Enhanced external counterpulsation for treatment of refractory angina pectoris

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Objective **Enhanced external counterpulsation (EECP) is a noninvasive, well-tolerated treatment, effective for managing patients with refractory angina pectoris. The aim of this study was to evaluate the efficacy of EECP to relieve symptoms, to decrease myocardial ischaemia and to improve cardiac performance in patients with intractable angina, refractory to surgical and medical treatment.**

Methods **Twenty-five patients (24 men and one woman, mean age 65 years) with persistent ischaemia notwithstanding optimal medical therapy or after interventional or surgical procedure, received EECP sessions for 35 h. Each patient underwent dobutamine stress echocardiography before and after treatment. We evaluated modifications in either cardiac systolic or diastolic function, and in wall motion score index.**

Results **Eighty-four percent of patients showed an increase in at least one functional angina class. We did not observe any significant changes in fractional shortening and diastolic function. Thirty-six percent of patients had a reduction in the area of inducible ischaemia at dobutamine stress echocardiography after treatment. Unfortunately, because of the small sample size, we did not find any statistically significant difference. There was a trend showing that patients who benefited the most were those with the worst systolic function and with severely compromised segmental kinesis (P = NS).**

Conclusions **EECP is effective in relieving symptoms in patients with refractory angina and may reduce inducible ischaemia at dobutamine stress echocardiography, especially in patients with reduced systolic function and compromised segmental kinesis.** ***J Cardiovasc Med*** **7:335–339 © 2006 Italian Federation of Cardiology.**

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Introduction

Treatment of patients with refractory angina pectoris is still challenging. Enhanced external counterpulsation (EECP) seems to be a noninvasive, well-tolerated therapeutic option for this kind of patients. This treatment may improve quality of life in patients with stable angina pectoris and reduce symptoms, by inducing favourable haemodynamic effects such as an increase in aortic diastolic pressure, an improvement in coronary perfusion, a decrease in afterload and oxygen consumption, and an increase in cardiac output [1]. The aim of this study was to evaluate the efficacy of EECP treatment in reducing angina symptoms, improving quality of life and reducing inducible ischaemia at dobutamine stress echocardiography (DSE) in patients with chronic angina refractory to appropriate medical, surgical or interventional therapy.

Methods

Patients

We evaluated 25 patients (24 men and one woman, aged between 55 and 80 years, mean age 65 years) with chronic angina and inducible ischemia at DSE despite appropriate medical, surgical or interventional therapy. Inclusion criteria were the following: (a) patients with severe and diffuse coronary artery disease involving one or more epicardial coronary arteries in whom surgical or interventional therapy was not feasible because of technical reasons or an unaffordable risk–benefit ratio; (b) patients who refused surgery or angioplasty; (c) patients with angina symptoms despite a previous revascularization procedure who showed a very small area of viable myocardium.

Eight percent of patients were in Canadian Cardiovascular Society (CCS) angina class II, 68% in CCS class III, and 24% in CCS class IV; 64% of patients experienced a previous myocardial infarction, 36% had diabetes mellitus, 68% arterial hypertension, and 92% hypercholesterolaemia. All enrolled patients had at least one critical stenosis (> 75%) of an epicardial coronary artery at coronary angiography; 36% received a previous angioplasty and 64% a previous bypass surgery.

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Table 1 Patient characteristics

No. patients	25
Hypertension	17 (68%)
Diabetes mellitus	9 (36%)
Hypercholesterolaemia	23 (92%)
Previous MI	16 (64%)
CCS angina class	
II	2 (8%)
III	17 (68%)
IV	6 (24%)
Previous PCI	9 (36%)
Previous CABG	16 (64%)
β-blockers	17 (68%)
Calcium-channel blockers	15 (60%)
Nitrates	22 (88%)
ACE-inhibitors	10 (40%)
Aspirin	23 (92%)
Statins	21 (84%)

MI, myocardial infarction; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme.

During the study all patients continued their own medical therapy, which included β-blockers (68%), calcium-channel blockers (60%), nitrates (88%), angiotensin-converting enzyme inhibitors (40%), aspirin (92%), and statins (84%). Patient characteristics are summarized in Table 1.

Exclusion criteria, according to previous studies [2], were a recent myocardial infarction (< 3 months); unstable angina pectoris; severe aortic insufficiency; congestive heart failure; left main stem disease (> 50%); permanent pacemaker; atrial fibrillation or other arrhythmias interfering with electrocardiographic triggering; peripheral arterial disease; deep venous thrombosis; haemorrhagic diathesis or therapy with warfarin; and severe lower limb skin disease.

After giving informed consent, patients were asked about their health status and particularly about CCS angina class, nitrate consumption, and perception of their quality of life. Each patient was scheduled for 35 EECP sessions of 1 h each for 7 weeks. Before and after treatment, patients underwent a cycloergometer stress test in order to detect an improvement of exercise capacity and of the ischemic threshold, and a DSE test in order to evaluate if any reduction in the area of inducible ischaemia was present.

Enhanced external counterpulsation

EECP is a noninvasive technique consisting in the application of three sets of cuffs wrapped around calves, upper and lower thighs, which are sequentially inflated from distal to proximal compression upon diastole and simultaneously deflated upon systole. It produces an improvement in coronary perfusion and a reduction in afterload resulting in increased cardiac output [1]. During each session, the electrocardiogram, oxygen saturation and plethysmography are recorded.

Dobutamine stress echocardiography

DSE was performed before and after treatment according to the recommendations of the American Society of Echocardiography (ASE) [3], using an ATL Platinum machine. In basal conditions, left ventricular dimensions, systolic and diastolic function were measured. The regional kinesis was analyzed and scored according to the recommendations of the American Society of Echocardiography [3]. The test was considered positive if new or worsening asynergy occurred, and a biphasic response was considered as a positive one. A horizontal or descendent ST-segment depression of at least 1 mV at 80 ms from the J point has also been considered as a positive response. Tests were interpreted separately by two expert echocardiographers, blinded to the results of coronary angiography. The wall motion score (WMS) was defined as the total score of the analyzed segments and the wall motion score index (WMSI) as the ratio between WMS and number of visualized segments. An index given by the difference between WMSI at peak and at baseline was used to measure the entity of reversible ischaemia: the bigger was the difference, the wider was the entity of ischemia.

Follow-up

Follow-up was performed at the end of treatment and at 6 months, and it was also scheduled at 1 and 2 years. It consists in answering a questionnaire (International EECP Patient Registry), also by telephone interview, before and after treatment, about perception of quality of life, nitrate consumption, CCS angina class, and occurrence of adverse cardiac events (death, myocardial infarction, congestive heart failure). In order to evaluate quality of life, patients had to choose their response in multiple-choice questionnaires. Each response corresponded to a rank (positive, negative and ties) and the difference before and after treatment was evaluated.

Statistical analysis

Data were expressed as mean ± SD or percentage. The Student's *t*-test was used to analyze paired data, and a P value of less than 0.05 was considered statistically significant. The Wilcoxon test was used for unpaired data and a Z value of less than 0.05 was considered statistically significant.

Results

At the end of treatment, an improvement in at least one functional angina class has been observed in 84% of patients ($Z < 0.000$); it lasted for at least 6 months in 52% of patients ($Z < 0.011$) (Tables 2 and 3). Nitrate consumption significantly decreased after treatment ($Z = 0.000$) and the benefit persisted at 6 months ($Z < 0.03$) (Table 2). In 13 patients perception of quality of life improved ($Z = 0.01$) (Table 2), in 2 patients it worsened, and in 10 patients it was unchanged. Exercise capacity at the cycloergometer stress test improved by

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Table 2 Modifications in angina symptoms, nitrate consumption and quality of life after enhanced external counterpulsation treatment

	No. patients with improvement	Z
Angina	21	0.000
Angina at 6 months	13	0.011
Quality of life	13	0.01
Nitrate consumption	20	0.000

Table 3 Modifications in the Canadian Cardiovascular Society (CCS) angina class after enhanced external counterpulsation (EECP) treatment

Before EECP		After EECP	
CCS class	No. patients	CCS class	No. patients
IV	6	IV	1
		III	2
		II	3
III	17	III	2
		II	13
		I	2
II	2	II	1
		I	1
Total	25	Improved	21
		Stable	4

21% (mean exercise time from 5.7 ± 1.9 to 6.9 ± 2.1 min; $P = 0.02$). The ischaemic threshold did not change significantly.

Thirty-six percent of patients had a reduction in the area of inducible ischaemia at DSE or a negative test at the end of treatment; no statistically significant reductions were observed in WMS and WMSI at baseline ($P = 0.128$ and $P = 0.103$, respectively) and at peak stress ($P = 0.56$ and $P = 0.6$, respectively); the difference between WMSI at peak and WMSI at baseline did not show any significant changes either ($P = 0.26$) (Table 4). A further data subanalysis showed that patients who benefited the most were those who, before treatment, had the most severe wall motion abnormalities at DSE peak stress. Unfortunately, the analysis did not reach statistical significance,

Table 4 Modifications in wall motion score index (WMSI) at baseline and at peak stress, before and after enhanced external counterpulsation (EECP) treatment

WMSID	
Before EECP	0.32 ± 0.2
After EECP	0.24 ± 0.2
WMSI	
Before EECP	
Baseline	1.5 ± 0.3
Peak	1.8 ± 0.4
After EECP	
Baseline	1.5 ± 0.3
Peak	1.7 ± 0.4

WMSID, difference between WMSI at peak and at baseline. WMSID before versus after EECP: $P = 0.26$; WMSI before versus after EECP at baseline: $P = 0.1$; WMSI before versus after EECP at peak stress: $P = 0.6$.

Table 5 Modifications in systolic and diastolic function after enhanced external counterpulsation (EECP) treatment

Ejection fraction[a]	
Before EECP	52 ± 8.7
After EECP	52 ± 8.7
Fractional shortening[b]	
Before EECP	25 ± 1.9
After EECP	26 ± 1.9
E wave[c]	
Before EECP	0.7 ± 0.2
After EECP	0.6 ± 0.2
A wave[d]	
Before EECP	0.7 ± 0.2
After EECP	0.7 ± 0.2
E/A ratio[e]	
Before EECP	1.2 ± 0.2
After EECP	1.0 ± 0.1

Before versus after EECP: [a]$P = 0.41$; [b]$P = 0.49$; [c]$P = 0.2$; [d]$P = 0.8$; [e]$P = 0.3$.

although a trend has been observed (WMS: $P = 0.087$; WMSI: $P = 0.08$).

Systolic (ejection fraction: $P = 0.41$; fractional shortening: $P = 0.49$) and diastolic function (E/A ratio: $P = 0.3$; Doppler index: $P = 0.23$), as well as left ventricular dimensions (end-diastolic diameter: $P = 0.55$; end-systolic diameter: $P = 0.68$; end-diastolic volume: $P = 0.24$; end-systolic volume: $P = 0.70$) did not show any significant changes (Table 5). Diabetic patients and patients who previously received surgical or interventional revascularization did not obtain more benefits.

Discussion

Consistent with the literature [4–7], our study demonstrated that patients who received EECP treatment showed an improvement in angina symptoms, with a reduction of at least one angina functional class that lasted for at least 6 months during follow-up. Patients reduced their nitrate consumption and subjectively felt an improvement in their quality of life. Treatment did not induce any relevant side effects and could be repeated several times.

Several hypotheses have been formulated to explain the mechanisms of such benefits: for example, an increased transmyocardial pressure gradient may open pre-existing collaterals or induce the development of new ones [1,8,9]. Chronic exposition of coronary and peripheral circulation to an increased shear stress may improve endothelial function, enhance the release of nitric oxide, prostacyclin, endothelial growth factor, and angiogenetic factors, and decrease endothelin and B-type natriuretic peptide levels, and these phenomena may further induce angiogenesis [1,9,10]. Benefits may also be related to treatment-induced peripheral conditioning and vascular tone improvement [1,9,11], as demonstrated by the fact that patients experienced an improvement in quality of life and exercise capacity but not a reduction in the ischaemic threshold induced by physical or pharmacological stress.

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To test the hypothesis of a placebo effect, a study has been performed in which patients were randomized to receive active or passive EECP. Both groups showed an improvement in angina symptoms, but only the subgroup who received active EECP had a prolongation of the time to exercise-induced ST-segment depression at stress test and an improvement in quality of life at 6 and 12 months [12].

No greater benefits were observed in diabetic patients or in those who previously received coronary artery bypass surgery or angioplasty; however, the number of these patients was too small to make a correct statistical analysis.

According to some studies, patients who benefited the most were the youngest ones, and those with the worst results were those with the most severe coronary artery disease [13,14]. Some evidence suggests that the greatest clinical benefits are obtainable in patients with improved diastolic function after treatment [15]. Data analysis showed a trend towards a reduction in the areas of inducible ischaemia at DSE; in fact, nine patients showed an improvement, although not statistically significant.

The discrepancy between our study and nuclear investigations [11,16] may be explained by a higher sensitivity of myocardial scintigraphy with respect to DSE; moreover, EECP may exert its benefits by inducing an improvement of endothelial function and microcirculation not detectable by stress echocardiography. Accordingly, several angiographic studies have failed to prove the development of collateral circulation after EECP treatment, whereas stress test and nuclear studies have demonstrated a reduction in exercise-induced areas of ischaemia [11]. The development of microcirculation and the improvement of endothelial function, which cannot be detected by DSE, are probably the means by which EECP induces its beneficial effects, and studies on myocardial perfusion should be carried out to test this hypothesis. A pioneering study of Masuda *et al.* [10] has already demonstrated by positron emission tomography an improvement of myocardial perfusion and of coronary reserve, and a reduction in B-type natriuretic peptide levels after EECP. Another possible explanation is that statistical analysis did not reach statistical significance because of the small sample size.

Patients who benefited the most from EECP treatment were those with the most severe segmental kinesis abnormalities. Systolic function (ejection fraction and fractional shortening), left ventricular dimensions (diameters and volumes) and diastolic function (E/A ratio) were unchanged at the end of treatment.

No patients stopped treatment because of serious side effects, such as myocardial infarction, congestive heart failure or death; only one patient underwent coronary artery bypass surgery after the end of EECP treatment. The most relevant side effect was skin lesions of the lower limbs in one patient who did not have to discontinue the treatment, after wrapping legs with a protective bandage.

A limit of the present study is the small sample size; moreover, only one woman was enrolled and, for this reason, it was not possible to match results for sex. Stress echocardiography with adenosine to study endothelial function and contrast echocardiography to assess myocardial perfusion may be useful to better understand EECP mechanisms of action. In addition, larger case–control studies aiming at evaluating whether the treatment may change prognosis in the studied population and aiming at better investigating its effects are advisable.

In conclusion, EECP is a noninvasive, well-tolerated, effective treatment for refractory angina pectoris. It reduces angina symptoms, improves angina functional class and exercise tolerance at the cycloergometer stress test and individual perception of quality of life, and decreases nitroglycerin intake. Several studies have also demonstrated an improvement of myocardial perfusion and a reduction in left ventricular end-diastolic pressure. Our study observed a trend towards a reduction in the area of inducible ischaemia at DSE, although not statistically significant. These results may be due to the small sample size; the apparent discrepancy with nuclear studies [14,16] may be explained by the fact that EECP plays its role by improving endothelial function and microcirculation, and DSE, which mainly studies epicardial coronary circulation, cannot detect these actions.

The treatment has a very low morbidity rate, mostly due to lesions of lower limb skin or muscle trauma [13]. Unfortunately, this technique is time-consuming and the equipment expensive (about €150 000); however, owing to the important and persistent beneficial effects, we believe that it can be advised for routine clinical management as a very useful treatment in patients with refractory angina pectoris. The application of EECP in patients with congestive heart failure seems to be very interesting [17,18].

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