

Enhanced External Counterpulsation (EECP) Therapy: Current Evidence For Clinical Practice And Who Will Benefit?

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INTRODUCTION

Treatment of ischemic heart disease (IHD) has moved on gradually from the use of simple vasodilator nitrates to complex multiple medications and interventional procedures including coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI). Current treatments for IHD are able to decrease the incidence of morbidity and mortality in many patients. In clinical practice physicians routinely see patients who have recurrent symptoms in spite of maximal medical therapy and who are not a candidate of conventional revascularization procedures like PCI and CABG and still have objective evidence of myocardial ischemia. This group of Refractory Angina poses a challenge to cardiologist and they are frequent visitors to outpatient clinics. In United States there are about 25,000 to 75,000 new cases of refractory angina patients are diagnosed annually. The overall new cases of symptomatic coronary artery disease (CAD) diagnosed each year are 400,000¹. It's reported that 10-15% of the patients with angina meet the criteria set for refractory angina². In India there are 40.9 million diabetic patients and more than 29.8 million people are with CAD³ the incidence of refractory angina is increasing at a very high rate due to increase in life expectancy and increase number of severe CAD patients now survive.

The current non-pharmacological treatment strategy available for refractory angina patients is Enhanced External Counterpulsation (EECP), Neurostimulation (NS), Percutaneous Transmyocardial Laser revascularization (TMR), percutaneous in situ coronary venous arterializations and gene therapy. Of these treatment modalities EECP therapy is the only evidenced based therapy which is able to address both the myocardial supply and demand in the management of Angina pectoris. EECP is offered as an effective non-invasive mechanical treatment through which we can increase the myocardial blood flow (MBF) to the ischemic region and simultaneously decreasing the myocardial oxygen demand by reducing the left ventricular (LV) systolic work load.

Enhanced External Counterpulsation (EECP) therapy is approved by USA FDA for stable and unstable Angina, heart failure (HF), cardiogenic shock and acute myocardial infarction (MI)⁴. The treatment is widely used for the first two indications

angina and heart failure and there are more than 150 papers published in peer reviewed medical journals support its uses in these selected group of patients.

HISTORY OF ENHANCED EXTERNAL COUNTERPULSATION

The concept of increasing the aortic diastolic pressure increase coronary perfusion pressure and blood flow was first introduced in USA by Kantrowitz in 1953⁵. He showed in an animal study that, if coronary arteries are perfused at elevated pressure during diastole the coronary blood flow can be increased by 20-40%. This concept of Counterpulsation leads to development of invasive Intra aortic balloon pump (IABP) Counterpulsation and non-Invasive Enhanced External (EECP) Counterpulsation. Initial equipment for non-Invasive Counterpulsation was hydraulic driven with a single water filled bladder applied in the lower limb⁶. In 1975 air driven pneumatic EECP system was developed. Several studies on MI and cardiogenic shock were reported during the 1970's. In 1992 the first clinical study was published with an enhanced version of external Counterpulsation, hence EECP using three sets of cuffs wrapped around the lower extremities with sequential inflation from the distal calf cuff to the lower and finally the upper thigh cuffs⁷. The hemodynamic effects of EECP were confirmed to achieve similar hemodynamic benefits as the invasive IABP.

EECP THERAPY

EECP therapy consists of three sets of pneumatic compression cuffs applied to the lower extremities of the patients. The inflation and deflation of the cuffs are synchronized with the patient's electrocardiogram such that with each cardiac cycle pressure is sequentially applied from distally to proximally in early diastolic phase of the cardiac cycle resulting in the creation of a retrograde flow in the arterial side and an increase in venous return from the lower extremities to the heart. This results in an increase in diastolic blood pressure, augmented central aortic pressure and thereby an increase in coronary perfusion pressure during diastole when the myocardium is at a relaxed state and resistance of blood flow to the coronary circulation is at its lowest point. In the venous end, there is an increase in venous

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return which in turn increases central venous return to the heart and provides a larger volume of blood to be ejected thus increasing cardiac output. All the pressure in the inflated cuffs are released just prior to the onset of systole of the next cardiac cycle, leaving behind an empty vasculature which serves to receive the cardiac output of the heart, decreasing the systemic peripheral vascular resistance and cardiac workload.

EECP treatment is now being used increasingly as a non-invasive outpatient treatment option for patient with refractory angina and HF symptom, who are on maximal medical therapy and in the opinion of a cardiologist or cardiothoracic surgeon are not candidates for surgical intervention such as PCI or CABG procedure⁸. The treatment is given as an outpatient basis one hour session per day, six days per week over six weeks for a total of 35 hours sessions. EECP can also be given 2 sessions per day for 3 weeks with a minimum of 1 hour break between two sessions.

MECHANISM OF ACTION

The mechanism of action of EECP is very complex. Many theories have been proposed to explain the clinical benefit of EECP in short term and in long term. The long time effect of EECP is presumably that of development of new collateral channels and by enhanced collateral flow. EECP has been shown to associate with significant increase of angiogenic factor including plasma vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF)⁹. The recruitment of new myocardial collateral arteries has been shown clinically by improved stress radionuclide coronary perfusion and N-ammonia positron emission tomography studies¹⁰⁻¹⁴. Recently direct evidence for arteriogenesis using pressure-derived coronary collateral index by catheterization assessment shows significant increase in coronary collateral post EECP¹⁵. In addition endothelial function has been shown to improve after a course of EECP treatment¹⁶. The improvement in endothelial function is due to increase flow velocity and shear stress on the endothelium with significant increase in plasma nitric oxide and reduction in plasma endothelin levels¹⁷⁻¹⁹. EECP therapy has shown to decrease the proinflammatory cytokines like tumor necrosis factor- α (TNF- α) and Monocyte chemoattractant protein-1 (MCP-1) and an increase of endothelial progenitor cells in patient with symptomatic CAD²⁰⁻²¹. Hemodynamically, EECP has similar effects as IABP counterpulsation. During EECP treatment the change in central Hemodynamic parameters are similar to that of the IABP except the increase in venous return (pre load) causes increase in right arterial pressure, pulmonary capillary wedge pressure and cardiac output²². The cardiac output has shown to increase up to 25%²³. When the cuffs inflate sequentially (see Fig 1) it increases the central aortic and intra coronary diastolic pressure increased up to 92% and 93% respectively and the intra coronary flow velocity increase by 150% and the coronary flow increased by 28%.

When the cuffs deflate simultaneously (Fig 2) it decreases the central aortic and intra coronary systolic pressure by 11% and 15% respectively. It lowers the left ventricular after load and thereby reducing myocardial work load²⁴. Table 1 is a summary of the published radionuclide stress perfusion studies demonstrating EECP treatment improves perfusion to ischemic regions of the myocardium. Fig.3 illustrates a summary of the mechanism and clinical benefit of EECP therapy.



Fig.1: Advanced EECP Lumenair treatment system

EECP IN REFRACTORY ANGINA PATIENTS

Since EECP therapy produces similar hemodynamic effects as IABP, the early application of EECP were concentrated in acute emergency situation like cardiogenic shock and MI. However, ever since the new design of EECP with sequential pneumatic cuffs, EECP has been used mostly in the US and Europe in patient with refractory angina pectoris. EECP treatment has shown consistently in many clinical trials improvement in clinical symptom of angina^{25,26}, decreases nitrate use²⁵⁻²⁷, increases exercise tolerance²⁸, enhances quality of life accompanied by favorable psychosocial effects, prolongation of time to exercise induced ST-segment depression^{29,30,31} and resolution of myocardial defects.

The EECP therapy clinical benefit has been shown in wider range of patients which includes severe triple vessel disease, diabetic, severe LV dysfunction³², elderly, ischemic cardiomyopathy, non-ischemic cardiomyopathy³³ and patients with systolic and diastolic dysfunction. EECP has not only been demonstrated to be effective in treating these group of patients with severe CAD, it has also been report to be safe during

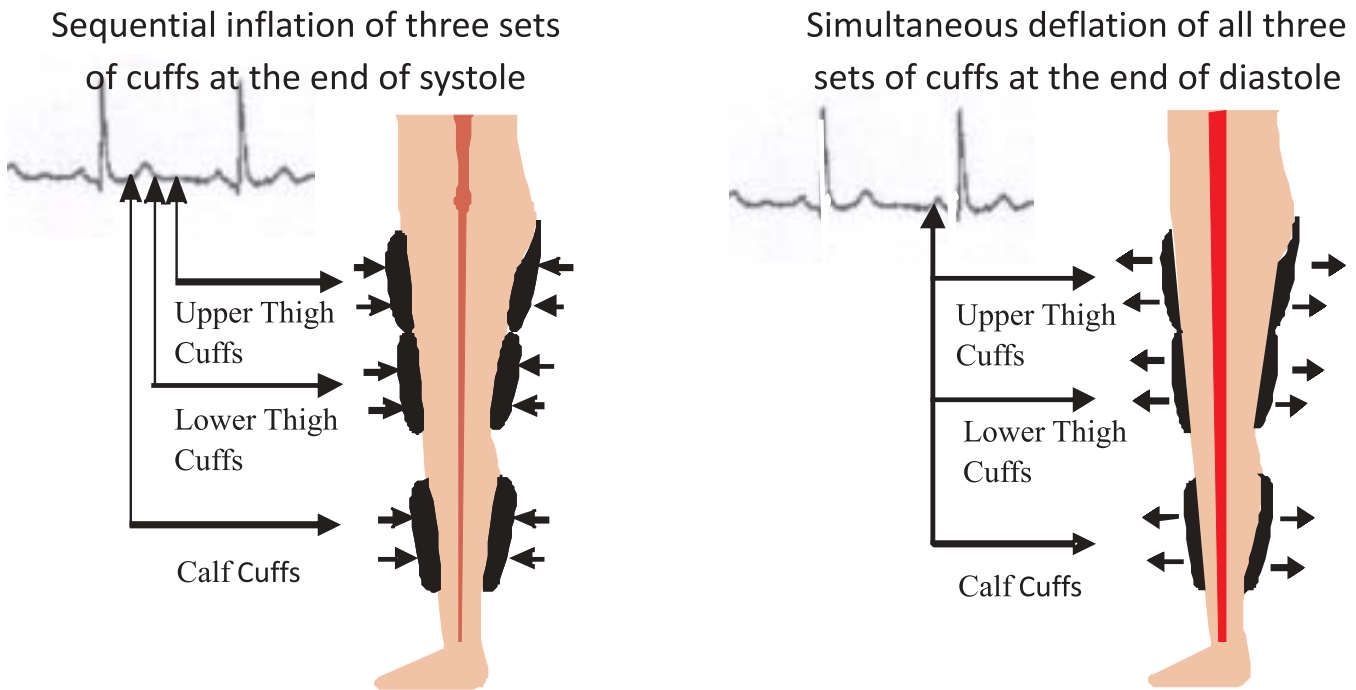


Fig 2: The QRS complex of the electrocardiogram is used to provide a triggering signal for the calf inflation valve to open around the peak of T-wave, the lower thigh valve will open 50 ms later, to be followed by the upper thigh valve another 50 ms later. The pressure in the cuffs will hold as long as possible to allow maximization of diastolic augmentation. Then all three-deflation valves will open at the same time around the peak of P-wave to let the emptied peripheral vasculature to receive the blood ejected by the heart, leading to systolic unloading.

Table 1: Summary of papers demonstrating EECF improves myocardial perfusion in patients with chronic stable angina

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)
Masuda et al	2001	PET	11	23% ↑ (overall) 47% ↑ (ischemic region)
Urano et al	2000	Thallium	12	46% ↑ (same workload)
Stys et al	2002	Thallium Sestamibi	175	83% pts ↑ (same workload)
Ramasamy.S				54% pts ↑ (maximal exercise)
Tartaglia et al	2003	Sestamibi	25	64% pts ↑ (maximal exercise)

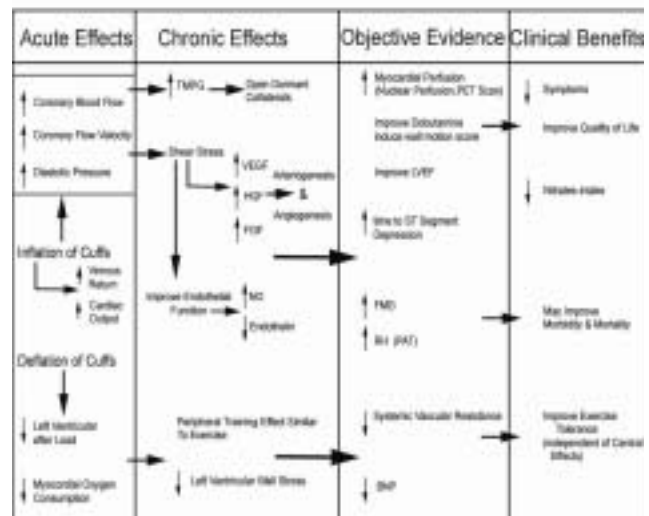


Fig 3 Mechanism of Action: TMPG – Trans Myocardial Pressure gradient, VEGF-Vascular endothelial growth factor, HGF-Hepatocyte Growth factor, FGF-Fibroblast growth factor, NO-Nitric, PET Scan-Positron emission tomography Scan, LVEF-Left Ventricular ejection fraction, FMD-Flow mediated vasodilatation, RH (PAT)-Reactive hyperemia peripheral artery tonometer.

treatment with only some side effects such as leg pain, skin abrasion and temporary paresthesias.

A multicenter randomized, double blinded, sham-controlled trial of Enhanced External Counterpulsation (MUST-EECP) showed that active EECP therapy significantly improved the time to ST segment depression during treadmill stress test using the Bruce protocol and frequency of angina occurrence when compared to sham group and baseline²⁹. A sub study of the trial at 12 months follow up also showed sustained improvement in health related quality of life in active EECP group when compared to sham group³⁴.

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. In another independent study, 18 refractory angina patients were followed up to 5 years and they have been shown to maintain the clinical benefit³⁵. Data from the IEPR using 1,015 refractory angina patients with end stage CAD reported 6 months post EECP treatment, the rate of hospitalization was significantly reduced by 83% when compared with 6 months prior to EECP treatment³⁶. Another study using the IEPR data on 4597 patients reported that the 35-hour treatment completion rate was 86%. When the results of those who have completed the treatment were compared with patients who didn't complete the treatment at one year follow up, even though baseline demography was comparable in both groups of patients, the group with completed treatment has a significantly lower MI, CABG and PCI and mortality rates³⁷. This result is remarkable because approximately 85% of the patients in the IEPR were suffering from really severe coronary heart disease having undergone either CABG or PCI and not amendable for further revascularization.

Repeat EECP therapy after completion of first course is necessary in 10% of the patients in one year follow up, 20% in two year follows up and 22% in three year follow up. Most common reason for the repeat EECP therapy is failure to complete at least 30 sessions, recurrent symptom or residual symptom after completing full course³⁸⁻⁴⁰.

EECP IN HEART FAILURE PATIENTS

Historically, EECP therapy was considered to be contraindicated in patient with LV dysfunction 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 LV dysfunction (EF <25%), EECP is not only shown to be safe but also effective in significantly improving their LV function but also decreasing their heart rate⁴¹. In another multicentre feasibility study reported by Soran and co-workers³³ in patient with stable HF NYHA class II and III with both ischemic and non-ischemic etiology EECP therapy was associated with significant improvement in peak oxygen uptake, exercise capacity and functional status. These benefits were sustained for a period of six months even after completion of

standard 35 sessions of EECP. This study leads to well controlled, randomized, single-blind, parallel-group, multicenter study of 187 patients called The PEECH (Prospective Evaluation of EECP in Heart Failure) with similar symptomatic stable HF with NYHA functional class II and III is undertaken. Results of the PEECH trial have shown that EECP therapy increased exercise duration, improve NYHA functional status and quality of life without significant increase in peak VO_2 ⁴². However with subgroup analysis of the of elderly patients age > 65 enrolled in the PEECH trial, EECP patients when compared with controls demonstrated a significant higher responder rate in their peak VO_2 consumption at 6 months follow-up⁴³.

In another report of 363 refractory anginal patients with history of LV dysfunction (EF <35%) from the International EECP patient registry, 84% had multi vessel disease and 93% were not candidate for further revascularization due to extent and severity of disease. Two years follow up have shown 83% survival rate with major cardiovascular event free survival rate of 70%. Even though the registry data lack control groups and therefore the results drawn from such data may not be as convincing as the randomized control study, the patients treated are from a wide range of population which reflects what we see in our real clinical practice³⁹. In another study of 450 patients with severe refractory angina with mean LV dysfunction (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 therapy⁴⁴. 98% of these patient groups were not a candidate for revascularization procedure and 93% had severe angina (Canadian Cardiological Society-CCS Class III-IV). Irrespective of their severe progressive disease 72% of the patients improved at least 1 class. EECP therapy can benefit stable angina patients with HF, who are on optimal medical management but still not able to achieve required functional benefit. These groups of patient are traditionally high risk group with repeated hospitalization and outpatient consultation, EECP therapy as per current evidence may be a viable alternative treatment for them to improve their clinical symptom, quality of life and also to improve the LV function. Overall benefit of EECP has also been shown to be similar in both diastolic and systolic HF patients groups⁴⁵.

PRECAUTION IN TREATING HEART FAILURE PATIENTS

In HF patient increasing pre-load by increased venous return is always considered risky as it may increase right arterial pressure and pulmonary wedge pressure which may cause pulmonary edema during the treatment. Even though data from registry and pilot study have shown EECP is safe in HF patients, still in 3-5% of patients suffered from worsening of their HF during EECP treatment⁴⁵. The reason for this adverse effect may be due to differential pressure from 80 mmHg to 300 mmHg given during

Table 2 : Current application of EECP in clinical practice.

Patient who will benefit from EECP:
<p>A. Patients whom PTCA or CABG is not contemplated.</p> <ul style="list-style-type: none"> ➤ Patient refused to undergo additional invasive revascularization procedures. ➤ Angiogram shows diffuse coronary atherosclerosis in distal vessels or challenging coronary anatomies. ➤ Target lesion is inaccessible. ➤ Patients have Co-morbid states like diabetes, renal dysfunction and pulmonary disease which create high risk. ➤ Severe LV dysfunction – High risk CABG. ➤ Restenosis after PTCA. ➤ CABG graft occlusion. <p>B. Patients with ischemic or idiopathic Cardiomyopathy.</p> <ul style="list-style-type: none"> ➤ Stable heart failure patients with NYHA class II & III. ➤ Recurrent hospitalization due to pulmonary edema. ➤ Have Left Ventricular dysfunction (EF <35%) <p>C. Cardiac Syndrome X (Microvascular Angina)</p>

Table 3.: Contraindication for EECP therapy

Contraindication:
<ul style="list-style-type: none"> ✓ Severe aortic regurgitation (would prevent diastolic augmentation). ✓ Aortic Aneurysm or dissection. (Increase diastolic pressure may cause rupture). ✓ Uncontrolled Arrhythmias that interfere with machine triggering. (Atrial fibrillation / flutter and very frequent ventricular premature contraction). ✓ Severe lower extremity vaso-occlusive disease which prevents retrograde blood flow. ✓ Active thrombophlebitis and deep vein thrombosis. ✓ Bleeding Diathesis or patient with anti coagulant in whom the international normalized ratio is not adjusted. ✓ Decompensated heart failure (increase venous return may cause pulmonary edema should be carefully monitored). ✓ Cardiac catheterization within past 2 weeks to reduce the risk of bleeding in femoral puncture site. ✓ Severe Pulmonary artery hypertension. ✓ Pregnancy.

the treatment. There is a controversy over lower pressure regime and high pressure regime in patients with HF⁴⁶. Using direct invasive hemodynamic monitoring, Isao Taguchi explained why EECP doesn't cause pulmonary edema and is safe⁴⁷. In their study 300 mmHg pressure significantly increased right arterial and pulmonary wedge pressure in the first 15 to 30 minutes, but during the subsequent 30 to 45 minutes there was a reduction in pressure in both compartments with significant increases in

cardiac index. Presumably this increase in cardiac index can be attributed to improve ventricular contraction and significant reduction in systemic vascular resistance. The increased cardiac output and reduced vascular resistance can shift the blood from pulmonary circulation to systemic circulation. This hemodynamic effect was further proved by Andrew and coworker while they were studying LV energetic during EECP by selection different cuff combination²⁴. The overall LV myocardial efficacy is unchanged because the increase preload is counterbalanced by decrease after-load assisted by cuff deflation at higher pressure. Giving lower pressure in patient with stable HF may not able to achieve the necessary after-load reduction required to shift the fluid from pulmonary to systemic circulation. So in patient with HF the treating physician should apply higher pressure to maximize systolic unloading and minimize the increase preload by cuff selection rather than decreasing the pressure which may be harmful.

EECP IN ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is characterized by impaired release of nitric oxide (NO). In general the maximum arterial wall shear stress occurs during the peak systolic period. However endothelium becomes dysfunction in an environment of low shear stress. During EECP the vascular shear stress increases more than two fold during the peak diastolic period⁴⁸. Evidence is accumulating to show that chronic shear stress during the course of EECP has significantly increased the release of NO. The increase in NO level is dose related and sustained even up to one month after completion of EECP course¹⁸. This observation has been confirmed by the Mayo clinic group in a paper which assessed peripheral endothelial function by a new non-invasive technique reactive hyperemia–peripheral arterial tonometry (RH-PAT). In this study RH-PAT index was significantly higher at one month after completion of 35 hours of EECP treatment when compared with baseline. In addition RH-PAT index was significantly higher in patients who have demonstrated an improvement in angina class than those patients who have no improvement¹⁶. Based on the results of these studies, a different perspective of EECP has been developed relating clinical improvement to endothelial improvement, peripheral vasodilatation, decrease peripheral vascular resistance and decrease in the myocardial oxygen demand. In another similar study Nichols and coworkers have reported that EECP improved arterial wall properties by reducing arterial stiffness and thereby reducing the wave reflection velocity and amplitude. The wave reflection timing in central aorta plays an important role in augmenting the central systolic pressure and increasing the LV load. The increased LV systolic pressure due to the reflected wave translated to energy being wasted against the reflected pressure waveform instead of contributing to blood flow. EECP is shown to reduce the reflected wave amplitude and velocity thereby reducing augmented central pressure and reducing LV

load and myocardial oxygen demand. This study was conducted non-invasively using a SphygmoCor device (Atcor Medical Sydney Australia)⁴⁹. This study demonstrated another mechanism of EECP giving an indication that it is possible EECP may improve clinical symptom without improving MBF. In summary, it is clear that EECP provides improvement in both myocardial supply and reduction in load thereby achieving a greater reduction in angina and heart failure symptoms.

This peripheral effect of EECP is also well documented and reported in 175 patients with chronic stable angina who underwent radionuclide perfusion treadmill stress test⁵. The study protocol compared two groups of patients, one with maximal stress test in 78 patients pre and posts EECP versus 97 patients with the same level of exercise pre and post EECP. In patient who underwent maximal exercise 54% showed improvement in myocardial perfusion but showed no change in double product. This result implied that even in patient with improved exercise time, their increased exercise tolerance is achieved without increasing the myocardial demand but rather achieved through improved myocardial supply. In patients who underwent same exercise level 83% of patients showed improvement in myocardial perfusion but this was achieved with significantly lower level of double product. This is a classical peripheral effect, as the myocardial demand is reduced due to decrease peripheral vascular resistance similar to that of exercise training.

INDIAN EXPERIENCE IN EECP THERAPY

Recently there are some interesting papers published in India which reconfirm the improvement in myocardial perfusion and improvement in LV ejection fraction in the Indian population. These effects were seen in both patients with refractory angina and ischemic Cardiomyopathy. The data from the Indian patient EECP registry which tracks both the subjective and objective improvements shown that the improvement in LV ejection fraction is predominantly due to reduction in end systolic volume demonstrating improvement in LV contractility after EECP therapy. In another interesting study a short course 10 sessions of EECP therapy done prior to performing high risk CABG has shown improvement in myocardial perfusion and LV function. In addition, patients in this study who went on to have CABG have decreased complication during and after their surgery. This result demonstrates EECP may have beneficial effect in surgical outcome in this group of patients. This hypothesis needed to be tested in large randomized study. Indian papers are summarized in Table 4.

CONCLUSION

Enhanced external Counterpulsation is a proven non-invasive treatment option to be considered for patients with refractory angina and HF. EECP therapy is the only mechanical therapy, which has shown not only effective in improving myocardial supply in angina patients but also shown to improve endothelial

Table 4: Published Indian papers on EECP and data from Indian patient EECP registry (IPER)

No of Patients	Study objective	Results	Presented
N=505	To assess Clinical symptom and LV function in patient with LV dysfunction.	Improves clinical symptom, EF, Stroke Volume and Cardiac output	American College of Cardiology March 2007. Indian Patient EECP registry (IEPR) (Smarpan Hospital Gujarat and People Medical college)
N=110	To assess Anginal Symptom and LV function in patients with severe LV dysfunction.	Improves, Anginal symptom and EF	European Society of Cardiology 2008. (Harvey Hospital Chennai). IEPR
N=16	Assess short course EECP effect in patients posted for High Risk CABG	Improves myocardial perfusion and gated LVEF	Heart Failure Society of America 2008. Frontier Lifeline & International center for cardiovascular and thoracic disease. Chennai
N= 50	Effect of EECP in ischemic Cardiomyopathy patients	Improves Myocardial perfusion and Gated LVEF	Cardiology Society of India 2008. Chennai. Frontier Lifeline & International center for cardiovascular and thoracic disease. Chennai
N=13	Pre-operative use of EECP in high Risk CABG.	Improve myocardial perfusion. Decrease IABP use and Hospitalization time	Indian Journal of thoracic and cardiovascular surgery Feb 2006. Frontier Lifeline & International center for cardiovascular and thoracic disease. Chennai
N=81	Evaluation of Endothelial function improvement in DM patients	Improve Brachial artery FMD.	Indian Heart Journal 2005. Escorts Heart Institute and Research center. Delhi
N=84	Evaluation of exercise capacity in chronic Angina Patients	Improved Exercise tolerance assessed by 6 min walk test	Presented in International EECP symposium China May 2006. Escorts Heart Institute and Research center. Delhi
N=46	Use of EECP as primary option in patients who are unwilling for Intervention	Improved Treadmill time and ejection fraction	Presented in International EECP symposium China May 2006. Institute of Preventive Cardiology. Mumabi

function and decrease the myocardial demand. Due to its effect on vascular endothelium and microvascular circulation it can also be used to treat patients with microvascular angina or cardiac syndrome X⁵⁰. Refractory angina and HF utilizes increase health care cost due to repeat hospitalization and revascularization. EECP is the most cost effective treatment for this selected group of patients. The utilization of EECP in earlier stage of CAD will be an attractive option and its needs further evaluation. The treatment is safe in patients with stable angina pectoris with mild to moderate LV dysfunction. Even though there were numerous studies published on the safety of EECP therapy in heart failure patients, these groups of patients should be carefully selected with stable and manageable edema without any severe valvular disease or pulmonary hypertension. HF centers using EECP therapy should have a proper backup to manage HF patients and should be treated by certified and trained persons so that clinical events during the therapy can be minimized.

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