Enhanced External Counterpulsation- A Review

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Introduction:

It has been more than 40 years since Kantrowitz and Kantrowitz first described the principle of "phase shift diastolic augmentation",[1] and a group of physicians and physicists at Harvard and elsewhere related this principle to the oxygen consumption difference between flow work and pressure work by the heart. This understanding led to the concept of mechanically-induced "counterpulsation" to provide assistance to patients with low cardiac output syndromes.

Early research used direct counterpulsation techniques first developed by Harken and associates at Harvard in the late 1950's. Through femoral cutdown and external pulse actuation, this technique withdrew and then returned the blood to the arterial system. In the early 1960's, Birtwell and Clauss, produced counterpulsation by introducing a catheter with a long slender balloon into the ascending aorta via the femoral artery (Intra-aortic Balloon Pump [IABP].[2] In the mid 1960's, several scientists were involved in the evolution of counterpulsation to a noninvasive technique using externally applied pressure generated by hydraulic systems. As the evolution of external counterpulsation devices progressed, hydraulic systems were replaced with pneumatics. During the late 1960', scientists at the National Institutes of Health suggested that results could be improved if blood was expressed from the extremities in a sequential manner. During the 1980's, Zheng and colleagues at Sun Yat Sen University in China, were first to report the benefit of external counterpulsation by using pneumatic counterpulsation device in a sequential manner.[3]

Favorable results reported by Chinese investigators, led scientists at the Health Sciences Center at the State University of New York at Stony Brook, to reassess the efficacy of this modality in the treatment of patients with chronic angina pectoris. In their study on 1992, Cohn and Lawson et al. assessed 18 patients who had incapacitating symptoms, refractory to medical therapy. Exertional myocardial ischemia was documented by thallium-201 perfusion imaging. Eight patients had previously undergone a total of 19 attempts at revascularization by coronary bypass or angioplasty. Following an initial symptom-limited stress thallium study, subjects received a total of 36 one-hour treatments with EECP over a 7 week period. Antianginal medications were continued at the initial or reduced doses. At the end of the treatment period, thallium testing was repeated, followed by routine maximal stress testing. All patients, treated with EECP showed a substantial improvement in symptoms, and 16 patients reported a complete absence on angina during their usual activities. Repeat thallium testing showed a reduction in myocardial ischemia in a significant proportion of patients: 12 (67%) demonstrated a complete absence of perfusion defects, and 2 (11%) demonstrated a reduction in the area of ischemia at the level of exercise achieved in the baseline study. Thereafter they undertook many open level studies between 1989 and 1998 using with EECP using subjective and objective en d points. These studies, although open and nonrandomized, showed statistical improvement in exercise tolerance by patients as evidenced by thallium-stress testing and partial or complete resolution of coronary perfusion defects as evidenced by radionuclide imaging studies.[4-8]

The researchers suggest that Enhanced external counterpulsation (EECP) is an effective therapy for patients with coronary artery disease who are

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not candidates for invasive revascularization procedures, such as balloon angioplasty, heart bypass or stent implantation.[9-15] It is noninvasive, non pharmacological, low risk, painless therapy for refractory angina pectoris and congestive heart failure. It uses timed, sequential inflation of pressure cuffs on the calves and thighs to augment diastolic pressure, decrease left ventricular afterload, and increase venous return.

As the survival of patients with primary coronary events continues to increase, the number of patients presenting with coronary artery disease unsuitable to further revascularization techniques and symptoms refractory to medical therapy also continues to rise. There is an estimated 300,000 to 900,000 patients in U.S. who have refractory angina pectoris (RAP). Between 25,000 and 75,000 new cases of RAP are diagnosed each year.16 These patients with refractory angina have recurrent, disabling symptoms, which markedly limit daily activities. In addition, despite advancement in cardiac care, the treatment of moderate to severe heart failure remains unsatisfactory. Approxmately 5 million Americans experiences heart failure, with 5,50,000 new cases per year reported.[16] So it places an enormous burden on the health care system.

External counterpulsation technique:
EECP treatment is typically provided on an outpatient basis. A full coarse of therapy ususlly consists of 35 hours. Treatment is administered 1-2 hours a day,5 days a weak, for 7 weeks, by a registered nurse under the supervision of a staff cardiologist.[17-18]

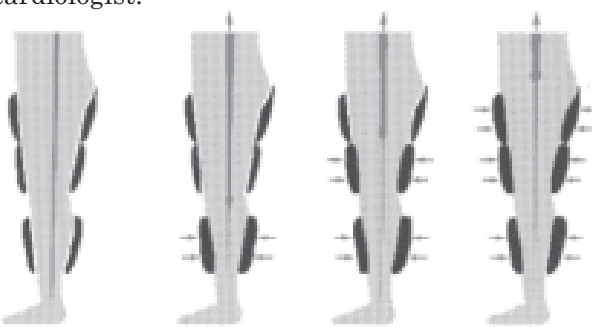

Fig.-1: *Technique of EECP*

Patient lies on a treatment table to received therapy. Compressive cuffs are wrapped around the patient's calves, lower and upper thighs (including the buttocks). These cuffs inflate in a distal to proximal sequence (Fig.1) in early diastole (upto 300 mmHg), and deflate simultaneously in late diastole just prior to the onset of systole. Inflation and deflation are specifically timed to the patient's ECG and occurs about 60 to 80 times per minute during an EECP session. The multiple components of the procedure include use of device itself, finger plethysmography to follow blood flow, continuous ECG to trigger inflation and deflation and optimal use of pulse oxymetry to measure oxygen saturation before and after treatment.

Hemodynamic effects:

Immediate effects:
During diastole, the cuffs inflate sequentially from the calves proximally, resulting in augmented diastolic central aortic pressure and increased coronary perfusion pressure. The coronary collateral flow to ischemic regions of the myocardium is increased. Compression of the vascular bed of the legs also increases venous return and cardiac output. Modification of the pulse pressure distribution in the aorta favors increased mean arterial pressure and; therefore, flow to the vital organs. The cuffs are deflated simultaneously just prior to systole, which produces a rapid drop in vascular impedance, a decrease in ventricular workload, increase in the stroke volume per unit work and an increase in cardiac output.[19-21] Ochoea et al, recently reported that, there is small and sustained increase in VO_2 during EECP, which in turn enhances the exercise tolerance.[22]

Effects on endothelial function:
The endothelium plays a crucial role in vascular homeostasis.[23] Whereas normal endothelium is atheroprotective, dysfunctioned endothelium is atherogenic.[24-25] Endothelial dysfunction is characterised by impaired bioavailabily of endothelium derived vasodilator eg. NO and increase in vasoconstrictor eg. Endothelin-1.[26] It is also associated with arterial stiffness, which increases systolic pressure.[27] This arterial stiffness is influenced by the functonal status of the arterial wall including bioavailabily of endothelium derived NO.

EECP plays an important role in the improvement of endothelial function. EECP-induced increase in blood flow enhances endothelial shear stress.[28-29] It acts a major stimulus for endothelial NO release by phosphorylating and activating NO synthetase of endothelium.[30-33] Longer exposure to higher shear stress level is also associated with a reduction of endothelial endothelin-1 release.[32-33]

EECP also affect oxidative stress. Although the exact mechanism is not clear, it has been shown

that reactive oxygen species and NO interact chemically to neutralize each other. EECP- induced lowering of angiotensin II level.[34] decreases vascular superoxide production and thus contributes to decrease in oxydative stress.[35]

Reactive hyperemia-peripherial artery tonometry (RH-PAT), a measure of peripherial endothelial function, detects pulsatile arterial volume changes following induction of reactive hyperemia. Following each session of EECP, there is an acute and sustain increase in the average RH-PAT index.[36] Similar results were demonstrated by flow mediated vesodilatation (FMD), measured by Doppler ultrasound of the brachial artery. Furthermore, improvement in endothelial function at rest and in response to Dipyridamole was also demonstrated by using ammonia positron emission tomography(PET).[37] In the recent studies, it has been found that EECP therapy stabilise the coronary endothelium.[38-39] It retards the atherosclerosis process by acting on the NF-kappa signaling pathways.[40] It also increases cyclic guanosine monophosphate level in the plasma, which regulates vascular smooth muscle tone and thereby improve peripheral arterial function.[41]

Effects on coronary collateral supply:
EECP increases collateral perfusion by opening preformed collateral channels, either directly via increasing diastolic pressure and flow or indirectly via release of vasodilatory mediators eg. NO. Shear stress induced by EECP may influence arteriogenesis (formation of large collateral arteries) and angiogenesis (de novo formation of capillary blood vessels). Growth factors (vascular endothelial growth factor [VEGF], platelet derived growth factor, hepatocyte growth factor) upregulated by vascular shear stress play crucial role in angiogenesis.[42-43] VEGF promote mobilisation and differentiation of endothelial progenitor cell thus help in vasculogenesis (formation of blood vessels involving bone marrow derived endothelial progenitor cells) which in turn lead to collateral formation.[44-45]

Peripheral effect:
EECP is associated with non specific peripheral training effect. After treatment there is a significant increase in exercise duration.[4]

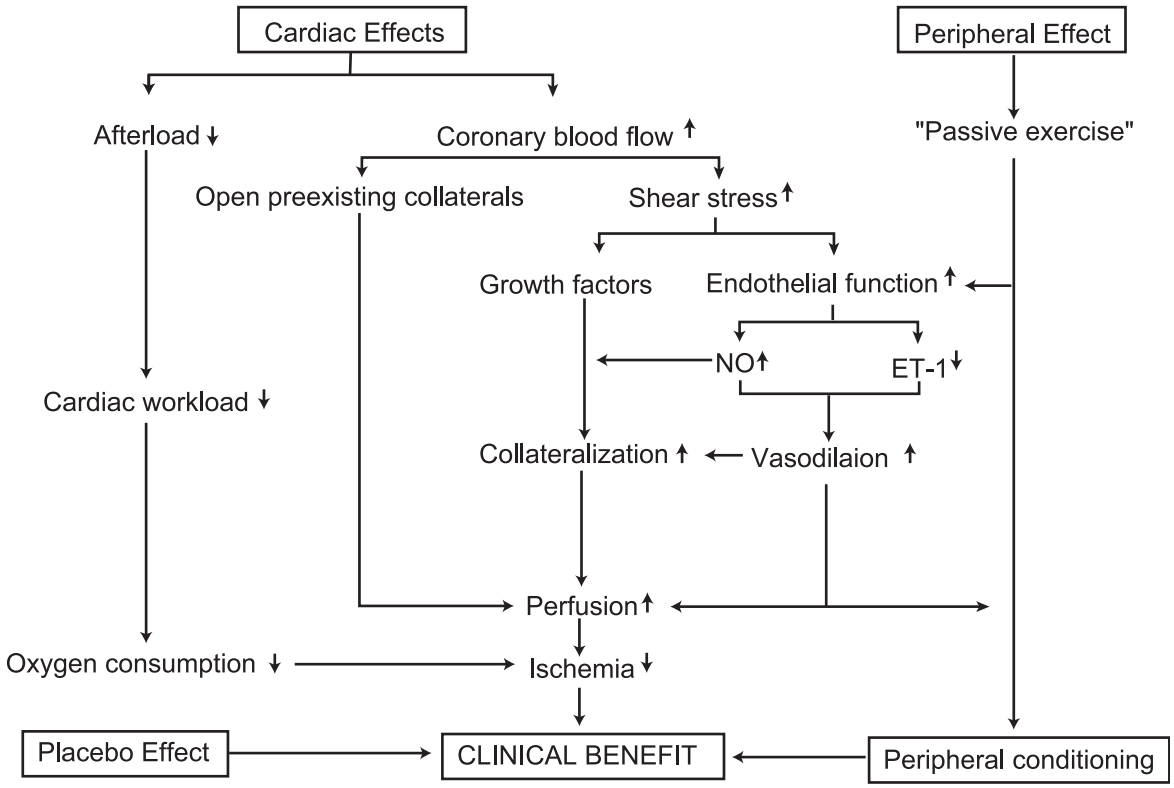

Fig.-2: *Possible mechanisms responsible for the clinical benefit associated with EECP. By increasing coronary blood flow, EECP is thought to promote myocardial collateralization via opening of pre-formed collaterals. Increased blood flow and shear stress may also improve coronary endothelial function favoring vasodilation and myocardial perfusion. Besides a peripheral training effect, a minor placebo effect is considered to contribute to the symptomatic benefit of EECP. ET= Endothelin; NO = Nitric Oxide.Adapted from Bonetti, et al.[25]*

Effect on ventricular function:
By reducing afterload and promoting venous return, EECP enhances cardiac output upto 25%.[46-47] However, increase in venous return raised the concern of inducing pulmonary edema in patients of heart failure and impaired left ventricular function. EECP impart beneficial effects on ventricular function by reducing atrial nitriuretic factor and brain nitriuretic factor.[37]

Non specific placebo effect:
Many patients experience significant improvement, even in absence of optimal diastolic augmemtation during treatment, indicates a placebo effect.[48]

Why the effects of treatment with EECP may be sustained:
It is postulated that the repeated and pulsed increases in diastolic pressure during therapy with EECP may enhance or stimulate the opening of collateral channels in the coronary vascular system, increasing perfusion of ischemic areas. Presumably, it is these newly opened collateral arteries that produced the sustained benefit that ECP provides to individuals after the ECP sessions are complete. Data from the follow-up studies at Stony Brook, demonstrate that some of these patients have had initial and sustained (3-year) improvement in myocardial perfusion of ischemic areas as demonstrated through thallium-201 imaging, and suggest that these patients may have responded to therapy with EECP through enhanced coronary collateral development or function.

Where to use:
Patients with angina [NYHA Class III or IV] or angina equivalents in whom there is failure, contraindication or intolerance to pharmacological management and who is not a candidate for angioplasty or revascularization or has undergone angioplasty or revascularization and continues to be symptomatic.[49-50] Heart failure patients in a euvolemic state with ischemic or idiopathic cardiomyopathy (EF <35%) are recomanded for EECP.[49,51,52]

It has been postulated that this collateral development is dependent upon the patency of neighboring vessels. It appears that an open non-obstructed conduit, either via native coronary flow or via bypass graft, provides the milieu for greatest benefit from EECP thus placing greater importance in the angiographic findings in patients in predicting who will benefit most from this treatment.[6]

Where not to use:
It is important to point out that EECP therapy is not for everyone. It is not recommended in patients with peripheral vascular disease or severe lower extremity vaso-occlusive disease, significant aortic insufficiency, significant unprotected left main disease, overt congestive heart failure, arrhythmias that interfere with machine triggering. Other contraindications are bleeding diathesis (including INR>2.0), active thrombophlebitis or deep vein thrombosis, presence

Table-I
Observed Clinical Effects of ECP

Biochemical Markers	Functional Measures	Clinical Outcome
Increase in Nitric Oxide levels	Increase in Time to ST depression	Improvements in CCS** Angina Class
Decrease in Endothelin levels	Increase in exercise tolerance	Reduction in Anginal episodes
Decrease in BNP levels	Improvement in peak Oxygen consumption	Reduction in use of Nitrates
Increase in VEGF levels	Increase in Cardiac Contractility	Improvement in 'Quality of Life'
	Reduction in systemic vascular resistance	Clinical benefits sustained long-term
	Decrease in peak systolic Pressure	** Canadian Cardiovascular Society
	Increase in ejection fraction	
	Increase in cardiac output	
	Increase in intracoronary Pressure and Blood flow velocity	

of a documented aortic aneurysm requiring surgical repair, pregnancy, B.P >180/110 mm Hg or a heart rate >120 beats /min.. For anyone else, however, the procedure seems to be quite safe.

Side Effects:

No major side effects or complications are reported yet. Common side effects are leg or waist pain, mild headache,mild dizziness,fatigue ,muscle aches,pressure sores, skin irritation, bruising or eccymosis in patients using coumadin when INR is not adjusted.[53-54]

Clinical outcome:

EECP and Angina:

Although most of the studies on EECP showed positive clinical response in patient with RAP, there was a question of biasness, since these studies were not double blind and good control groups were lacking. But the Multicenter Study of Enhanced External Counterpulsation(MUST-EECP study), a randomized, double blind, sham control trial, showed about two-thirds of the people receiving EECP benefited from the treatment . This study randomly assigned 139 people with angina from seven US hospitals to receive either active EECP or a placebo (inactive) procedure for 35 hours over four to seven weeks. Compared with the people who received the placebo procedure, those who completed the active EECP sessions had significantly less angina and tended to need fewer nitroglycerins. Also, people who received the active EECP were able to exercise longer before experiencing chest pain. Ten people dropped out of the study because of adverse events – half of them because of leg pain or chafing.[12]

International EECP Patient Registry (IEPR) enrolled 7,500 patients in more than 100 international centers. The treatment outcome (decrease in anginal symptoms and nitroglycerin usage, improvement in quality of life) reported by the IEPR confirmed those seen in MUST-EECP study. Moreover, follow-up data revealed that the clinical benefits are sustained for 5 years in patients with favorable initial clinical response.[15, 55-57]

In 2007, the American College of Cardiology/ American Heart Association (ACC/AHA) Task Force on Practice Guidelines updated the UA/ NSTEMI guideline. After discussing other anti-ischemic therapies it stated "Other less extensively studied therapies for the relief of ischemia, such as spinal cord stimulation and prolonged external counterpulsation are under evaluation. These have not been applied in the acute setting for UA/ NSTEMI".[58]

The ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) 2005 practice guideline for percutaneous coronary intervention states that ECP appears to decrease symptoms in patients with refractory angina who have no vessels suited for revascularization.[59]

The American College of Physicians clinical practice guideline for the primary care management of chronic stable angina and asymptomatic suspected or known CAD stated that ECP should be used only in patients who cannot be managed adequately by medical therapy and who are not candidates for interventional or surgical revascularization.[60]

The European Society of Cardiology views EECP therapy as an interesting modality available for treatment of RAP with more clinical trials needed to define its role in treating RAP.

ECP for Heart Failure:

Heart failure is a clinical syndrome resulting from impaired ability of the heart ventricles to fill or eject blood. Most patients with heart failure have impaired left ventricle (LV) function, or systolic dysfunction, although diastolic dysfunction is common. Therapy for CHF depends on the stage of the disease. Early stage therapy includes lifestyle modification. Late-stage CHF is treated by either cardiac transplant or supportive care.

Because ECP increases right ventricular filling pressure by augmenting venous return during diastole, it was thought that ECP therapy in patients who had left ventricular dysfunction and heart failure would be contraindicated. Studies have concluded that arterial hemodynamic effects of ECP are similar to those of intra-aortic balloon counterpulsation with similar diastolic augmentation and decreased afterload.

Soran et al. (2006) used IEPR data to evaluate the two-year outcomes of patients (n=363) who had severe LV dysfunction treated with ECP for angina pectoris. Immediately post-ECP therapy, 77% of the patients improved more than one angina class, and 18% had no angina. At two years, 73% (n=265)

of the patients completed follow-up, and 55% had sustained improvement in angina class. At baseline, 58% improved quality of life compared to 63% at two-year follow-up. This study had no control group to assess outcomes.[61]

The PEECH study[62] compared ECP to protocol-defined pharmacologic therapy (PT) or PT alone in 187 patients with NYHA functional class II–III heart failure with EF d" 35% of ischemic or idiopathic etiology, and PT consisting of angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker (for at least one month) and a beta-blocker (for at least three months) unless they were not tolerated (Feldman, et al., 2006). Two co-primary end points were predefined: the percentage of subjects with a 60-s or more increase in exercise duration and the percentage of subjects with at least 1.25 ml/min/kg increase in peak volume of oxygen uptake (VO2) at six months. Patients who were randomly assigned to receive ECP received 35 one-hour sessions over a period of seven to eight weeks. Patients were seen in follow-up at one week, three months, and six months after treatment. By the primary intent-to-treat analysis, 35% of subjects in the ECP group and 25% of control subjects increased exercise time by at least 60-s ($p=0.016$) at six months. However, there was no between-group difference in peak VO2 changes. NYHA functional class improved in the active treatment group at one week ($p<0.01$), three months ($p<0.02$), and six months ($p<0.01$). The Minnesota Living with Heart Failure score improved significantly one week ($p<0.02$) and three months after treatment ($p<0.01$).

Fewer patients completed the study in the active treatment group (76%) than in the control group (86%), largely due to more patients in the ECP group discontinuing therapy due to an adverse experience (11.8% ECP versus 3.2% PT). Adverse events that occurred in relation to the application of ECP therapy resulting in discontinuation include sciatica (one patient), leg pain (one patient), and arrhythmia, which interfered with application of the therapy (two patients). One other ECP subject suffered a non–Q-wave myocardial infarction during the treatment period not attributable to the therapy. During the follow-up period, six additional subjects from the ECP group discontinued due to worsening heart failure. Adverse events in the control group leading to discontinuance included two deaths during the treatment period and one instance of atrioventricular block during the follow-up period. The authors state the number of predefined clinical events that occurred during the trial was not different between the group of patients who received ECP and those in the control group. The number of adverse events and the number of serious adverse events were equal in the two treatment groups. In a prospective cohort study, Lawson et al. (2005) studied the immediate and one-year benefit from ECP in angina patients with diastolic versus systolic heart failure (n=746). Regardless of the degree of left ventricular dysfunction, ECP benefited anginal symptoms in heart failure patients. However, more rigorous evaluation of the impact of ECP on clinical outcomes will require a randomized trial. Lawson et al. (2001) analyzed ECP results of 1957 patients, 548 (28%) of whom had histories of CHF at baseline; all 1957 patients were reassessed at six months. Immediately after ECP, 68% of the CHF cohort demonstrated a CCS class improvement of one or more levels, and 0.9% demonstrated a worsening in functional class. The improvement was maintained over the six-month period. In addition, 58% felt their overall health had improved, and 55% felt their quality of life had improved. The mean improvement in CCS functional angina class was less in the CHF cohort than in the non-CHF cohort, and the CHF cohort was significantly more likely to discontinue treatment, generally due to exacerbation of CHF symptoms.

The Cardiomedics External Counterpulsation Patient registry used relevant heart failure outcomes to study a patented graduated-pressure treatment regimen. The patients (n=127) had angina and heart failure NYHA class III–IV. The CardiAssist device was used with gradual increasing pressure applied over a seven-week period. The use of lower pressure was thought to prevent heart failure exacerbation.

Patients were divided into three groups based on their low/mid/high diastolic to peak systolic pressure (D/S) ratios. For angina patients, the most effective D/S ratio is thought to be 1.5–2.1 which may be too high for heart failure patients. The

study is limited due to lack of a control group and the small populationn.[63]

In 2002, Soran et al. reported on an uncontrolled feasibility study of ECP as treatment for CHF in 26 patients. The study suggests that the treatment was safe and well tolerated. Based in part on the results of this study, a multicenter, prospective, randomized, controlled clinical trial, the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH), was launched.

The 2005 ACC guidelines for the evaluation and management of chronic heart failure in the adult state that early trials of ECP therapy in patients with heart failure and low EF have been encouraging, but until more data is available, routine ECP use for the management of patients with symptomatic reduced LVEF is not recommended (Hunt, 2005). The ACC commented to the Center for Medicare & Medicaid Services (CMS) that they agree with their March 2006 coverage decision to not cover ECP therapy for heart failure.[64]

ECP for other Indications:

Taguschi et al.[65] studied 60 minutes of ECP treatment for a physiological comparison to intra-aortic balloon pump following acute myocardial infarction (MI). This study did not provide information about the effect of ECP on clinical outcomes. Werner et al.[66] performed a prospective, randomized study of 20 patients with acute central retinal artery occlusion (CRAO) or branch artery occlusion (BRAO). ECP accelerated recovery of perfusion in ischemic retinal areas, but too few patients were included to draw conclusions regarding efficacy and safety.

Conclusion:

External counterpulsation (ECP) has got clearance by the U.S. Food and Drug Administration (FDA) to treat stable or unstable angina pectoris, and heart failure. Enhanced external counterpulsation therapy is a valuable outpatient procedure providing acute and long-term relief of anginal symptoms and improved quality of life among this group of patients. But it is not an altenative therapy to conventional revascularization; rather it could be regarded as an adjunctive therapy.

Conflict of interest - None

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