Cardiodiabetes Update

A Textbook of Cardiology

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Forewords

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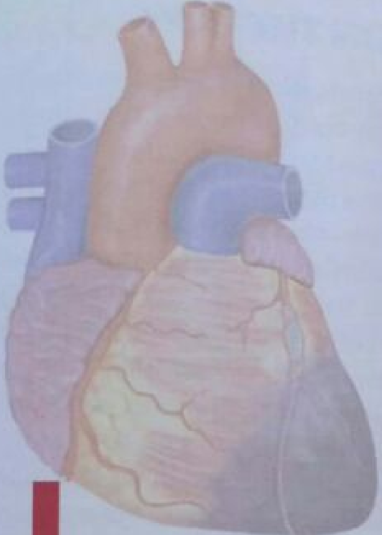

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CHAPTER

Role of Enhanced External Counterpulsation: Future Perspectives

Sanjay Mittal, S Ramasamy

INTRODUCTION

The treatment for refractory angina and heart failure poses a great challenge to the cardiologists since these patients have recurrent symptoms, demonstrable residual ischemia, repeat emergency visit, repeat hospitalization, and poor quality of life in spite of optimal medical management and exhausted or not amendable for further interventional procedures. The presence of diabetes in these groups is usually associated with worse outcomes with higher rate of restenosis[1,2] graft occlusion[3] and higher complication rate when repeat revascularization procedures are attempted.[4] Currently, the evidence shows clear role of revascularization in patients with unstable coronary syndrome, but still these procedures like coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA) role in stable patients beyond improving the quality of life is not clearly understood and still under investigation.[5,6] The recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and (Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) randomized trials have supported the view that patient's benefit derived from optimal medical management is comparable to that of intervention without any difference in rate of death or myocardial infarction (MI). This has recently increased attention on the US Food and Drug Administration (FDA) approved noninvasive treatment options like enhanced external counterpulsation (EECP) to improve the patient's symptoms and decrease the ischemic burden when added above optimal medical therapy. The treatment strategy other than standard interventional procedures like CABG and PTCA were EECP treatment, stem cell-induced neovascularization, gene therapy, intramyocardial angiogenic growth factor delivery, neurostimulation, percutaneous transmyocardial laser revascularization, and extracorporeal shockwave myocardial revascularization. Of all these treatment modalities, EECP is the widely used treatment as its mechanism of action is well established and also supported by two randomized trial showing its benefit in angina and heart failure patients.

HISTORY OF ENHANCED EXTERNAL COUNTERPULSATION

Evolution of counterpulsation from beginning to the current advance form is designed to achieve two important hemodynamic treatment goals, to augment diastolic pressure and to reduce left ventricular afterload. This was expected to have a favorable effect in patients with coronary artery disease by improving coronary perfusion pressure and reducing myocardial oxygen consumption. Augmenting diastolic pressure concept was first tested in 1953 by Kantrowitz and showed in an animal study that coronary blood flow could be increased by 20–40% by elevating the pressure during the diastolic phase.[7] Sarnoff and colleagues described myocardial workload is directly proportionate to the left ventricular contraction time and pressure.[8] Then in 1957, Birtwell combined both the principle of Kantrowitz and Sarnoff and design a counterpulsation device as a circulatory-assist device. In 1963, Denis and coworkers began clinical studies using a G-suite (hydraulic compression of legs), a rigid case enclosing a single pant-like bag filled with water, put around the lower extremities of the patients. Water was pumped in and out of the rigid metallic case in synchronization with patients electrocardiogram (ECG).[9] The initial clinical objective of the device is to support and stabilize the patients with acute myocardial infarction (AMI) and cariogenic shock. Early clinical papers in 1960s to 1970s were on these two acute indications. This leads to development of two parallel research in counterpulsation treatment—one led by Moulopoulos in developing invasive intra-aortic balloon pump (IABP) counterpulsation and other led by Birtwell in developing noninvasive EECP.[10,11] One randomized control trial on AMI by external counterpulsation demonstrated by applying 1–4 hours of counterpulsation within first 24 hours of onset of MI, there is significant reduction in mortality when compared to control group.[12] In 1964, Birtwell device showed by applying external pressure to the arterial system demonstrated similar benefit of increased diastolic pressure and reduce myocardial oxygen consumption, when compared to IABP. Cohen in 1973 showed EECP increases cardiac output by an average of 25% compared with 4% for IABP. This effect is due to increase venous return achieved by the compression of lower extremities.[13] In 1975, the water-driven hydraulic system was replaced by the advanced air-driven pneumatic counterpulsation for humans. In 1983, finally addition of the upper thigh cuffs or buttocks cuff and sequential pattern of inflation was introduced into the EECP system. The system performance significantly improved within increased diastolic augmentation (DA) and afterload reduction with these new additions. The current EECP system is shown in the Figure 1.

Fig. 1: Enhanced external counterpulsation (EECP) treatment system

ENHANCED EXTERNAL COUNTERPULSATION THERAPY

Enhanced external counterpulsation therapy system is an electromechanical system consisting of a specialized treatment table with integrated valve regulatory system, attached to specialized two sets three cuffs and a treatment console. The console comprises air compressor and touch screen panel to control inflation and deflation of the cuffs in synchronization with the patient's own ECG with microsecond precision. The cuffs inflate sequentially from lower calves proceeding upwards to lower thigh, then to upper thigh with a 50 millisecond delay with each cuff inflation in order to milk the blood flow in early diastolic phase and deflate simultaneously at the end of the diastolic or presystolic phase (Fig. 2). This sequential compression results in increased retrograde blood flow from the femoral artery towards the descending aorta. When the movement of column of blood reaches the root of aorta exactly during the diastole, the aortic valve will be in closed position and thereby significantly increasing blood flow to the coronary arteries at the time when coronary vascular resistance is at its lowest level. This is called DA. The inflation of the cuffs also increases the retrograde venous blood flow to the right side of the heart, providing greater ventricular filling and increase cardiac output. At the end of diastole and when the ventricle is prepared for systole all three cuffs simultaneous deflate, results in significant reduction in total systemic peripheral vascular resistance leaving the heart to empty the stroke volume into relatively lesser resistance peripheral vascular pathway and intern significantly reducing the after-load of the heart and overall myocardial oxygen demand. The cuff pressure can be increased from 80 mm Hg to 300 mm Hg. The central DA can be roughly estimated by using finger plethysmography. The pressure is adjusted in the cuffs to reach the DA ratio of more than one, which has been shown to have a favorable hemodynamic effect. The treatment is given on an outpatient day care basis, 1 hour session per day, 6 days per week over 6 weeks or 2 hours per day, 6 days per week for 3 weeks as tolerated for a total of 35 hours. In some patients a short course of 15, one-hour session is given to prepare the patients for high-risk CABG.

Major Randomized Trial of Enhanced External Counterpulsation

Multicenter study of enhanced external counterpulsation (MUST-EECP) is a multicenter, prospective, randomized, blinded, and control trial of EECP in angina patients with proven coronary artery disease and positive exercise treadmill test.[14] They were treated with either active

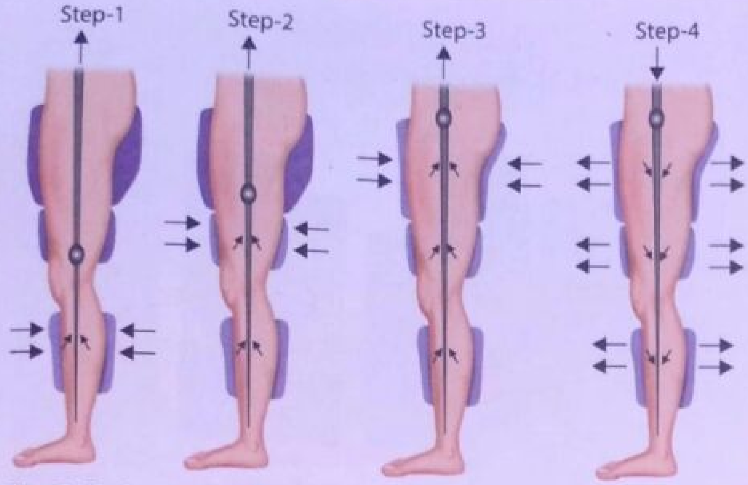


Fig. 2: Technique of enhanced external counterpulsation (EECP) therapy. Three pairs of pneumatic cuffs are applied to the calves, lower thighs, and upper thighs. The cuffs are inflated sequentially during diastole, distal to proximal. The compression of the lower extremity vascular bed increases diastolic pressure and flow and increases venous return. The pressure is then released at the onset of systole. Inflation and deflation are timed according to the R-wave on the patient's cardiac monitor. The pressures applied and the inflation-deflation timing can be altered by using the pressure wave forms and electrocardiogram on the EECP therapy monitor

(Adapted from Manchanda and Soran)

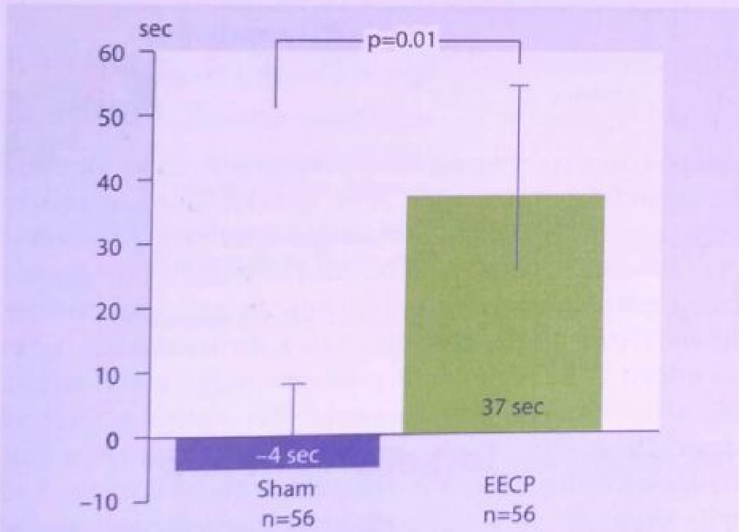


Fig. 3: Change in time to exercise-induced ST-segment depression significant in active treatment group

counterpulsation (applied cuff pressure upto 300 mm Hg) and inactive counterpulsation (<75 mm Hg). Time to 1 mm ST-segment depression increased significantly from baseline in active group compared with inactive group (p = 0.01) (Fig. 3). The treatment also significantly reduces the number of angina episodes and nitroglycerin usage in the active group. A substudy with 12-month follow-up also showed sustained improvement in health-related quality of life in active EECP group when compared to sham group.[15]

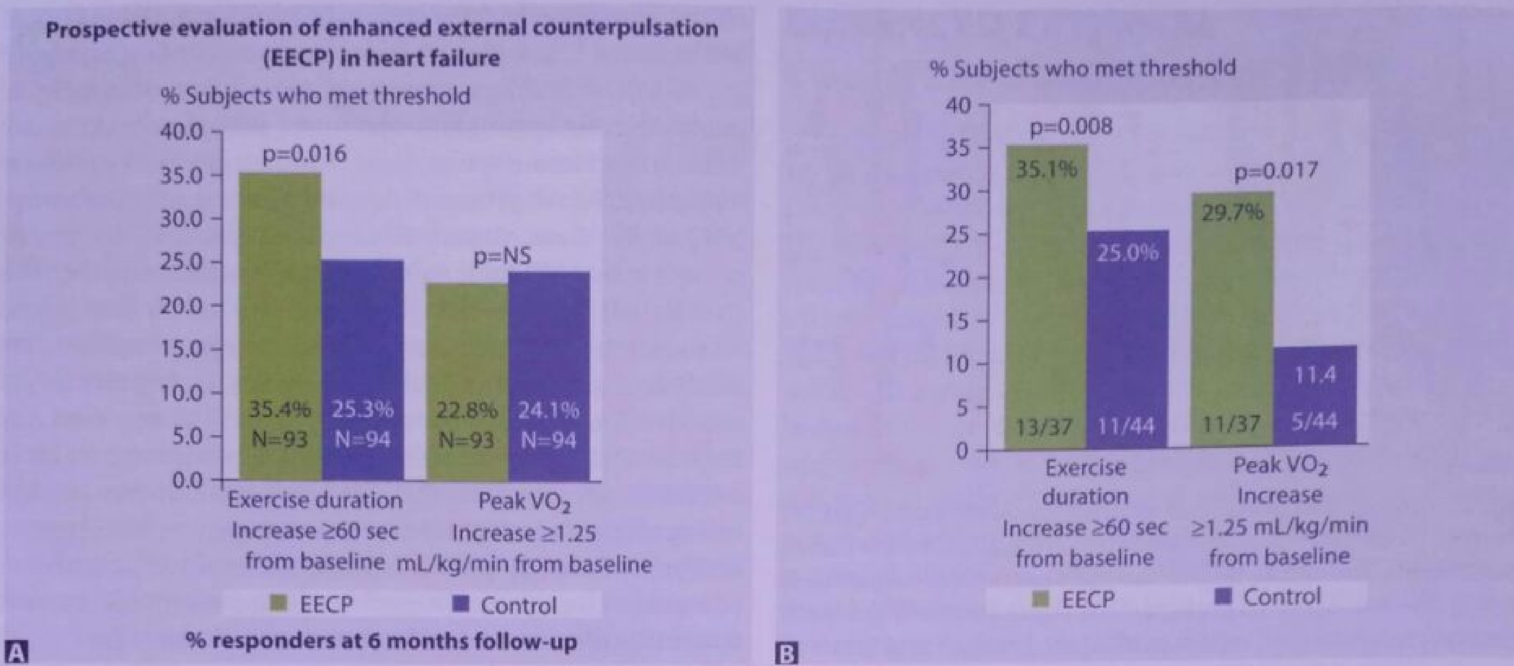
PEECH-EECP is a prospective evolution of enhanced external counterpulsation in heart failure patients with mild- to-moderate symptoms.[16] Patients are randomized to either EECP with protocol-defined pharmacologic therapy (PT) or PT alone. About 35% in EECP and 25% in control groups increased their exercise time by at least 60 seconds (p = 0.016) at 6 months (Figs 4A and B). New York Heart Association (NYHA) functional class improved in the active treatment group significantly at 1 week, 3 months, and 6 months. The Minnesota Living with Heart Failure score also improved significantly in the treated group at 1 week (*p* < 0.002) and 3 months (p = 0.01) after treatment, versus no significant changes in the control group. In subgroup analysis of elderly patients 65 years or older in addition to mean changes in exercise duration, peak oxygen consumption from baseline were significantly increased when compared to the control at 1 week, 3 months, and 6 months following completion of treatment.[17]

Acute Hemodynamic Benefit during Enhanced External Counterpulsation

Enhanced external counterpulsation hemodynamic effects are similar to that of IABP counterpulsation. During EECP treatment, the cuff pressure given in the lower extremities results in significant change in central hemodynamic circulation similar to that of what achieved in IABP except the increase in venous return (preload). When the cuffs inflate sequentially, it increases the central aortic and intracoronary diastolic pressure up to 92% and 93%, respectively, and the intracoronary flow velocity increase by 150% and the coronary flow increase by 28%.[18] Similarly, the cuff inflation also causes increase in venous return, which causes increase in right arterial pressure, pulmonary capillary wedge pressure, increase in blood flow into left ventricle, and cardiac output.[19] During EECP, cardiac output has shown to increase up to 25%.[20] When the cuffs deflate simultaneously, it decreases the central aortic and intracoronary systolic pressure by 11% and 15%, respectively. It lowers the left ventricular afterload and thereby reduces myocardial workload.[18]

Enhanced Myocardial Blood Flow

The long-time effect of EECP is presumably achieved through the development of new capillaries from the pre-existing vessels and by enhancing the collateral flow. EECP has been shown to associate with significant increase of



Figs 4A and B: (A) Increase in exercise duration and peak VO_2% responders at 6-month follow-up; (B) Increase in exercise duration and peak VO_2 in older patients ≥65% responders at 6-month follow-up

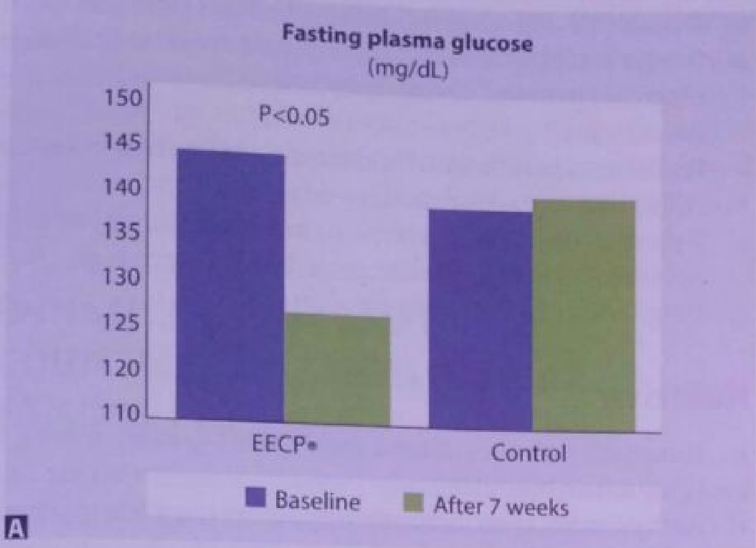
TABLE 1: Summary of the published radionuclide stress perfusion studies demonstrating EECP treatment improves perfusion to ischemic regions of the myocardium

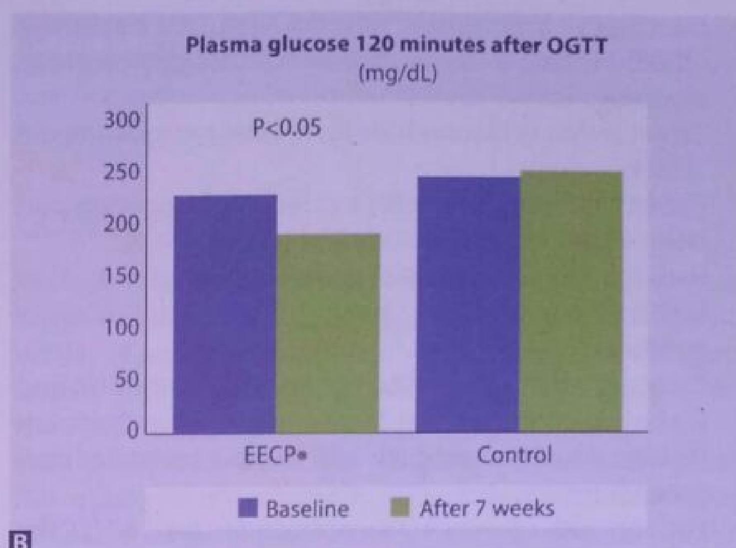
Author	*Year*	*Method*	*n*	*Perfusion changes*
Lawson et al.	1992	Thallium	18	78% pts (↑Maximal Exercise)
Sjukri et al.	1995	Thallium	35	87% pts (↑Maximal Exercise)
Urano et al.	2000	Thallium	12	46% (↑same workload)
Masuda et al.	2001	PET	11	23% (↑overall) 47% (↑ischemic region)
Stys et al. Ramasamy S	2002	Thallium sestamibi	175	83% pts (↑same workload) 54% pts (↑maximal exercise)
Tartaglia et al. Ramasamy S	2003	Sestamibi	25	64% pts (↑maximal exercise)

angiogenic factor including plasma vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basis fibroblast growth factors (bFGF).[21] The recruitment of new myocardial collateral arteries has been shown clinically by improved stress radionuclide coronary perfusion and N-ammonia positron emission tomography studies.[22-26] The improvement in myocardial blood flow is further confirmed by 2 randomized control trials by measuring pressure-derived collateral flow index (CFIp) and pressure-derived fractional flow reserve (FFR).[27,28] Both the parameters improved significantly in EECP treated group while there is no change in control group. Table 1 shows all the study done using myocardial perfusion scan.

Improves Endothelial Function

The increase in pressure and velocity in circulation achieved through counterpulsation by compressing the lower extremities not only causes shear stress to the vascular endothelium in coronary vascular bed but also to the entire systemic vascular system. The improvement in endothelial function is achieved by significant increase in plasma nitric oxide and reduction in plasma endothelin levels.[29] This plasma change in nitric oxide and endothelin were sustained even after the completion of EECP treatment up to 3 months. So in addition to improvement in coronary blood flow, endothelial function also has been shown to improve after a course of EECP treatment.[30]





Figs 5A and B: (A) Fasting blood sugar reduce significantly in treatment group 143.9 ± 8.5–127 ± 66 mg/dL ($p < 0.05$) and no change in control group; (B) Two hours after an oral glucose tolerance test (OGTT) with 75 g of glucose, plasma blood sugar reduce significantly in treatment group 224.4 ± 24.6–196.1 ± 24.7 mg/dL ($p < 0.05$) when compared to control group

EECP therapy has also shown to decrease the proinflammatory cytokines like tumor necrosis factor- α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule, and increase of endothelial progenitor cells, which are actually a circulating repair cells in patient with symptomatic coronary artery disease.[31,32]

Enhanced External Counterpulsation in Diabetes

Patients with diabetes are at greater risk of adverse cardiovascular events and they respond poorly to revascularization and aggressive antiplatelet therapy when compared to patients with no diabetes. Patients who are high-risk and diabetic with prior surgical and catheter-based revascularization and currently not an eligible candidate for further intervention who have undergone EECP treatment for their symptom relief, have shown similar reduction in angina symptoms compared to patients without diabetes. In 1-year follow-up study, both the groups maintain their benefit in anginal class and on demand nitrate intake. The incidence of PTCA, CABG, and MI are also similar in both these groups. When these groups of patients with diabetes treated with EECP compared to patient treated with elective PCI in National Heart, Lung, and Blood Institute (NHLBI) dynamic registry of coronary intervention and BARI the cumulative 1 year mortality are comparable with no increase in mortality in EECP-treated diabetic group.[33]

Enhanced external counterpulsation mechanism of action of improving the nitric oxide bioavailability and peripheral arterial function has also shown to manage better glycemic control in patients with abnormal glucose tolerance (AGT), which is a prediabetic status with greater risk of developing diabetes and cardiovascular disease. This was shown in a randomized control trial, where fasting plasma glucose declined 16.9 mg/dL (Fig. 5A) and plasma glucose 120 minutes after initiation of oral glucose tolerance testing decreases 28.3 mg/dL (Fig. 5B) significantly in EECP group while there was no change in the control group. In addition, the homeostasis model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance decreases by 31%, while the whole body composite insulin sensitivity index (CISI) increases by 21% in the EECP-treated group and no change in the control group. There was also 47% increase in glucose transporter 4 (GLUT-4) protein expression only in the EECP group.[34] This provides evidence that EECP sensitizes transport of insulin into skeletal muscle thereby providing help to manage glycemic control in patient with AGT. In another study the patients with left ventricular dysfunction (LVD) are grouped into diabetes and nondiabetes and the effect of EECP was studied. In this study, ejection fraction (EF), cardiac output, and stroke volume increases similarly in both groups. The effect of EECP seems to be independent of the status of diabetes.[35]

ENHANCED EXTERNAL COUNTERPULSATION INDICATIONS

Enhanced External Counterpulsation as Primary Treatment

- Chronic stable angina patients symptomatic with optimal medical management but not willing or not a candidate for PTCA or CABG.

- Coronary angiogram shows diffuse coronary atherosclerosis in distal vessels or challenging coronary anatomy.
- Target lesion is inaccessible for stenting or grafting the vessels.
- Patient symptomatic with evidence of ischemia and lesions are nonflow limiting and less than 70%.
- Patients with multivessel disease without left main involvement and only partial revascularization is possible.
- Patients with comorbid states like uncontrolled diabetes, chronic renal failure stroke or pulmonary disease which create high-risk for any interventional procedures.
- Patients with severe LVD recommended for CABG if the risk is higher than the benefit.
- Patients with cardiac syndrome X (microvascular angina).

Preparation for High-Risk Coronary Artery Bypass Graft

- Severe LVD with hibernating myocardium to improve myocardial blood.
- Flowing to stabilize the cardiac function prior to CABG.
- Waiting for CABG.

Enhanced External Counterpulsation as Secondary Treatment

- Post-CABG/post-PTCA residual ischemia and symptomatic.
- Restenosis after PTCA.
- Graft occlusion after CABG.
- Native vessel disease progression post-CABG and post-PTCA, where further intervention is not planned.

Enhanced External Counterpulsation in Heart Failure

- Symptomatic heart failure patients.
- Recurrent admission due to left ventricular failure/pulmonary edema.
- Ischemic and non-ischemic cardiomyopathy.

ENHANCED EXTERNAL COUNTERPULSATION CONTRAINDICATIONS

Absolute

- Severe aortic insufficiency (reduced coronary perfusion).
- Aortic aneurysm more than 5 cm or dissection (diastolic augmentation can cause rupture).
- Decompensated heart failure with fluid overload.
- Severe peripheral vascular disease/aortoiliac occlusive disease (prevent retrograde blood flow beyond the obstruction).
- Right heart failure with fluid overloads (increase venous return can cause pulmonary edema).
- Severe pulmonary hypertension (pulmonary artery pressure systolic pressure more than 50 mm Hg).
- Pregnancy (safety study not done).

Relative

- International normalized ratio (INR) greater than 2.5 (may cause bleeding).
- Arrhythmias interfering with system triggering (atrial fibrillation/flutter and frequent premature ventricular contraction).
- Uncontrolled severe hypertension more than 180/110 mm Hg (further augmenting diastolic pressure may be deleterious).
- Deep vein thrombosis (may cause pulmonary embolism).
- Thrombophlebitis and cellulitis.

ENHANCED EXTERNAL COUNTERPULSATION IN REFRACTORY ANGINA PATIENTS

Refractory angina poses a great challenge to the treating physician as these patients have already exhausted all treatment options and are in maximal tolerated medical management with objective evidence of ischemia. EECP treatment has shown consistently in many clinical trials improvement in clinical symptom of angina, decreases nitrate use, increases exercise tolerance, enhances quality of life accompanied by favorable psychosocial effects, prolongation of time to exercise induced ST-segment depression, and resolution of myocardial reversible perfusion defects.[36-39] The EECP therapy clinical benefits has been shown in wider range of patients, who include severe triple vessel disease, diabetes, LVD, elderly, patient with systolic, and diastolic dysfunction.[40,41] EECP has not only been demonstrated to be effective in treating these groups of patients with severe coronary artery disease, it has also been reported to be safe during treatment with only minor side effects, such as leg pain, skin abrasion, and temporary paresthesia. The International EECP Patient Registry (IEPR) with follow-up study of 1 year, 2 years, and 3 years has shown EECP benefits are sustained during the follow-up period in 75–85% of the patients.[42-44] In another independent study, 18 refractory angina patients were followed upto 5 years and they have been shown to maintain their clinical benefits.[45] Repeat EECP therapy after completion of first course is necessary in 10% of the patients in 1 year follow-up, 20% in 2 years follow-up, and 22% in 3 years follow-up. Most common reason for the repeat EECP therapy is failure to complete at least 30 sessions, recurrent symptoms, or residual symptoms after completing full course.[46]

ENHANCED EXTERNAL COUNTERPULSATION IN HEART FAILURE PATIENTS

Enhanced external counterpulsation therapy initially was considered to be contraindicated in patient with LVD based on path physiological reasoning that EECP increases preload and therefore may precipitate pulmonary edema. However, it has been reported that in patients with severe LVD (EF <25%), EECP is not only shown to be safe but also effective in significantly reducing systolic and diastolic volume and improving their LV function.[47] In a multicenter feasibility study, Soran and coworkers reported in patients with stable heart failure NYHA class II and III with both ischemic and nonischemic etiology, EECP therapy was associated with significant improvement in peak oxygen uptake (+27%), exercise capacity (16%), and functional status. These benefits were sustained for a period of 6 months even after completion of standard 35 sessions of EECP.[41] In IEPR patients with history of LVD (EF < 35%), who completed EECP treatment, 2 years follow-up have shown 83% survival rate and major cardiovascular event-free survival rate of 70%.[48]

In another prospective cohort study of 450 patients with LVD (EF < 30 ± 8%) a course of EECP therapy has significantly reduced all-cause emergency department visit by 78% and hospitalization rate by 73% at 6-months follow-up period, when compared to 6 months before EECP therapy.[49]

Enhanced external counterpulsation treatment has also shown significantly decrease in the heart failure readmission when started 90 days in post-discharges patients. The rehospitalization for heart failure reduced to 6% compared to predicted rate of 30–34%. These patients also show a significant improvement in 6 minutes walk distance, NHYA class, and Duke Activity Status Index (DASI) score suggesting that improvements in functional status and symptoms were contributing to very low rates of rehospitalization.[50]

Enhanced external counterpulsation therapy as per current evidence is on effective treatment option for patients with heart failure to improve their clinical symptoms, exercise tolerance, heart failure readmission, quality of life, peak oxygen consumption, and also to improve the LV function. The overall benefit of EECP has also been shown to be similar in both diastolic and systolic heart failure patients.[38]

CONCLUSION

Enhanced external counterpulsation treatment has been under focus in recent times due to its application in wide variety of patients' population who are high risk with poor quality of life. Its role in restoring blood supply to the ischemic myocardium by angiogenesis has opened up a lot of opportunity in this subgroup of patients who are not willing or not a candidate for revascularization. Any reduction in ischemic burden or improvement in quality of life with increase in exercise time will immensely benefit these patients. EECP's potential role in improving glycemic control in type II diabetic patients and favorably altering endothelial function by shear stress on vascular wall can protect or possibly can reverse the progression of vascular disease. EECP may play a greater role as cardiovascular protection therapy in patients with refractory angina and heart failure. The American College of Cardiology foundation guidelines for patients with stable ischemic heart disease recommends it as a class IIb (level of evidence B). The European Society of Cardiology guideline on the management of stable coronary artery disease recommends it as a Class IIa (level of evidence B). EECP is a validated, effective, safe, and noninvasive outpatient treatment for patients with angina and heart failure.

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