Enhanced External Counterpulsation (EECP) in Refractory Angina Pectoris; Six Months Follow-Up

ABDELMAKSOUD A. EL GANADY, M.D.1; DINA Y. NASSAR, M.D.2; AHMAD M. IBRAHIM, M.D.3; MOHAMED H. ALLAM, M.D.4; AHMAD A. EMAM, M.D.5; GAMAL A. EL-ATTAR, M.D.6 and SALAMA H. OMAR, M.D.7

The Departments of Cardiology1-6 and Critical Care Medicine7, Faculties of Medicine, Al-Azhar1,2, Cairo7 and Suez-Canal6 Universities and National Heart Institute4,5

Abstract

Introduction: Enhanced External Counterpulsation (EECP) is a new non-invasive procedure that is used as a therapeutic option for ischemic patients who are not eligible for other therapeutic options.

Objectives: The aim of the present study was to evaluate the immediate and 6 months response to EECP sessions in patients with chronic refractory angina where no other options for surgical or percutaneous revascularization procedures are left.

Methods: 48 patients (15 Females, 33 Males) were treated by EECP. All patients were subjected to 35 sessions over 7 weeks (5days/week). Each session lasted for one hour. We looked at Canadian cardiac society class (CCS) nitroglycerine use per week and echocardiographic analysis (EF and SWMA) and adverse events where evaluated prior to EECP, at the end of study and six month later. And the results were compared.

Results: 73% of the patients responded by improving one CCS class and 10% by more than 2 CCS class. 83% of those patients showed sustained improvement over 6 months. The mean nitroglycerin weekly consumption significantly decreased from 8.25 tablets/week to 3.12 tablets/week immediately and continued decreasing even after 6 months. $p$-value=0.003. Segmental wall motion abnormality significantly improved. In 40% of the patients there was an improvement of 3 or more segments in the immediate phase, this improvement was maintained at the end of 6 months at 90% of the cases. The mean EF improved from 35.8% to 39.3% in the immediate phase and 38% at 6 months. The therapy was discontinued in two patients.

Conclusion: EECP is a non invasive procedure that can reduce the symptoms of Ischemic heart disease like Angina and heart failure. It improves both (CCS) and New York Heart Association (NYHA) classifications, decreases in weekly angina episodes and nitroglycerin use. It improves SWMA, EF and Pro-BNP as a marker of LV dysfunction was significantly decreased. The study confirms the safety and efficacy of EECP in patients with refractory angina when other options are not available.

Key Words: Enhanced External Counterpulsation (EECP) — Refractory angina pectoris.

Introduction

ENORMOUS advances have achieved in the last years in the management of coronary artery disease (CAD), including medical, interventional (PTCA/stent) and surgical (CABG) techniques. However, despite these developments, more than 10% of patients with CAD may not be good candidates for revascularization techniques, as there is a limit to how many repeat revascularization attempts can be made in a given patient because of the patient’s coronary anatomy, conduit availability, left ventricular function, age, co-morbidity, such as renal insufficiency, pulmonary disease, left ventricular dysfunction, etc.

Current non pharmacological options available for these patients with RAP with or without underlying HF include neurostimulation (transcutaneous electrical nerve stimulation and spinal cord stimulation), enhanced external counterpulsation (EECP) therapy, laser revascularization techniques, gene therapy, etc. EECP therapy represents the only truly noninvasive technique for which both a reduction of angina symptoms, improvement in objective measures of myocardial ischemia, and improvement in left ventricular function (both systolic and diastolic) have been shown [1-3]. In addition it is the only FDA-approved non-pharmacological approach to refractory angina that has been supported by sham-controlled data. It is recommended by the American Heart Association as a potential therapy for refractory angina as a class IIb indication [4].
Enhanced external counterpulsation (EECP) is based on the concept of counterpulsation and consists of 3 pairs of pneumatic cuffs placed around the lower extremities. The deflation of the cuffs at the beginning of systole will decrease the afterload that the heart has to pump against. Because of this, myocardial oxygen demand will decrease during the EECP session. This is a relatively short-term improvement, however, and is limited to the session of EECP.

The inflation of the cuffs during diastole (when the aortic valve is closed) increases blood flow to the myocardium. This is because, unlike the tissues of the rest of the body, the myocardium receives the majority of its blood during diastole. The increased flow during diastole caused by EECP is believed to promote the formation of collateral arteries in the coronary circulation.

Presumably, it is these newly opened collateral arteries that produced the sustained benefit that EECP provides to individuals after the EECP sessions are complete. While EECP has been in use since the 1980s, the mechanism in which it provides a lasting clinical benefit is still poorly understood. One theory is that ECP exposes the coronary circulation to increased shear stress, and that this results in the production of a cascade of growth factors that result in angiogenesis.

Patients and Methods

Patients study conducted at Erfan Hospital Cardiology Centre and Saudi German Hospital, Jeddah, Saudi Arabia. 48 patients (33 males and 15 female) were included in the study between December 2009- and November 2010. Coronary artery disease was documented by prior MI, ECG, Echocardiography, treadmill exercise, CABG & coronary angiography.

Forty Eight patients were not candidate for further revascularization either due to =favourable anatomy for revascularization in 37 pt and/or associated comorbidity were 15 patients had renal impairment, 5 patients had global hypokinesia and poor LV functions.

Patients referred for EECP were using the maximally tolerated anti anginal medications including B-blockers, nitrates, calcium antagonist for at least two months before starting EECP.

Supervisors are advised to instruct patients about the importance of keeping a daily "diary" of their angina symptomology. Each patient should be instructed to record each anginal attack, its time of occurrence, duration, severity, its relationship to precipitating factors, and the average number of nitroglycerin tablets used to ease the attack per week. All data were measured and compared before treatment, immediately after EECP course and 6 months later.

Angina severity was assessed using the Canadian Cardiovascular Society classification system.

Physical examination:

It is recommended that at each visit and before treatment begins; the patient's resting blood pressure, pulse and respiratory rates, should be taken and recorded. The patient's legs should be examined for areas of redness, ecchymosis, and/or signs of other vascular problems. Heart auscultation and chest examination should be done before, during and after each sessions.

Echocardiographic data: Including EF% and regional wall motion abnormalities were assessed before and after 6 months of treatment to visualize and score the 17 segments according to its contraction using all available tomographic pictures parasternal long and short axis and long axis and give a score of 1 in normal, 2 in hypokinetic, 3 in a kinetic, 4 to dyskinetic and 5 to aneurysm. The number of segments that showed changes in score were recorded and compared.

All patients were instructed to continue all their medications:

Exclusion criteria included:

- Unstable angina.
- Acute MI <3 month.
- Significant valvular heart disease or any degree of aortic regurgitation.
- Significant unprotected left main disease.
- Atrial fibrillation and arrhythmia that interfere with EECP triggering.
- Overt fibrillation and arrhythmia that interfere with EECP triggering.
- Systemic hypertension >180/100 despite treatment.
- Haemorrhagic diathesis, (including INR >2.0).
- Active deep venous thrombosis.
- Severe peripheral vascular diseases, use of anti-coagulant pregnancy and
- Abdominal aortic aneurysm.

All patients signed written consent form before study:

Study protocol used for EECP treatment:

We used the EECP device provided by Vaso-medical Model TS4. Fig. (1).
The EECP device consists of three paired pneumatic cuffs applied to the lower extremities (Vasomedical, Westbury, NY, USA). Patients are typically treated for a 1-h daily program for a total of 35 sessions over 7 weeks. Three sets of pneumatic cuffs, wrapped around the patient’s calves, lower thighs, and upper thighs (Fig. 2).

The cuffs are inflated sequentially at the onset of diastole and released at the onset of systole, producing a decrease in systolic pressure. A computer-controlled pneumatic system with a display console is used to inflate and deflate the series of compressive cuffs, and inflation and deflation are triggered by events in the cardiac cycle through microprocessor-interpreted electrocardiography signals. The compression is triggered by the electrocardiographic R-wave, with the delay being adjusted until the induced retrograde pulse wave enhances the cardiac output as reflected by an optimally augmented blood pressure and blood flow wave during cardiac diastole.

The protocol we adopted in our study dictated that diastolic Pressure should be titrated as needed to achieve the most optimal diastolic augmentation pressure inflation starting from 70mmHg and increasing gradually by 10mmHg every 15min to achieve a peak diastolic pressure to peak systolic pressure ratio D/S ratio started 0.7/1 and increased to become between 1.3/1 and 1.5/1 at the end of 1st 3 sessions. If patient status remained stable and hemodynamics allow, the pressure was gradually increased in the following sessions to reach to the maximum D/S ratio of 2/1 at the end of the in the last 2 sessions considering that the maximum pressure applied to the cuff not exceeding 300mmHg.

A finger plethysmogram was utilized throughout treatment to monitor diastolic and systolic pressure wave forms (Fig. 3).

Pulse oximetry was monitored continuously during treatment sessions and the patient’s clinical status reevaluated if oximetry dropped by >4%.

EECP should be withheld and postponed if blood pressure increased above 180/110, or decreased below 80/50mmHg and if patient developed pulmonary congestion, lower limb edema and if 02 saturation dropped more than 5%. Therapy also was stopped if anginal pains increased.

Canadian Cardiovascular Society (CCS) Classifications were assessed and graded each visit and recorded in patient’s file.

Results

The baseline and follow-up data of our patients before and after EECP were analyzed. Events occurring up to 6 months from the start of EECP therapy have been also analyzed.
Statistical methods:

Events have been analyzed using the paired sample t-test which compares the means of two variables.

Results are presented as percentages or means / (± SD). Ap-value of <.05 was considered statistically significant for comparison of groups.

All our 48 patients were analyzed (13 Females & 35 Males) Mean age 61.39 years (Table 1).

Table (1): Patient population.

<table>
<thead>
<tr>
<th>Gender</th>
<th># of Pt</th>
<th>Total % of patient breakdown by gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33</td>
<td>68.75</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>31.25</td>
</tr>
<tr>
<td>Total # of Study Cases</td>
<td>48</td>
<td>100</td>
</tr>
</tbody>
</table>

38 of our patients had a history of hypertension, 31 patients had hyperlipidemia, 21 were smokers and 25 had diabetes mellitus (Fig. 4 & Table 2).

Thirty nine pts has multi vessel disease. 35 pt had previous myocardial infarction Fig. (5).

Twenty six patients were subjected to CABG, 35pts had previous PCI and 19 had both revascularization procedure (Fig. 6 & Table 3).

Forty eight patients were treated and completed a course of EECP treatment. 60.5% of patients (29 pt) were in Canadian CLASS II and (19 pts) 39.5% were in CCS III prior to EECP Table (5). Immediately post-EECP, angina improved by at least one CCS class in 73% and by two classes in 10%. At 6 month follow-up, sustained improvement in CCS was observed in 83% of the patients. At the end of the study 25 patient were in class one (Fig. 7 & Table 4).
There was a statistically significant reduction in angina class (p<.001) from pre- to post-EECP. The most frequent angina class was reduced from II to I after EECP and improvement was maintained at 6 months after completion of treatment. Episodes of angina and on-demand sublingual nitroglycerin use were also reduced during the follow-up period.

### Table (4): Canadian class before, immediately after & six months after EECP.

<table>
<thead>
<tr>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Functional Canadian Class</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>After</td>
<td>25</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Fig. (7): Canadian class before, immediately after & six months after EECP.

The MEAN weekly nitroglycerin use were significantly reduced immediately after EECP from 8.25 to 3.13 tablets/week after and 3.75 tablets after 6 month follow-up p<0.0001; data (Fig. 8 & Table 5).

### Table (5): The average weekly use of nitroglycerine, before, immediately after & six months after EECP.

<table>
<thead>
<tr>
<th>Nitroglycerine/Week</th>
<th>Total</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Nitroglycerine/Week</td>
<td>8.25</td>
<td></td>
</tr>
<tr>
<td>After Nitroglycerine/Week</td>
<td>3.13</td>
<td></td>
</tr>
<tr>
<td>After 6 Months Nitroglycerine/Week</td>
<td>3.75</td>
<td></td>
</tr>
</tbody>
</table>

The mean values of the echocardiographic data of ejection fraction and segmental wall motion abnormalities pre- and 6 months post-EECP treatment are presented.

The mean EF improved from 35.8% to 42.3% after 6 months treatment. 16.7% had normal LV systolic functions before EECP Table (6).

56.3% showed average 6.23% improvement in EF while 43.7% did not show significant difference in.

### Table (6): Ejection fraction before & immediately after EECP.

<table>
<thead>
<tr>
<th>EF % Before</th>
<th>EF % After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.83%</td>
<td>42.3%</td>
</tr>
</tbody>
</table>

Wall motion were improved in more than 2 segments in 31% of patient and in 1-2 segments in 44% while 25% had no significant changes including those with global hypokinesia (Table 7 & Fig. 9).

### Table (7): Segmental change in regional wall motion by ECHO.

<table>
<thead>
<tr>
<th>Segmental wall motion abnormality</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global all the time</td>
<td>7</td>
</tr>
<tr>
<td>No change</td>
<td>5</td>
</tr>
<tr>
<td>2 segments</td>
<td>20</td>
</tr>
<tr>
<td>More than 2</td>
<td>16</td>
</tr>
</tbody>
</table>

Adverse events: Related to treatment were low. One 65 Y old patient developed pulmonary congestion during the 3rd session, we stopped EECF for 2 weeks and increased the doses of diuretics.
and ACE and restarted at a lower pressure and gradually increased it over the next sessions.

One patient had skin redness. We stopped one week, and patient advised to wear cotton pants and to use antihistaminics.

**Discussion**

Enhanced external counterpulsation (EEEP) is a noninvasive outpatient procedure intended to reduce the symptoms of myocardial ischemia in patients who have angina, but are not candidates for surgical or interventional procedures.

EEEP therapy is a valuable outpatient procedure providing acute and long-term relief of anginal symptoms and improved quality of life among a group of patients with symptomatic ischemic heart disease with or without congestive HF.

EEEP role in improving endothelial function might be beneficial in the treatment of patients with Cardiac Syndrome X, which is marked by severe chest pain caused by myocardial dysfunction, often without detectable atherosclerosis. Mayo Clinic investigators have reported successful treatment of Cardiac Syndrome X with severely symptomatic coronary endothelial dysfunction in the absence of obstructive CAD with standard 35-h course of EEEP therapy [6].

Throughout the world, EEEP therapy has been also studied for various potential uses other than heart disease (Table 8) [7-12].

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Year/Country</th>
<th>Number of Pts</th>
<th>Treatment Duration (h)</th>
<th>Potential uses of EEEP therapy in conditions other than RAP and HF</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werner et al.</td>
<td>2005/Gennany</td>
<td>19</td>
<td>2</td>
<td>Hepatorenal syndrome Safety: EEEP therapy was tolerated by healthy and cirrhotic patients alike</td>
<td>Potential role of EEEP therapy in diuresis and increased urinary flow in patients with end-stage liver disease who are awaiting transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Efficacy: EEEP therapy increased MAP and increased urinary production (urinary flow rate) in patients with end-stage cirrhosis and hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Restless leg syndrome Relief of symptoms and change in the IRLS score from 28.8 to 6.0 after EEEP therapy</td>
<td></td>
</tr>
<tr>
<td>Rajaram et al.</td>
<td>2005/U. S.</td>
<td>6</td>
<td>35</td>
<td>Benefit sustained for 6 months; IRLS score was 3.3 at the end of 6 months</td>
<td>It was a small, uncontrolled case series</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potential role of EEEP therapy in improving vascular flow in mild nonulcerative peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>Hilz et al.</td>
<td>2004/Gennany</td>
<td>38</td>
<td>1</td>
<td>Peripheral vasodilation and skin effects similar to those during exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improvement in postural instability and ataxia in EEEP treatment group as compared with control</td>
<td>EEEP therapy had no significant effect on the physiological parameters considered to be the best for predicting performance in endurance-type sportsmen: VO2, lactate levels, work tolerance time</td>
</tr>
<tr>
<td>Nike Sports Research Lab</td>
<td>2004/U. S.</td>
<td>19 vigorously active men in training</td>
<td>35</td>
<td>Increase in the penile artery flow by 200%, and 11 of 13 reported improved erectile function</td>
<td>Case series looking at EEEP therapy and erectile dysfunction</td>
</tr>
<tr>
<td>Froschmeraier et al.</td>
<td>1998/Gennany</td>
<td>13</td>
<td>35</td>
<td>Treatment of sudden deafness and tinnitus (vascular in origin)</td>
<td>Hearing threshold increased in 28%, on average by 19 dB</td>
</tr>
<tr>
<td>Offergeld et al.</td>
<td>1998/Gennany</td>
<td>30</td>
<td>5-10</td>
<td>Tinnitus decreased in 47% of the patients by an average of 16 dB</td>
<td>Improvement persisted at 1-year follow-up</td>
</tr>
</tbody>
</table>

However, it is important to realize that EEEP therapy is an option for patients with refractory angina pectoris (RAP) to medical treatment who are not candidates for interventional or surgical revascularization. The American Heart Association recommends it as a Class IIb, Level of Evidence: B) and transmyocardial laser revascularization (Class IIa, Level of Evidence: A) [4].

The European Society of Cardiology views EEEP therapy as an interesting modality available for treatment of RAP with more clinical trials needed to define its role in treating RAP [13].
Most of the studies on EECP therapy cannot be double-blind and lack good control groups because of technical limitations, which have frequently raised questions of operator bias in the past. But the MUST-EECP study, a randomized, double-blind, sham-controlled trial, also showed the clinical benefit of EECP therapy in patients with chronic stable angina and positive exercise stress tests [141]. In this study, 139 patients (mean age 63 years, range 35 years to 81 years) with angina pectoris (typical Canadian Cardiovascular Society classes I, II, and III angina) and documented coronary ischemia were equally randomized to hemodynamically inactive counterpulsation with EECP versus active counterpulsation. Patients in the active EECP therapy group showed a statistically significant increase in time to exercise-induced ST-segment depression when compared with sham and baseline, and reported a statistically significant decrease in the frequency of angina episodes when compared with sham and baseline. Exercise duration increased significantly in both groups; however, the increase was greater in the active EECP group. Moreover, a MUST-EECP substudy showed a significant improvement in quality-of-life parameters in patients assigned to active treatment, which was sustained during a 12-month follow-up period [15].

Our study showed significant improvement in angina in more than 80% of the patient and 50% of them remained in class 1 angina and stopped using sublingual nitroglycerine after 6 months of the study. Although this improvement was not equal to improvement in EF and SWMA which might be explained by the increase in exercise tolerance attributed to the 7 weeks of training.

Results from the International EECP Patient Registry [16,17,18] and the EECP Clinical Consortium [19] have shown that the symptomatic benefit observed in controlled studies also translates to the heterogeneous patient population seen in clinical practice. Moreover, follow-up data indicate that the clinical benefit may be maintained for up to 5 years in patients with a favorable initial clinical response [20].

The acute haemodynamic effects have been impressive. Hemodynamically, EECP acts like intra-aortic balloon counterpulsation by augmenting diastolic blood flow in multiple vascular beds, including the coronary arteries, and by reducing cardiac afterload [21] but what is most surprising has been the sustained clinical improvement in anginal symptoms [15].

Reasons for continued relief of angina of 3 years [15] and 5 years [22] in the Stony Brook series and at 1 year in the multicenter U.S. study (MUST-EECP) [9] are unclear. Increased transmyocardial pressure gradients could open collaterals. Chronic exposure of the coronary and peripheral arterial bed to the augmented blood flow and increased shear forces produced by enhanced external counterpulsation could also lead to increased endothelial cell production of nitric oxide and prostacyclin, powerful mediators of vasodilation, as well as vascular endothelial growth factor and other angiogenic factors, or even possibly anti-inflammatory substances.

Endothelial function has been shown to improve after a course of EECP therapy [23]. Wu et al., showed that EECP therapy has a sustained, dose-related effect in stimulating endothelial cell production of the vasodilator nitric oxide (NO) and in decreasing production of the vasoconstrictor endothelin [24]. Qian et al., in another study showed that the NO level increased linearly in proportion to the hours of EECP treatment [25].

Anti-inflammatory effect is another effect that was suggested as one potential benefit there was significant increase in the anti inflammatory markers interleukin-1 B [26].

Casey et al., [27] published randomized controlled study examining the effect of EECP therapy on inflammatory and adhesion molecules in patients with CAD indicated that EECP therapy has an anti-inflammatory effect in patients with angina pectoris. Patients were randomly assigned to receive active EECP or sham treatment. Plasma tumor necrosis factor-a, 152 Angina Pectoris monocyte chemoattractant protein-1, and soluble vascular cell adhesion molecule-1 were measured before and after a full course of 35 1-hour sessions of EECP or sham treatment. Patients in the EECP group demonstrated reductions in tumor necrosis factor-a and monocyte chemoattractant protein-1 after treatment, whereas those in the sham therapy group showed no changes. EECP therapy decreased circulating levels of proinflammatory biomarkers in patients with symptomatic CAD.

In addition, EECP therapy has been associated with the release of growth factors, such as vascular endothelial growth factor (VEGF) that promotes the formation of collaterals in the coronary circulation [28].

Finally, EECP therapy may result in a "training effect" by decreasing peripheral vascular resistance in the same manner as physical exercise [29].
Limitations of our study:

1. Patients were not blinded to therapy; these benefits of EECP therapy may be attributable to a placebo effect,
2. There was no controlled group,
3. Need for longer term follow-up, and
4. Myocardial perfusion was not assessed.

Summary:

We concluded from our study that:

- EECP is a non invasive procedure that can reduce the symptoms of heart failure and improving systolic function significantly in 1/3rd of patients and improving chest pain by more than one class in 2/3rd of cases that sustained up to 6 month patients. SWMA improved in some cases. Significant improvement in Canadian Cardiovascular Society (CCS) classifications decreases in weekly angina episodes and nitroglycerin use.

- Further large controlled studies are needed to elucidate both the mechanism of action and the overall effects of EECP therapy, or a combination of the above mechanisms that may explain the sustained benefit from EECP therapy in the clinical trials.

- Further need to see the effect with patients with non-ischemic etiology.

- Finally EECP is a simple procedure without any serious side effects Improvement in symptoms that helps more than 80% of patients is considered a great achievement in patients having no other alternative way to help them to live without pain when they do their ordinary tasks.

It is important to point out that EECP therapy is not for everyone. This noninvasive outpatient procedure can be somewhat uncomfortable for patients because of the high-pressure sequential compression of the cuffs. It is not recommended for certain types of valvular heart disease (especially aortic insufficiency), or for those with recent cardiac catheterization, an irregular heart rhythm, severe hypertension, significant blockages in the leg arteries, or a history of deep venous thrombosis. For anyone else, however, the procedure seems to be quite safe.

References


