Research article
Efficacy of enhanced external counterpulsation in improving six minutes’ walk test in heart failure patients

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ABSTRACT

Introduction and Aim: Enhanced External Counterpulsation (EECP) is an outpatient treatment to improve myocardial perfusion in chronic stable angina patients. We studied the clinical response of heart failure patients' improvement in the functional class and exercise tolerance with EECP.

Materials and Methods: We prospectively evaluated twenty-six patients, who had completed a course of EECP with pre and post six minutes’ walk test, functional ability assessed by the New York heart association (NYHA) classification, renal parameters, lipid profile, and diastole to systole(d/s) ratio in terms of Peak amplitude (P) and Area (A) under the curve value.

Results: The study group's mean age is of 56 years. The mean left ventricular ejection fraction (LVEF) is 31.44±5.5%. Patients' demography includes 81% were male, 30% with hypertension (HT), 50% with diabetes mellitus (DM), 30% chronic smokers, 61% of them had triple vessel disease (TVD). All the patients improved by a minimum of one NYHA class improvement, Serum urea reduced from 34.37 ± 20.28 to 27.24 ± 18.73 mg/dL (P = 0.002), C-Reactive protein (CRP) reduced from 4.6± 8.0 to 3.76 ± 5.1 mg/dL (P = 0.62). In the measured lipid panel test, only low-density lipoprotein (LDL) reduction from 94.41 ± 38.66 to 80.51 ± 35.09 mg/dL was statistically significant (P = 0.03). The six-minute walk test, post-EECP, improved significantly from 340.14 ± 68.5 to 385.5 ± 73.9 meters (P=0.0004). The LVEF increased from 31.44 ± 5.5 to 38 ± 8.69 % (P=0.001).

Conclusion: EECP treatment significantly improves shortness of breath, six minutes walking distance, and ejection fraction in heart failure patients. The treatment significantly reduces serum urea and LDL level. These positive changes may be due to a sudden increase in cardiac output and hyperdynamic circulation during the treatment.

Keywords: Enhanced external counterpulsation; heart failure; six minutes’ walk test; diastolic augmentation; C-reactive protein.

INTRODUCTION

Heart Failure is an end-stage heart disease that causes a considerable economic burden and is clinically challenging to treat. The prevalence of heart failure across the globe is 64.34 million. It is estimated to cause expenditure of 346.17 billion USD (1). In addition, heart failure is emerging as a leading cause of hospital admission in patients age over 65 yrs. In India, with advancing age group, it is estimated that HF prevalence range from 1.3 to 4.6 million and has an incidence of 491,600 to 1.8 million per annum (2). We set to evaluate emerging new treatment strategies to improve the patient's quality of life. Recently Enhanced External Counterpulsation (EECP) has shown promising results in chronic stable angina patients and patients with compromised LV dysfunction (3-5). Therefore, we designed a study to assess the efficacy of EEC in this group of high-risk Heart failure patients with reduced ejection fraction (HFrEF). EEC, based on its hemodynamic effect, can improve myocardial contractility by enhancing coronary perfusion, improving renal blood flow (6), enhancing renal function, increasing systolic blood pressure (7), resolving hypotension, and overall enhancing the quality of life. These effects can play a crucial role in the treatment of refractory heart failure patients.

MATERIALS AND METHODS

A total of 26 patients who underwent EECP in Chettinad Hospital and research center were recruited for the study. The study protocol was cleared by the Chettinad Academy of Research and Education Institutional Human Ethics Committee. For all the patients who were recruited for the study, signed informed consent was taken. The eligibility criterion for inclusion of patients in this study was heart failure with reduced ejection fraction (HFrEF). The left ventricle ejection fraction measured by ECHO should be 40% and less. The patients should be classified with New York Heart Association class II-IV. Patients were excluded if they have fluid overload with signs
Before starting EECP treatment, all the patients provide twelve hours of fasting blood investigation for a complete lipid profile, C-reactive protein (CRP), serum urea, and creatine. In addition, patients were subjected to six minutes walk (6MWT) test and echocardiography to assess their functional ability to exercise and myocardial contractility. In both these tests, the physicians who performed were blinded to whether it was pre or post to eliminate observer error. All these patients went through their entire course of 35 hours (1 hour daily) of EECP treatment.

**Six-minutes’ walk test (6MWT)**

The study cohort patients have poor exercise capability directly linked to their current heart failure status. The Gold standard technique to assess the functional exercise capacity is cardiopulmonary exercise testing (CPET). However, due to its cost and need for a separate lab facility with trained professionals, we choose to do the simple six-minute walk test. This test is an effective alternative, simple to perform, and even acceptable for patients with severe compromise in exercise ability (8-10). Studies have shown that in patients with reduced ejection fraction six-minutes' walk test can serve as a predictor of poor outcome (11).

Enhanced External Counterpulsation Therapy (EECP)

Enhanced External Counter Pulsation therapy system operation consists of three easily inflatable cuffs similar to the blood pressure cuffs tightly wrapped around the calves’ muscles, the lower and upper thighs muscles. The patient is connected to a 3-lead ECG cable and finger plethysmography. These are connected to the touch screen control console, which continuously monitors the ECG and arterial pressure waveform. The cuffs are rapidly and sequentially inflated with microsecond precision based on the ECG trigger mechanism, starting from the lower calves, and progressing upward to the upper thighs during the diastolic phase of each cardiac cycle.

The pressure in the cuffs reaching around 260-300mmHg creates a firm arterial compression stimulating a retrograde flow towards the heart during the closure of the aortic valves, thereby significantly increasing blood flow to the coronary arteries. The inflation of the cuffs also facilitates the reverse venous blood flow to the right side of the heart. This provides a greater ventricular filling and cardiac output (12,13). During the Presystolic cardiac cycle, when the heart is in early stage of contraction, all three cuffs simultaneously deflate, thereby significantly reducing the hearts workload and the myocardial muscle oxygen demand.

Diastolic augmentation / Peak Value (P) and Area Value (A) analysis

Diastolic augmentation is an increase in diastolic pressure achieved by cuff inflation. The diastolic augmentation can be measured and interpreted through Diastole/ Systole Ratio (D/S ratio). This ratio is obtained non-invasively through finger plethysmography. The D/S ratio is measured in terms of two values, the peak amplitude value or P-value and the area under the curve value or A-value. The two values are automatically generated by the system when the freeze button in the console is pressed. The value can also be calculated manually from the waveform. This waveform with the calculation method is shown in (Fig.2).

![EECP Pressure Cycle Diagram](image-url)
In our study, we divided the 35 sessions of treatment into three phases. The first phase consists of the initial five days, the second phase is the mid-treatment phase of 15-20 days, and the third phase is the final five days of the treatment. The P-value and A value are calculated during all three phases. The D/S ratio derived from these parameters roughly determines the patient's progress during the treatment. Higher diastolic augmentation has shown to predict better patient clinical benefits (14).

Statistical analysis

The primary analyses of cardiac parameters were performed with the intention to treat the study population. All statistical analysis of this study was executed using Statistical Package for The Social Sciences (SPSS 21). The change in all cardiac parameters, including six-minutes’ walk test, lipid profile, left ventricular ejection fraction, and CRP level before and after the EECP treatment, were assessed using parties sample t-test. Statistical significance was set at p<0.05.

RESULTS

<table>
<thead>
<tr>
<th>Table 1: Patients’ baseline characters</th>
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<tbody>
<tr>
<td><strong>Patient Demographics</strong></td>
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<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Mean Age</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Diabetic Mellitus</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Smokers</td>
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<tr>
<td>Myocardial Infarction</td>
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<td>Triple Vessel Disease</td>
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<td>Mean EF</td>
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Between Jan 2019 to Jan 2020, twenty-six consecutive patients with Heart failure with reduced ejection fraction were recruited for the study. All the patients completed the treatment without any adverse events forcing them to discontinue or delay the treatment. The baseline patient's characters are shown in (Table1).

The mean age of the study patients was 56 yrs and predominantly male 81%. In the study cohort, 50% were diabetic, 30% were hypertensive, and 30% were current smokers. All the patients had a history of myocardial infarction. A total of 61% had severe triple vessel disease with sparred Left main coronary artery. 55% of the patients were advised either PTCA or CABG, but the patients were not willing for intervention due to high risk.

Six-minute walk test

All the patients completed pre- and post-EECP six-minute walk tests. Pre EECP walk time of 340.14 ± 68.5 meters increased to 385.5 ± 73.9 after completing the 35 days entire course of EECP treatment. This increase is statistically significant (P =0.0004). It is noted that the patients with baseline walk time less than 300 meters achieved greater improvement in walking distance post EECP.

LV ejection fraction

The baseline mean ejection fraction was 31.44± 5.5%. The lowest ejection fraction in the study group is LVEF 20%. In the total of 18 patients, EECP treatment improved the ejection fraction from 31.44± 5.5% to 38.38 ± 8.69 %, an increase of 7 points is statistically significant (P=0.001). Thus, overall, in eighteen patients, four patients, their LV ejection fraction increased 10 points and above falls under the new category of Heart failure with improved ejection fraction classification.

Lipid parameters

All the patients are on statin therapy, and their dosage was not altered. The total cholesterol level decreased from the baseline of 155.18 ± 51.98 to 141.18 ± 44.24 (P= 0.07), Triglyceride decreased from 137.14 ± 79.83 to 132.91 ± 95.43 (P=NS), HDL level did not show any change from the baseline 39.92 ± 11.57, LDL level decreased from 94.41 ± 38.66 to 80.51 ± 35.09 (P=.03), VLDL decreased from 27.37 ± 15.95 to 22.65 ± 11.13(. P=NS).

Renal and CRP

Serum urea decrease from 34.37 ± 20.28 to 27.24 ± 18.73 (P = 0.002), Serum creatinine decrease from 1.16 ± 0.79 to 1.14 ± 0.76 (P= NS), C-reactive protein (CRP) decrease from 4.6± 8.0 to 3.76 ± 5.1 (P = 0.62).
Peak amplitude value (P) and area under the curve value (A)

The P and A values measured at the start, mid, and towards the end of EECP treatment sessions show a linear increase in both parameters. P-value increase from start to mid 0.81 ± 0.24 to 1.14 ± 0.33 (P=0.0001), and from mid to end 1.14 ± 0.33 to 1.4 ± 0.39, (P =0.0001). A value increase from start to mid 0.98 ± 0.34, to 1.44 ± 0.45 (P=0.0001), and from mid to end 1.44 ± 0.45 to end 1.96 ± 0.77 (P =0.0005). All the results are summarized in the Table/ Fig-4.

DISCUSSION

In this study, we demonstrated that patients with symptomatic heart failure with reduced ejection fraction who completed 35 one-hour EECP treatment sessions improved in functional ability and exercise tolerance. The functional ability measured through the New York heart association (NYHA) classification improved at least one NYHA class improvement in all the patients. Worsen their symptoms better there improvement. Fifty percent of patients have more than 2 NYHA class improvements. The previous PEECH trial has shown similar improvement in NYHA functional class in patients with mild to moderate heart failure with reduced LV ejection fraction.

However, the more objective parameter Peak VO2 did not show improvement (4). In our study, we have studied the six-minutes’ walk test as a more objective measure. In normal healthy adults, the average six-minutes’ walk test ranges from 400 to 700 meters (15). The pre EECP baseline average six-minute walk test is 340.14 ± 68.5 meters, which is increased to 385.5 ± 73.9 after completing the 35 sessions of EECP treatment. This increase of 45 meters is statistically significant (P =0.0004). The baseline mean Left ventricular ejection fraction increased from pre-EECP 31.44 ± 5.5 to 38.38 ± 8.69 % post- EECP, increasing 7 points (P=0.001). In ten patients, the improvement in LVEF is 10 points. Interestingly in four patients, the ten points improvement has made

Fig.3: Results: A- Six Minute Walk test, B-Ejection Fraction, C- CRP (C-Reactive Protein), D-Urea, E-LDL, F-Diastolic Augmentation (P & A Value).
the LVEF greater than 40%. As a result, these patients now come under the new classification of heart failure with improved ejection fraction (HFIEF) (16). This improvement in LVEF is clinically crucial as this may alter the decision regarding the need for device-based therapy and may also reduce the need for mineralocorticoid receptor antagonists (MRA) therapy. In addition, recent evidence now points out that these patients who come under HFIEF will have a substantial reduction in all-cause and cardiovascular mortality (17).

The serum lipid profile is one of the traditional risk factors of coronary artery disease. Therefore, moderate exercise training change in lipid profile positively impacts cardiovascular health (18). Conversely, in heart failure patients with compromised exercise capacity, lack of physical exercise may have a negative impact on lipid profile. EECP by improving flow across the systemic circulation may stimulate intensive aerobic exercise. In our study, there is a trend towards the reduction of Total cholesterol, Triglyceride, HDL, and LDL cholesterol. However, the LDL reduction of 15% only reached statistical significance. This reduction of 15% in LDL in 6 weeks is higher than the reported reduction in LDL by exercise training for 3 to 6 months duration (19). Previous EECP studies with a higher sample size have shown to reduce all lipid parameters with increased HDL levels (20, 21).

Most heart failure patients with a reduced ejection fraction do have renal impairment. In our study, the baseline creatine level of 1.16 ± 0.79 is within the normal limits showed that the cohort of patients studied does not have the cardiorenal syndrome. In addition, slightly raised urea level reduced significantly from the baseline value of 34.37 ± 20.28 to 27.24 ± 18.73 mg/dL (P = 0.002). This reduction is probably due to improvement in renal perfusion. Another previous study in healthy volunteers and patients with liver cirrhosis has shown that EECP treatment could increase GFR by 24% and renal plasma flow by 21-30% (6).

In our study, we continuously monitor the diastolic augmentation obtained from the finger plethysmography during three phases of the treatment. Earlier studies have shown that patients obtaining higher diastolic augmentation towards the end of the treatment attained greater symptom reduction (14). We observed that the peak and area D/S ratio linearly increased from the initial phase through the mid and end of the 35 sessions period. This improvement in D/S is much more pronounced in heart failure patients than in previous observations in preserved LV function. The P-value increase from the baseline 0.81 ± 0.24 to mid 1.14 ± 0.33 to end 1.4 ± 0.39, (P =0.0001), similarly the A-value increase from the baseline 0.98 ± 0.34 to mid 1.44 ± 0.45 to end 1.96 ± 0.77 (P=0.0005). The increase in diastolic augmentation as the treatment progress is a definitive marker of improved vascular compliance. This is due to the hyperdynamic circulation achieved during EECF, which reverses endothelial dysfunction, increases nitric oxide production, and decreases endotherlin secretion (22,23). Further, the linear increase in the diastolic augmentation also improves myocardial perfusion and overall improvement in Left ventricular ejection fraction, as observed in our study. The inflammatory marker CRP, which is within normal level pre-EECP, did not change, shows the hyperdynamic circulation enhanced by EECP does not cause any inflammatory response. In another animal study, they have demonstrated hs-CRP level significantly reduced post EECP, showing the anti-inflammatory effect of EECP (24).

Limitation of the study

Our study limitation is the small sample size and absence of a control group to compare. Since Post investigation is not made mandatory, some patients have skipped post echocardiography. All patient's medications are as closely monitored as possible without any change. However, some patient's physicians might have changed the medication as needed.

CONCLUSION

EECP treatment in symptomatic heart failure patients with reduced ejection fraction improves exercise tolerance, quality of life, and left ventricular ejection fraction. In addition, the treatment has been shown to increase the renal blood flow, reduce the harmful renal parameters, enhance systemic circulation, and have favorable changes in lipid parameters without causing any harmful systemic inflammatory response. However, these reported benefits needed to be confirmed through further Randomized control trials.

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CONFLICT OF INTEREST

Authors hereby declare that there is no conflict of interest.

REFERENCES

1. Lippi, G., Sanchis-Gomar, F. Global epidemiology and future trends of heart failure. AME medical journal. 2020; DOI: 10.21037/amj.2020.03.03


Lakshmi, M.V., Kennard, E.D., Kelsey, S.F., Holubkov, R., Michaels, A.D. Relation of the pattern of Diastolic Augmentation During a course of Enhanced External Counterpulsation (EECP) to Clinical Benefit. (From the International ECP Patients Registry (IEPR)). The American Journal of Cardiology Vol. 89, June 1, 2002.


