly improved anginal symptoms assessed by reduction in mean sublingual nitrate consumption per day compared with the control group (4.2 ± 2.7 nitrate tablets vs. 0.4 ± 0.5 nitrate tablets, p <0.001 and 4.5 ± 2.3 nitrate tablets vs. 4.4 ± 2.6 nitrate tablets, p = 0.87, respectively) and improvement in mean CCS angina class compared with the control group (3.5 ± 0.5 vs. 1.9 ± 0.3, p <0.0001, and 3.3 ± 0.6 vs. 3.5 ± 0.5, p = 0.89, respectively) (Fig. 2). At the end of the study, no patient from the ECP group had CCS angina class IV; 1 patient (5%) had CCS angina class I, 17 patients (85%) had class II, and 2 patients (10%) had class III. These two patients had CCS angina class IV at baseline. In the control group, however, there was no significant change in the CCS angina class from baseline (Fig. 2).

DISCUSSION

This study demonstrates for the first time that short-term ECP intervention compared with controls results in significant improvement of brachial artery endothelial function in CAD patients with severe refractory chronic angina pectoris. Endothelial dysfunction is not only confined to the coronary arteries but may represent a systemic disorder that also affects the peripheral vascular beds, including both conduit arteries and small resistance vessels in the extremities (31). Our results reinforce the hypothesis that shear stress induced by ECPT could lead to increased endothelial cell production and the release of NO, a powerful mediator of generalized vasodilation in coronary beds, leading to improved myocardial perfusion and coronary flow reserve in CAD patients with angina (10,15). This hypothesis is also supported by the recent observation that sustained exercise in dogs increased endothelial NO synthase gene expression and coronary vascular NO production (32). Serum NO levels, myocardial perfusion, and coronary flow reserve were also increased by ECPT in patients with chronic stable angina (15). Recently, Bonetti et al. (33) also demonstrated that ECP improved endothelial function assessed by reactive hyperemia peripheral arterial tonometry (a novel, noninvasive technique to assess peripheral microvascular endothelial function in the finger) in 23 symptomatic CAD patients despite administration of optimal medical therapy.

There are several potential mechanisms that underline the beneficial effects of ECPT in CAD patients with refractory angina pectoris; ECPT reduces exercise-induced myocardial ischemia (11) in association with improved left ventricular diastolic filling and a decrease in plasma brain natriuretic peptide levels (12); ECPT enhances the vascular endothelium by increasing shear stress to express platelet-derived growth factor A and B, vascular endothelial growth factor, and fibroblast growth factor-2 from vascular smooth muscle and endothelial cells, leading to open or enhanced development of collateral channels (16,34) and angiogenesis (16); ECPT decreases cardiac afterload (35).

Our current results demonstrate a significant improvement in peripheral vascular endothelium-dependent FMD in CAD patients with refractory angina pectoris, treated by short-term ECP, suggesting that ECP-increased NO production and release from peripheral arteries lead to a decrease in peripheral vascular resistance (15).

In the present study, patients were used as their own

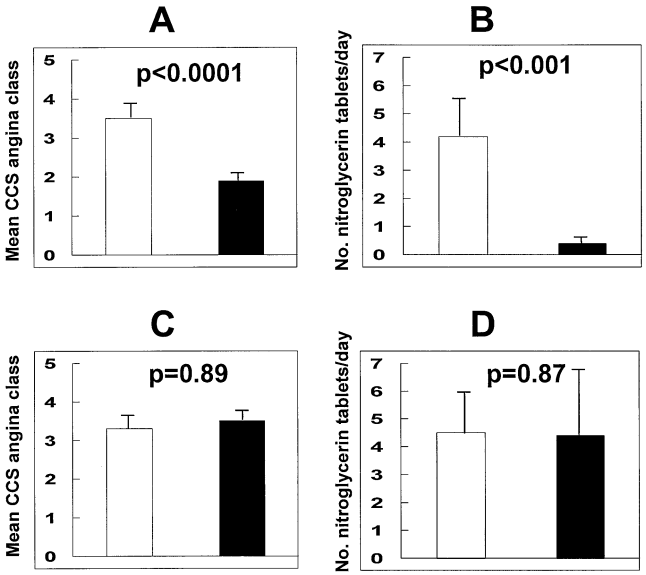

Figure 2. Bar graphs showing the beneficial effects of short-term external counterpulsation (ECP) before **(open bars)** and after **(closed bars)** two months of treatment on **(A)** mean Canadian Cardiovascular Society (CCS) angina class, and **(B)** mean number of daily sublingual nitroglycerin tablets consumed in the ECP group (n = 20), compared with no significant change in the control group (n = 20) **(C and D)**. Data are expressed as mean ± SD.

controls. Whereas CAD is largely unpredictable in its course, regression would not be expected to occur over a six- to seven-week period in a group of patients whose angina had been disabling or progressive over a period of months or years. The enrolled patients did not undergo any simultaneous therapy such as strict diet, aggressive lipid reduction, weight loss, or a supervised exercise program. Sublingual antianginal medications were significantly decreased during the course of the study in all patients, and CCS angina class significantly improved. The study cohort was predominantly male, and, therefore, definitive conclusions regarding efficacy in females should await future studies.

External counterpulsation therapy was well-tolerated by all patients enrolled in the study. No patient withdrew after enrollment, and there were no complications resulting from ECPT.

Study limitations. We studied a small number of stable CAD patients with near-optimal lipid values. In addition, it is possible that the impact of ECP intervention on the brachial artery FMD was underestimated due to the relatively low-risk population. Following our results, further studies are indicated comprising a larger number of CAD patients who are at higher risk.

There is both biologic and measurement variability in the ultrasound assessment of brachial artery FMD. However, previous studies have demonstrated the feasibility of this approach, if performed carefully, for detecting change in relatively small sample sizes (24,25,36).

Perhaps the major limitation of this study is the lack of a double-blind treatment for patients with refractory angina pectoris.

Conclusions. In conclusion, our study demonstrates that ECPT in CAD patients with refractory angina pectoris, unsuitable for coronary interventions, results in significant improvement in brachial artery endothelial function and anginal symptoms, suggesting a potential mechanism whereby ECPT could beneficially improve anginal symptoms.

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