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Is There Any Positive Remodeling after Enhanced External Counter Pulsation in Patients With Severe Refractory Angina?

Majid Kiavar, MD [1]; Naser Aslanabadi, MD [2,*]; Azin Alizadehasl, MD [3]; Ahmad Ahmadzadeh Pournaky, MD [4]; Arash Hashemi, MD [5]; Rezvanieh Salehi, MD [2]; Mitra Chitsazan, MD [1]; Sormeh Nourbakhsh, MD [6]; Morteza Abdar Esfahani, MD [7]

[1]Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[2]Madani Cardiovascular, Medical and Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran
[3]Rajaie Cardiovascular, Medical and Research Center, Echocardiography Lab, Iran University of Medical Sciences, Tehran, IR Iran
[4]Cardiology Department, Urmia University of Medical Sciences, Urmia, IR Iran
[5]Cardiology Department, Erfan General Hospital, Tehran, IR Iran
[6]Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[7]Cardiology Department, Isfahan University of Medical Sciences, Isfahan, IR Iran

*Corresponding author: Naser Aslanabadi, Madani Cardiovascular, Medical and Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran. Tel: +98-4113363880, Fax: +98-4113363880, E-mail: alizadeasl@gmail.com

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Background: Patients with severe refractory cardiac angina who are not candidates for any form of invasive treatment and are already on optimal medical therapy have few therapeutic options. Enhanced external counter pulsation (EECP) offers an alternative palliative and possibly therapeutic option for these patients. EECP achieves this by inducing hemodynamic effects much similar to those of the intra-aortic balloon pump.

Objectives: We sought to further evaluate these therapeutic effects, especially on the basis of echocardiographic data.

Patients and Methods: Thirty-two patients who had severe refractory angina despite full anti-ischemic medication and were poor candidates for invasive procedures were evaluated. After undergoing 35 sessions of EECP, the patients were followed up for 6 months for adverse events, change in quality of life, severity of the remaining symptoms according to the Canadian Cardiovascular Society (CCS) classification, and echocardiographic changes.

Results: After receiving standard EECP treatment regimen, the patients showed a marked increase in quality of life scores; a significant decrease in left ventricular (LV) end-diastolic volume index after 6 months (P = 0.045), in tandem with an increase in the LV myocardial performance index (P = 0.04) with no significant change in the LV ejection fraction; and a significant decrease in the CCS scores (P = 0.01). In addition, physical performance measures, including time to unset of angina during the exercise test, were significantly increased.

Conclusions: EECP is a useful and low-risk additive therapeutic option in patients with end-stage and non-responsive angina symptoms who are receiving optimal medical conventional treatments and are not good candidates for invasive procedures. This treatment can induce some positive remodeling in the LV.

Keywords: Enhanced external counter pulsation (EECP); Positive Remodeling; Severe Refractory Angina; Myocardial Performance Index (MPI); Echocardiography

1. Background

Angina pectoris is mainly due to a mismatch between supply and demand and is an indicator of the shortage of oxygen delivery to the heart. Therapeutic options, whether invasive or noninvasive, often work in this equation by increasing the supply and/or reducing the demand as well as improving the efficacy of the delivery system. There are numerous measurement systems for the evaluation of the severity of angina, the first and foremost among which is the Canadian Cardiovascular Society (CCS) classification (1, 2). Conventional options for patients are optimal medical therapy, invasive procedures aiming to achieve some degree of revascularization, and cardiac rehabilitation exercises. There are some unconventional methods, including enhanced external counter-pulsation (EECP) and transmyocardial laser therapy (TMLR), which are used as an additive therapy and as a last resort for patients refractory to more conventional methods (3, 4). EECP is a noninvasive device that consists of three sets of cuffs and a monitoring device. It works through continuous inflation and deflation of these cuffs, inducing pressure in the lower extremity ar-

teries, such that they are compressed from distal to proximal in diastole (2). Another proposed mechanism of action for EECP is that the milking action of the lower-limb cuffs creates a suctioning effect on the blood in deflation point and thus increases the flow to the heart from the limbs. Some studies have suggested a placebo effect in some patients (5-8).

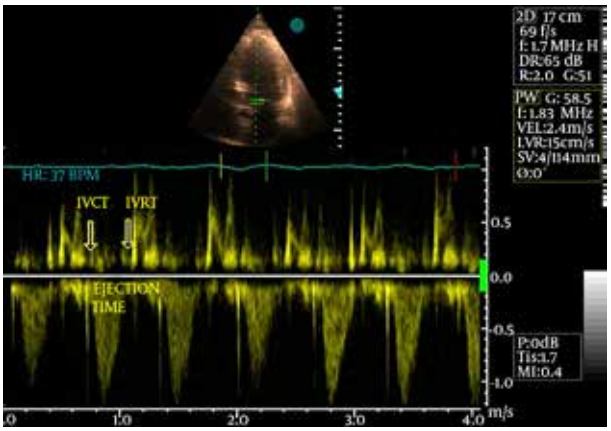
2. Objectives

We aimed to evaluate the effects of EECP, especially echocardiographic changes, in patients with severe refractory angina as an additive to conventional therapeutic options.

3. Patients and Methods

We evaluated 32 consecutive adult patients with severe refractory angina referred for EECP treatment. Inclusion criteria comprised: 1) desire to enter the study; 2) complaint of a severe refractory angina non-responsive to optimal medical therapy with no invasive treatment options; 3) coronary artery disease unsuitable for percutaneous coronary intervention (PCI) and/or coronary artery bypass graft surgery (CABG); and 4) continued ischemic symptoms post-PCI or CABG despite optimal medical therapy and unsuitability for another revascularization attempt. Exclusion criteria included: 1) refusal to participate in the study or to undergo EECP treatment; 2) conditions such as arrhythmias, specific valvular diseases (e.g. severe aortic insufficiency or stenosis and severe mitral stenosis), and aortic aneurysm precluding EECP treatment; 3) bleeding tendencies; and 4) pregnancy. After the selection of the study population, the patients' scores were measured based on the CCS score classification. All the patients were evaluated using a quality of life scoring system (SF36), were subjected to echocardiographic evaluation, and had their current medication checked. Also, myocardial perfusion scan was performed for the whole study population. Each patient received a total of 35 one-hour EECP sessions, upon the completion of which and subsequently 6 months afterward, reevaluation was performed. Full echocardiographic evaluation was conducted via standard methods in all the patients and was interpreted by the same cardiologist. Two-dimensional conventional, pulse, and transthoracic echocardiographic study was performed using a commercial GE Vivid 7 System (Horten, Norway), equipped with an M3S multi-frequency harmonic phased-array transducer. Images were acquired from the subjects at rest, lying in the left lateral supine position at the end of expiration. Two-dimensional electrocardiogram (ECG) was superimposed on the images, and end-diastole was considered at the peak R-wave of the ECG. Left ventricular (LV) global systolic function was evaluated using a modified biplane Simpson method for calculating the LV ejection fraction (LVEF) by measuring end-diastolic and end-systolic volumes in the two-dimensional images. Additionally, the myocardial performance index (MPI) of the LV was investigated by two-dimensional Doppler study (Figure 1). Data analysis was done using SPSS statistical package (version 15.0). The paired samples t-test and the chi-squared test were employed to compare the continuous and categorical variables, respectively. A P value ≤ 0.05 was considered statistically significant.

Figure 1. Time Intervals for Measuring Myocardial Performance Index (MPI) in Doppler Study



IVCT, Isovolumetric contraction time; IVRT, Isovolumetric relaxation time

4. Results

The quality of life questionnaire (SF36) score at the beginning of the treatment was 40.22 ± 9.55. The score improved (45.85 ± 11.00) after the 35 EECP sessions (P = 0.033); however, the improvement in the score was significant (47.75 ± 12.1) 6 months after the end of the 35 sessions (P = 0.001). Almost all the patients reported improvement in their CCS classification scores following the termination of the 35 sessions and then 6 months afterward (P value = 0.01); nevertheless, there was no statistically significant improvement between the scores at the 6 months' follow-up and at the end of the 35 sessions (P = 0.3). Interestingly, sub-group analysis demonstrated that the number of the patients in the severe ischemic symptoms group (18 patients) was significantly decreased: only 7 patients remained in the severely symptomatic group after treatment. At the initiation of this study, the usage of anti-ischemic medications among the patients was as follows: nitrates 7.85 ± 5.86 mg , beta blockers 45.30 ± 33.29 mg, and calcium channel blocker (CCB) (Amlodipine) 12.5 ± 7.5 mg. After the completion of the 35 sessions, these dosages decreased to 7.71 ± 7.54 mg for nitrates, 47.23 ± 36.25 mg for beta blockers, and 12.5 ± 7.5 mg for the CCB, which was not significant in any drug group (P = 0.35, 0.61, and 1, respectively). This was also the case for angiotensin-converting enzyme (ACE) inhibitors, which showed a drop in their daily dosages from 28.25 ± 2.3 mg to 25 ± 1.5 mg (P = 0.3). Time to onset of ischemic symptoms in the exercise test at the end of the 35 sessions was improved from 336.67 ± 124.17 seconds to 397.22 ± 123.21 seconds (P = 0.039), but there was no improvement between this time and that at the 6 months' follow-up. Metabolic equivalents

Table 1. Summary of Findings Last Column Refers to Improvement between the Findings at the End of 35 Sessions and at 6 Months' Follow-up (n = 32) [a]

Index	After 35 Sessions	P Value	After 6 Months	P Value	Continued Improvement
QOL score	Improved	0.033	Improved	0.001	Yes
CCS scores	Improved	0.01	Improved	0.01	No
Nitrates	No sig. change	0.35	No sig. change	0.34	No
BB	No sig. change	0.61	No sig. change	0.7	No
CCB	No sig. change	1	No sig. change	0.8	No
ACE Inhibitors	No sig. change	0.30	No sig. change	0.26	No
Time to Ischemia	Improved	0.039	Improved	0.001	No
EF	No sig. change	0.501	No sig. change	0.237	No
WMSI	No sig. change	0.65	No sig. change	0.74	No
METs Achieved	Improved	0.049	Improved	0.001	Yes
LV MPI	No sig. change	0.09	Improved	0.048	Yes
LVEDVI	No sig. change	0.14	Improved	0.045	Yes

[a] Abbreviations: CCS, canadian cardiovascular society; QOL, quality of life; BB, beta blockers; CCB, calcium channel blockers; ACE, angiotensin-converting enzyme; EF, ejection fraction; WMSI, wall motion scoring score; METs, metabolic equivalents; LV MPI, left ventricular myocardial performance index; LVEDVI, Left ventricular end-diastolic volume index

(METs) achieved by the patients at the beginning was 5.34 ± 2.05, which was increased to 6.39 ± 2.16 after the 35 sessions (P = 0.049). Echocardiographic evaluation showed an increase in the EF from 41.53 ± 10.99 to 43.33 ± 10.25 after the 35 sessions and 44.79 ± 11.47 at the 6 months' follow-up, both of which were non-significant. (P = 0.501 and 0.237, respectively). The wall motion score index (WMSI) exhibited some improvement (1.42 at base, 1.46 after 35 sessions, and 1.45 after 6 months); the difference, however, constituted no statistical significance (P = 0.65 and 0.74, respectively). Interestingly, the left ventricular end-diastolic volume index (LVEDVI), which is a specific indicator for LV remodeling, decreased significantly from 93 ± 21 cc to 83 ± 18 cc at 6 months post treatment (P = 0.045). No change was reported in the LVEDVI after the 35 sessions. Moreover, the results confirmed that the LV MPI had a non-significant decrease after the completion of treatment (P = 0.090) and a significant decrease at the 6 months' follow-up (51.05 ± 5.34 to 42 ± 3.9; P = 0.048).

5. Discussion

EECP has been used as an additive and possibly alternative treatment option for patients with severe refractory angina as well as sometimes in patients with various degrees of heart failure (4). The standard protocol is to treat the patient in a medically supervised environment for 35 one-hour sessions in a period of 7 weeks. The procedure is done by carefully orchestrated series of inflation and deflation in cuffs wrapped around the patient's lower limbs, particularly calves and lower and upper thighs, while the patient is being monitored by ECG and finger plethysmogram. The main physiological effects of EECP are not fully understood, but the proposed mechanisms include increased coronary perfusion, along with a reduction in myocardial oxygen demand, through the milking effect of the cuffs around the lower limbs. Some authors have even suggested an intra-aortic balloon pump-like effect. There are some studies suggesting a possible effect on the thyroid hormone milieu by EECP that may be partly responsible for its effects on ischemic symptoms by influencing the efficacy of cardiac contraction-energy consumption interactions (5, 9-11). In 2003, Health Technology Assessment by the Medical Advisory Secretariat reported that there were insufficient data and evidence to support EECP usage in patients with CCS class 3 and 4 and patients with heart failure (5). Some studies have reported astonishing results in the form of enhanced quality of life and reduced severity of angina symptoms as reported by the patients, which were maintained for as long as 2 years after the end of treatment sessions (4, 7). In one study in 2008, the authors concluded that EECP improved quality of life almost immediately after a course of treatment; and in the majority of the patients, the beneficial effects were sustained for 3 years (6, 7, 9, 10). In a systemic review in 2009, the authors reported a significant improvement in exercise-induced ischemia in the EECP group in comparison to the control group, but there was no statistically significant change in exercise duration, self-reported angina episodes, or daily nitroglycerin use from baseline until the end of treatment and also the clinical significance of the limited benefits was unclear (7). Furthermore, they concluded that the results of a single randomized controlled trial (MUST-EECP) could not provide solid and firm evidence of the clinical effectiveness of EECP in the treatment of refractory chronic stable angina (7, 12). Our results demonstrated that EECP could confer improvement in quality of life and decrease in the CCS classification scores but no statistically significant reduction in anti-ischemic medications. Other important findings in the present study included increase in time to initiation of ischemia in the exercise test, improvement in METs achieved by the patients, decrease in the LV global MPI (as a valid factor of the LV function), and reduction in the LVEDVI. There were no statistically significant improvements in the WMSI and LVEF (13, 14). It is possible that some of these findings are related to placebo effects; nonetheless, some parameters such as the LV MPI and LVEDVI can confirm the benefit of

EECP. In addition, it is worthy of note that these patients are refractory to conventional treatments and any treatment with any effect that helps relieve their symptoms should be considered (14, 15). Our study showed that EECP is a successful, relatively low-risk additive and alternative treatment to optimal medical therapy. It can be useful and should be considered in patients with refractory significant angina pectoris-related symptoms who are receiving optimal medical therapy and are not good candidates for invasive procedures such as CABG or PCI (Table 1).

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