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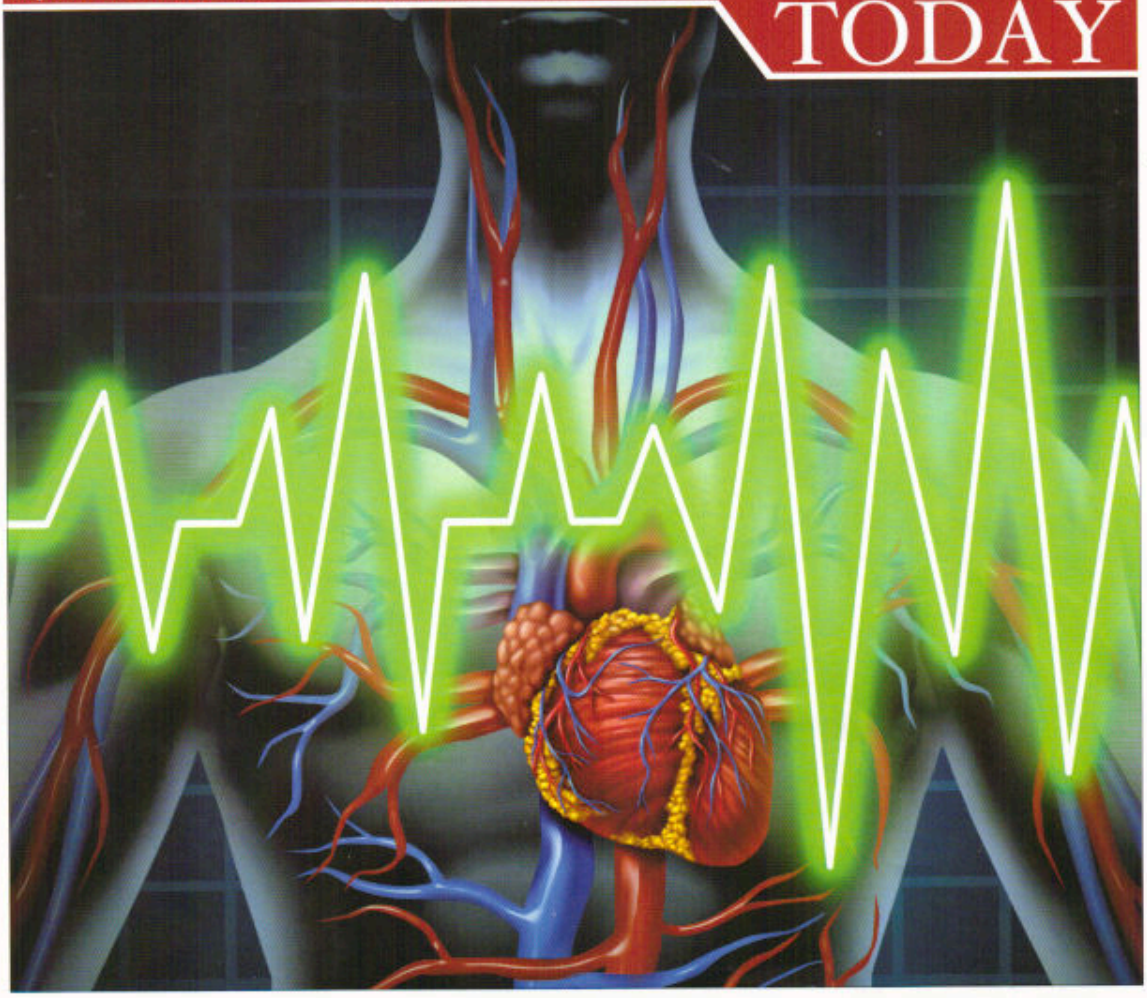

Review Article

Cardiovascular Disease Protection and Regenerative Potential of Enhanced External Counter Pulsation Therapy

Dr. S. Ramasamy, Dr. Pradeep G. Nayar, Dr. M. Chokkalingam, Dr. C. Arumugham, Dr. N. Ganesh

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REVIEW ARTICLE

Cardiovascular Disease Protection and Regenerative Potential of Enhanced External Counter Pulsation Therapy

S. RAMASAMY, PRADEEP G. NAYAR, M. CHOKKALINGAM, C. ARUMUGHAM, N. GANESH

Keywords
- cardiovascular
- enhanced external counter pulsation
- endothelial dysfunction
- atherosclerotic

Due to the significant rise in cardiac risk factors like diabetes, hypertension, and dyslipidaemia, in both urban and rural areas, reducing morbidity and mortality due to coronary artery disease (CAD) is the greatest challenge faced by the cardiologists. The current medical management of CAD includes antiplatelets, β-blockers, angiotensin-converting-enzyme (ACE) inhibitors and statin therapy. Along with medical therapy, the diet, exercise and lifestyle modification provide an added advantage in CAD treatment. Currently, enhanced external counter pulsation (EECP) therapy is a non-invasive, daycare treatment option for patients with refractory angina and heart failure. This article reviews the effect of this cyclic ECG synchronized rhythmic increased blood flow benefit to the cardiovascular system.

INTRODUCTION

Coronary artery disease (CAD) management is one of the major problems for the health care providers and policy makers in our country. Due to the significant rise in cardiac risk factors like diabetes, hypertension, and dyslipidaemia, in both urban and rural areas, reducing morbidity and mortality due to CAD is the greatest challenge faced by the cardiologists. The current medical management of CAD includes antiplatelets, β-blockers, angiotensin-converting-enzyme (ACE) inhibitors and statin therapy. Along with medical therapy, the diet, exercise and

Dr. S. Ramasamy is EECP Consultant, Dept of Cardiology at Dr. K. M. Cherian's Frontier Lifeline Hospital, Chennai; Prof. Dr. Pradeep G. Nayar is the Chief Cardiologist and Associate Professor Dr. M. Chokkalingam, Dr. C. Arumugam, Dr. N. Ganesh are Cardiologists at Dept. of Cardiology Chettinad Academy of Research and Education, Kanchipuram

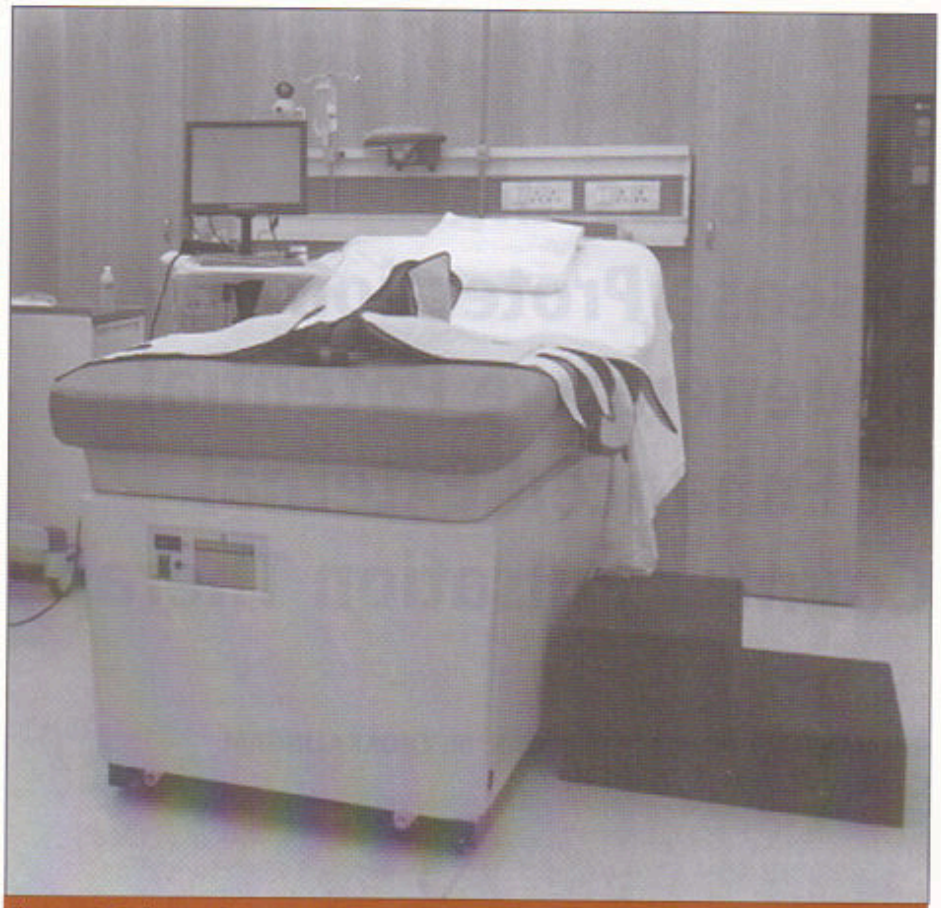


Figure 1. Enhanced external counter pulsation treatment station

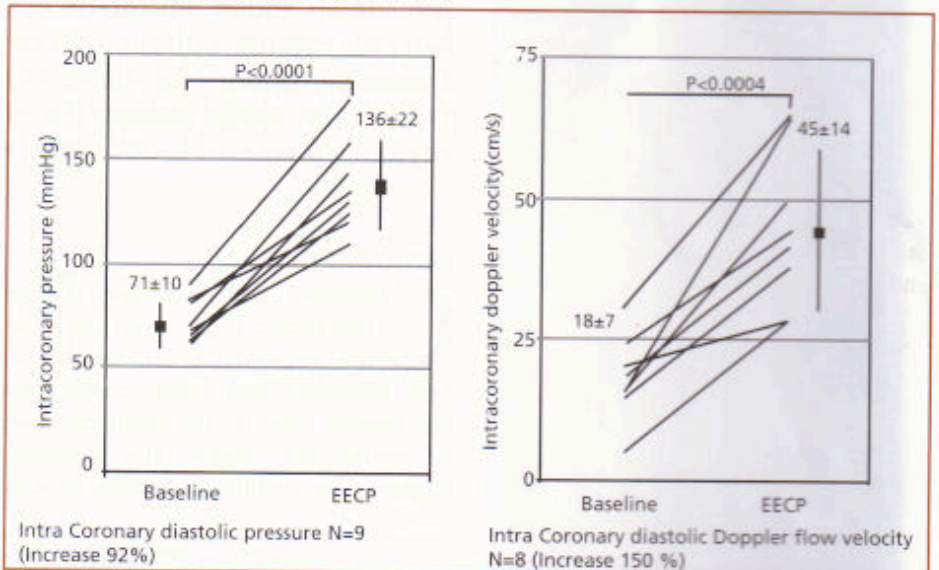
lifestyle modification provide an added advantage in CAD treatment. Coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), even though reduce ischemic burden and improve exercise tolerance and quality of life, they don't modify or alter the atherosclerotic disease progression. Their role in patients with chronic stable angina beyond ischemic symptoms reduction is still debated.[1-6]

Currently, enhanced external counter pulsation (EECP) therapy is a non-invasive, daycare treatment option for patients with refractory angina and heart failure.[7-10] The treatment works by promoting angiogenesis in coronary vascular bed[11-13] and improving endothelial function. The overall effect of EECP in CAD management is an emerging field of interest.

ENHANCED EXTERNAL COUNTER PULSATION THERAPY

Enhanced external counter pulsation therapy system (Figure 1) consists of three sets of inflatable pressure cuffs similar to the blood pressure cuffs which are wrapped around the calf muscles, the lower and upper thigh muscles. The cuffs are rapidly and sequentially inflated with microsecond precision based on ECG trigger mechanism, starting from the lower calf and proceeding upward to the upper thigh during the diastolic phase of each cardiac cycle. The pressure in the cuffs reach around 260-300 mmHg creating a strong arterial compression stimulating a retrograde flow towards the heart during the diastole when the aortic valve is in closed position and thereby significantly increasing blood flow to the coronary arteries at a time when coronary vascular resistance is at its lowest level. The inflation of the cuffs also increases the retrograde venous blood flow to the right side of the heart, providing greater ventricular filling and cardiac output.[14,15] During the systole when the heart begins to contract, all three cuffs simultaneously deflate, which significantly reduces the total peripheral vascular resistance leaving the heart to empty the stroke volume in to relatively lesser resistant peripheral vessel and thereby significantly reducing the afterload of the heart and the cardiac muscle oxygen demand (MVO_2).

Patients during EECP treatment are exposed to the repeated timed cyclic inflation/deflation of the cuffs. This is monitored and coordinated constantly by a microprocessor that interprets electrocardiogram signals and the trained physician to adjust the inflation and deflation timing manually whenever it's required. This article will review the



Intra Coronary diastolic pressure N=9 (Increase 92%)

Intra Coronary diastolic Doppler flow velocity N=8 (Increase 150 %)

Figure 2. Intra coronary pressure and flow velocity during EECP treatment

effect of this cyclic ECG synchronized rhythmic increased blood flow benefit to the cardiovascular system.

EECP ACUTE HAEMODYNAMIC AND EXERCISE TRAINING EFFECT

During EECP treatment, the pressure given in the lower extremities results in significant change in haemodynamics in central circulation. A study has demonstrated that optimal cuff pressure achieved during EECP will increase coronary perfusion pressure and velocity in coronary vascular bed measured by catheter sensor-tipped guide wire.[16]

The coronary peak diastolic pressure increase 93% form baseline 71±10 mmHg to 137±21 mmHg (P<0.0001) and mean intracoronary pressure increase 16% from baseline 88±9 mmHg to 102±16mmHg (P=0.006) with decrease in systolic pressure 15% from baseline 116±22 mmHg to 99±26 mmHg. Similarly the intracoronary average peak velocity measured by intra coronary Doppler increases by 109% from baseline 11±5 cm/sec to 23±5 cm/sec. The peak diastolic flow velocity increases by 150% from the baseline (Figure 2).

This increased pressure and velocity in circulation is not only experienced in coronary vascular bed but also by the entire systemic vascular system. This exposes the vascular endothelium lining to shear stress, which is a friction caused by flowing blood to the endothelial wall of the arteries. EECP augments shear stress, which is equivalent to moderate to vigorous physical exercise.[17] In animal model it is shown that EECP can increase the blood flow velocity by 132% and the endothelial sheer stress more than >200%.[18] In human models it is shown that EECP can increase antegrade brachial endothelial shear stress up to 75% and retrograde popliteal endothelial shear stress by 402%.[19] Also the cuff pressure has shown to cause 4-fold increases in posterior tibial artery pulsatility index and reactive hyperemia leading to significant dilatation of the posterior tibial artery after one hour of EECP therapy.[20] This shows significant reduction in peripheral vascular resistance, which is safe in patient with peripheral vascular disease. During EECP, the entire cardiovascular system along with major organs are exposed to dual blood supply and shear stress, once during augmented systole due to increase cardiac output achieved by increase in preload and again during diastole due to diastolic augmentation achieved by cuff inflation synchronized to ECG. This overall vigorous exercise type training effect during EECP is beneficial in the symptomatic patient who has restricted activity and cannot exercise due to their severe symptoms. During EECP based exercise training, the patients are not exposed to the risk for vigorous exercise training,[21-23] since during treatment his heart rate, blood pressure, double product and MVO_2 are not raised. In contrary, EECP works as a passive exercise program by decreasing the MVO_2.

Lawson in his study has demonstrated the exercise training effect due to 35 sessions of one hour EECP treatment.[24] Normal exercise haemodynamic response is increase in heart rate, blood pressure and double product (heart rate x systolic blood pressure). Lawson in his study showed patient who responded to EECP had improved exercise tolerance in treadmill and improved myocardial perfusion assessed by radionuclide stress perfusion imaging. They were able to achieve this without significant increase in blood pressure and double product with lower than expected heart rate increase. All patients have shown significant improvement in myocardial perfusion which can explain patient symptoms improvement and improved exercise tolerance blunting the normal exercise haemodynamics. It is the result of both improvement in myocardial perfusion (demonstrated by improved stress radionuclide perfusion) and decrease in peripheral vascular resistance similar to exercise training effect.

Interestingly 20% of the patients who have not shown improvement in stress radio nucleotide perfusion, did not show improvement in exercise duration but show significant decrease in double product post EECP. This explains that even in non-responders, in whom improved perfusion cannot be demonstrated, EECP exerts the exercise training effect. But resulting exercise training effect by reducing peripheral vascular resistance alone may not be able to improve the exercise tolerance unless accompanied by improved myocardial perfusion.

Stys and his colleagues conducted a large multi-centre study of 175 patients.[12] Some centres in the study group performed the same level of exercise pre- and post-EECP treatment. In this group, 81 of 97 patients (83%) had significant improvement in radionuclide perfusion treadmill stress test (RPST) perfusion defects. Other centres performed RPST post-EECP to a maximal cardiac workload. In this group, 42 of 78 patients (54%) showed improvement in RPST defects, 33 (42%) patients had unchanged RPST and 3 (4%) patients revealed worsening of RPST. Interestingly, the patients who underwent RPST at same level of cardiac work load, showed significantly lowered double product similar to Lawson study[24] and patients who underwent RPST at maximal cardiac work load showed no significant change in double product, indicating that myocardial demand is not altered so the decrease in ischemic area is due to increase myocardial perfusion via angiogenesis and recruitment of dormant collaterals. The improvement in myocardial blood flow by collateral growth (arteriogenesis) is further confirmed by 2 randomised control trials by measuring pressure derived collateral flow index (CFIp) and pressure derived fractional flow reserve (FFR) - both improved significantly in EECP treatment group while no change in sham group.[25,26]

Campbell evaluated the acute and chronic effect of EECP in systolic and diastolic blood pressure in 108 consecutive patients to determine the blood pressure reduction and exercise training effect due to change in peripheral vascular resistance.[27] The pressure at baseline, at the end of each EECP session, at the end of complete course of EECP and 6 week after the completion of the final EECP session were measured. The patient baseline systolic blood pressure was stratified in the following groups ≤100 mmHg (n=16), 101 to 110 mmHg

(n=26), 111 to 120 mmHg (n=20), 121 to 130 mmHg (n=27), 131 to 140 mmHg (n=7), and ≥141 mmHg (n=12). The baseline diastolic blood pressure was then stratified in to following groups ≤60 mmHg (n=37), 61-70 mmHg (n=39), 71-80 mmHg (n=22) and ≥ 81 mmHg (n=10). EECP has differential response to systolic and diastolic blood pressure based on the baseline measurement. EECP significantly lowered the SBP in each baseline stratum from 101 to ≥141, whereas in the lowest stratum (<100 mmHg) a rise in systolic blood pressure was observed after completing a course of EECP and 6 week after EECP. The diastolic pressure change in each baseline stratum from 61 to ≥81 mmHg is similar to that of the systolic pressure observed in both after completing a course of EECP and 6 weeks after EECP. The raise in diastolic pressure in the observed in lowest stratum (≤60 mmHg) is also similar to the systolic blood pressure after completion of treatment and after 6 weeks of the treatment.

The reduction of systolic blood pressure after completion of every one hour session, and maintained up to 6 week post EECP, explains the exercise training effect due to EECP is sustained long term. This observation can also be used to assess the correct application of inflation and deflation timing so that to achieve the reduction in peripheral vascular resistance during each one hour session. The increase in systolic blood pressure in patient with systolic pressure ≤100 mmHg and increase in diastolic pressure in diastolic pressure ≤60mmHg shows EECP is safe in patient with hypotension. This finding also support the possibilities that patient with heart failure and low cardiac output EECP is safe and may improve the cardiac output.

EECP AS REGENERATIVE THERAPY

Progenitor cells are similar to stem cell but have already differentiated to become specific target cells, while stem cell has the potential to differentiate to any cell type. Regenerative potential endothelial progenitor cells (EPCs) are usually seen in circulation, bone marrow and adhering to the vessel wall. The levels are usually low in the presence of vascular risk factors and established coronary artery disease.[28-30] Ischemia is a very potent stimulant to increase endothelial progenitor cells (EPCs) in circulation.[31] It has been well established that exercise therapy shown to increase the peripheral circulation of EPCs.[32,33]

Since EECP mimics exercise effect in the vascular system by reducing peripheral blood pressure, Barsheshet and colleagues checked their hypothesis, whether external counter pulsation therapy can have similar effect in the circulating EPCs.[34] Overall, 25 patients with symptomatic coronary artery disease were recruited for the study; 15 patients were treated with external counter pulsation therapy and 10 patients served as a control group who refused the treatment. The numbers of EPCs were assessed by a flow activated cell sorter (FACS) and EPCs function was assessed by counting the number of colony forming unit (CFU). Blood sample were taken 1 week before and 1 week after in the treatment group and 9 week follow-up period in the control group. In the treatment group, angina score decrease from 3.0 to 2.0 (P<0.001), EPCs number assessed by FACS increased from 10.2 to 17.8/105 mononuclear cells (P<0.05), EPCs function assessed by CFU increase from 3.5 to 11.0 (P=0.01), brachial artery flow mediated dilatation (FMD) improved from 7.4 to 12.2% (P<0.001). Asymmetric dimethylarginine (ADMA) is a naturally occurring endogenous inhibitor of nitric oxide synthase and a marker of endothelial dysfunction decrease from 0.70 to 0.60 µmol/l (P<0.01). In the control group, all these parameter did not change during the follow-up. Interestingly both in treatment and control arm there is no significant change in vascular endothelial growth factor (VEGF) and C-reactive protein (CRP).

Kiernan and his colleagues studied the effect of EECP on circulating haematopoietic progenitor cells (HPCs) which are closely linked to angiogenesis.[35] They included 13 consecutive severe refractory angina patients who are on CCS class III-IV with advance age (mean: 71 years). They measured HPCs cell at baseline before commencement of EECP, early during the course of treatment, at the end of the treatment and one month after the completion of last session of EECP. HPCs level significantly rose during the treatment and maintained up to one month. The raise in HPCs count correlates with DASI a measure of functional status

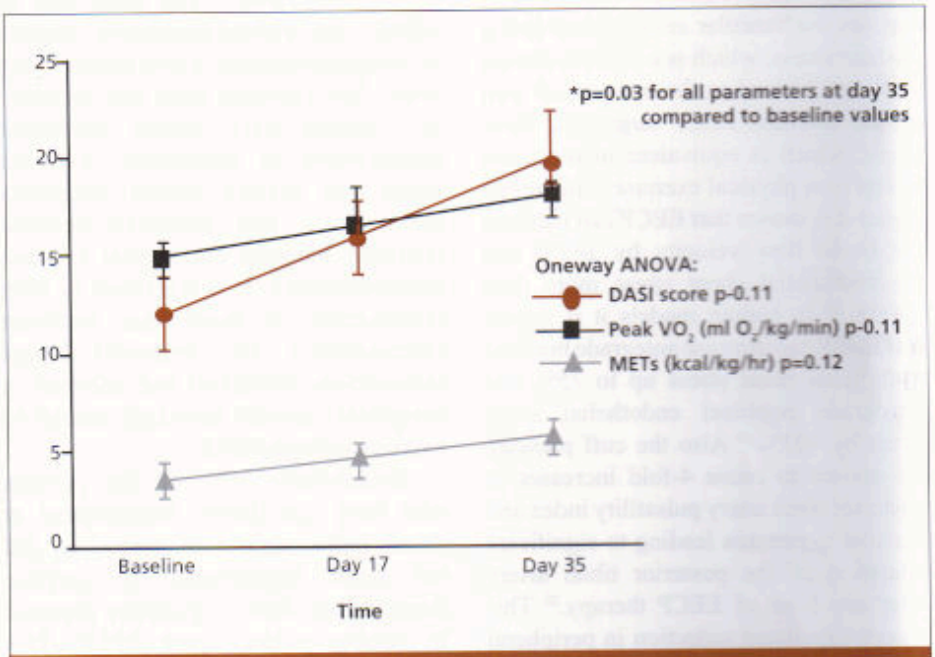


Figure 3. Effect of EECP treatment on DASI score, Peak VO_2 and METs at baseline, 17 days and 35 days

of the patient. Overall there is significant increase is DASI score (12±2 vs. 19±3), derived Maximum VO_2 (14.7±0.8 vs. 18.0±1.1), metabolic equivalents or METs (3.4±0.5 *vs.* 5.5±0.7), P=0.03 from baseline to completion of one hour sessions on EECP treatment (Figure 3).[35]

In another study of 9 patients with CAD by Jewell and co-workers,[36] they compared the baseline value of EPCS and HPCs before first day of treatment with 1st, 2nd and 4th week of treatment. After the 4th week, there was a significant increase in EPCs from 3.59±1.18 to 4.92±0.86 (P=0.014) and HPCs from 7.93±2.32 to 10.91±1.84 (P=0.008).

All these studies showed that external counter pulsation therapy increase the circulating EPCs and HPCS. The increase in the progenitor cells also correlated with the patient functional improvement, quality of life and brachial flow mediated dilatation (FMD). This absolute increase in FMD may be due to increased bio availability of nitric oxide (NO) and normalisation of endothelial function. The possible mechanism by which EECP may be able to achieve this result is by exerting shear stress on the vascular endothelium due to rhythmic compression of cuffs in lower extremities creating retrograde blood flow in femoral and aortic arteries and antegrade flow in brachial arteries. This shear stress can lead to mechanical dislodgment of progenitor cells from the bone marrow and from endothelial surface and significantly increase EPCS cells in circulation. These circulating cells may play important role in repairing the endothelial cells and myocardial cells and restoring them towards normalcy. This regenerative potential of EECP may help in post myocardial infarction period and in heart failure to augment the EPCs and HPC potential in repairing and homing in myocardial region with ischemia.

SHEAR STRESS AND ENDOTHELIAL RESPONSE

Endothelial dysfunction is an early finding in atherosclerotic vascular disease and later manifested as symptomatic cardiovascular disease. Endothelium is the type of epithelial cell, which form a monolayer protective and functional cover of the internal surface of arterial, venous and lymphatic blood vessels. Arterial endothelial cell regulates the vasomotor function by secreting vascular protective Nitric oxide a vasodilator and endothelin (ET-1) a potent vasoconstrictor. The imbalance between nitric oxide and endothelin (ET-1) secretion favouring vasoconstriction is characteristic of endothelial dysfunction. Endothelial dysfunction leads to increase arterial stiffness due to vasoconstriction, is believed to be the linking factor between various cardiac risk factors and how it exerts its effect in cardiovascular mortality and morbidity.[37,38] Endothelial dysfunction can be improved by physical exercise,[39] lowering cholesterol level,40 anti-oxidant,[41] ACE inhibitor,[42] hormone replacement therapy,[43] and L-arginine supplementation.[44]

One of the proven effects of EECP is its impact on vascular endothelial cells. The shear stress it causes can lead to change in endothelial function directly or mediated through progenitor cells which can repair or replace the endothelial cells. Increased shear stress created by EECP therapy has been demonstrated to increase nitric oxide, decrease endothelin (ET-1) and augment the vascular protective effect of the nitric oxide. The graded dose related increase in plasma nitric oxide and decrease in plasma endothelin-1 (ET-1) was not only changed during EECP but were also sustained 1 to 3 months after the completion of EECP therapy. This shows the improvement in endothelial function is long lasting even when the active stimulus is stopped.[45,46] The mechanism of how EECP increase nitric oxide level is seems to be mediated through increase gene expression of endothelial nitric oxide synthase (eNOS). This hypothesis was confirmed by Zhang and his co-workers.[47] In their study in 35 pigs randomly assigned to 3 groups, controlled with normal diet, high cholesterol diet and high cholesterol diet plus EECP. The eNOS protein was significantly reduced in the cholesterol group when compared to the control diet group. The eNOS protein level in the cholesterol plus EECP group was 3.16 times higher when compared to the cholesterol diet group.

In another study by Mayo clinic,[48] peripheral endothelial function was assessed by reactive hyperaemia – peripheral arterial tonometry (RH-PAT). This device measures the reactive hyperaemic response in finger. Reactive hyperaemia is dilatation of small vessels in the finger which is mediated by endothelial derived NO. This is an indicator for endothelial function. In this study, the RH-PAT index improved significantly from baseline, during the treatment, completion of treatment and maintained one month after the treatment. Another finding in the study is that, 26% of refractory angina high cardiac risk profile patients who did not show any change in symptoms also showed no significant improvement in the RH-PAT index. This corroborates the direct relation of endothelial function improvement and improvement in functional status of the patients. All these trails have uniformly shown that the effect of EECP treatment in endothelial function is maintained up to three months after completion of the last session of EECP. But long time follow-up study of EECP 35 hour's treatment clinical benefit has shown to last up to 3-5 years.[49-51]

IMPROVED ARTERIAL STIFFNESS

Increasing endothelial dependent NO level by shear stress is shown clearly as the mechanism of EECP's clinical benefit in patient with advanced coronary artery disease refractory to conventional medical and interventional treatment. Studies mentioned in detail in this review have shown that improved endothelial function may contribute towards reduction in arterial stiffness. Arterial stiffness is an independent predictor of cardiovascular mortality and morbidity.[52-55]

Nichols and co-workers tested their hypothesis that improvement in wave reflections, which is the determinant of central and peripheral arterial stiffness may explain the clinical benefit of EECP treatment.[56] Early wave reflection from the lower body with increase in amplitude and travelling velocity occur when the arteries are stiffer and less compliant. This wave reflection when arrives in the central artery during systolic phase will

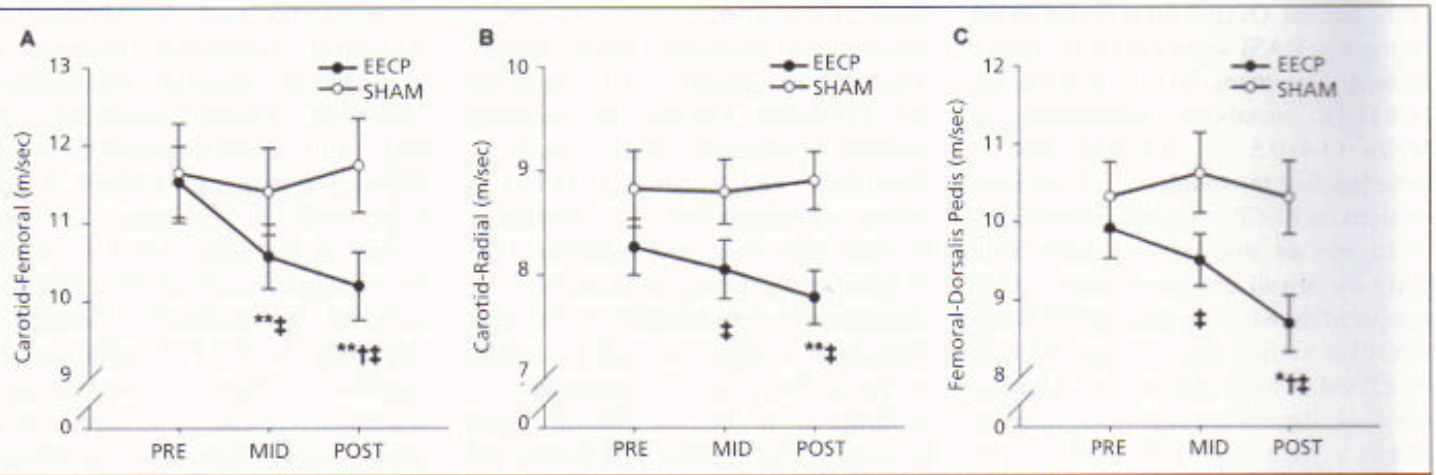


Figure 4. Pulse wave velocity (PWV) between the carotid and femoral artery; (A) carotid and radial artery, (B) femoral and dorsalis pedis artery, (C) before and after 17 (MID) and 35 sessions (POST) of EECP and Sham treatment
Data are mean±SEMs. *P<0.05 versus PRE; **P<0.01 versus PRE; †P<0.05 versus MID. ‡P<0.05 versus Sham.

augment the central aortic pressure and increase the left ventricular pressure and energy needed to eject the blood forward in to the aorta. This will increase the myocardial oxygen demand. This increase demand results in further sub endocardial ischemia in patient with epicardial stenosis where this increase demand may not be met with corresponding increase in supply due to obstructed path in the coronary artery.

In 20 patients with refractory angina having multi vessel disease, radial arterial tonometry using SphygmoCor device was used to assess the arterial stiffness and wave reflection characteristic. In this study, EECP treatment found to reduce both peripheral and central systolic and pulse pressure. There was also drop in mean and diastolic pressure. The treatment reduced amplitude and transmission velocity of the reflected wave from the major reflecting site from the periphery resulting in overall reduction in total arterial stiffness comprising both the elastic and muscular artery stiffness. The treatment also caused significant reduction in wasted left ventricular pressure and energy. This improvement in arterial stiffness translated in to significant improvement of 1 CCS class in 2 patients (10%), by 2 class in 17 patients (85%) and by 3 class in I patient (5%).

In another study by Casey and his colleagues, they overcome the present study limitation of being open label with no control group or placebo group with a new study. They conducted a randomised sham controlled study.[57] They included pulse wave velocity (PWV) to assess the central elastic artery stiffness by carotid-femoral PWV and peripheral muscular artery stiffness by carotid-radial PWV and femoral-dorsalis pedis PWV independently (Figure 4).

Augmentation index, a measure of reflected wave from the peripheral reflecting site expressed as percentage which is the determinant of both elastic and muscular artery stiffness, is also measured. They also measured peak oxygen uptake, total exercise duration, peak time to angina, angina episodes and nitroglycerine usage as both objective and subjective measurement to evaluate the patient clinical improvement. In treatment group there was a significant reduction in brachial and central systolic, diastolic and pulse pressure after 35 sessions. Mean arterial pressure decrease was achieved even with 17 sessions, while there is no change in any of the parameters in sham group. Carotid-femoral PWV decreased after 17th and 35th sessions, carotid-radial and femoral-dorsalis pedis PWV were decreased after 35 sessions and there was no change in central or peripheral PWV in sham group. The treatment also led to improvement in all clinical parameters with no change in sham group.

These findings on reduction in central elastic artery stiffness independent of pressure were also observed in another study by Levenson using high-resolution ultrasound echo-Doppler evaluation of the diameters of the common carotid artery.[58] Pressure independent β stiffness and carotid vascular resistance was significantly reduced and carotid blood significantly increased in the EECP treatment group in this study.

Decrease in arterial stiffness of both central elastic and peripheral muscular artery is mediated through shear stress and release of endothelial derived NO. The increased NO plays a major role in relaxation of smooth muscle tone both in elastic and muscular artery. Since the distribution of smooth muscle fibre are relatively few in elastic artery when compared to muscular artery, the decreased stiffness in large elastic artery may be due to both reduced smooth muscle tone or may possibly due to decrease in collagen or increase in elastin content.

In another landmark randomised control study by Martin and his co-workers in subjects with non-insulin dependent abnormal glucose tolerance,[59] they have reconfirmed improvement in flow mediated dilatation (FMD) in brachial artery (27%), popliteal artery (52%), increased plasma nitrite/nitrate (30%), and increase angiogenesis stimulating vascular endothelial growth factor (VEGF; 75%). First time it was shown that EECP treatment decreased fasting plasma glucose (FPG) up to 17 mg/dL which was 13.3% reduction similar to

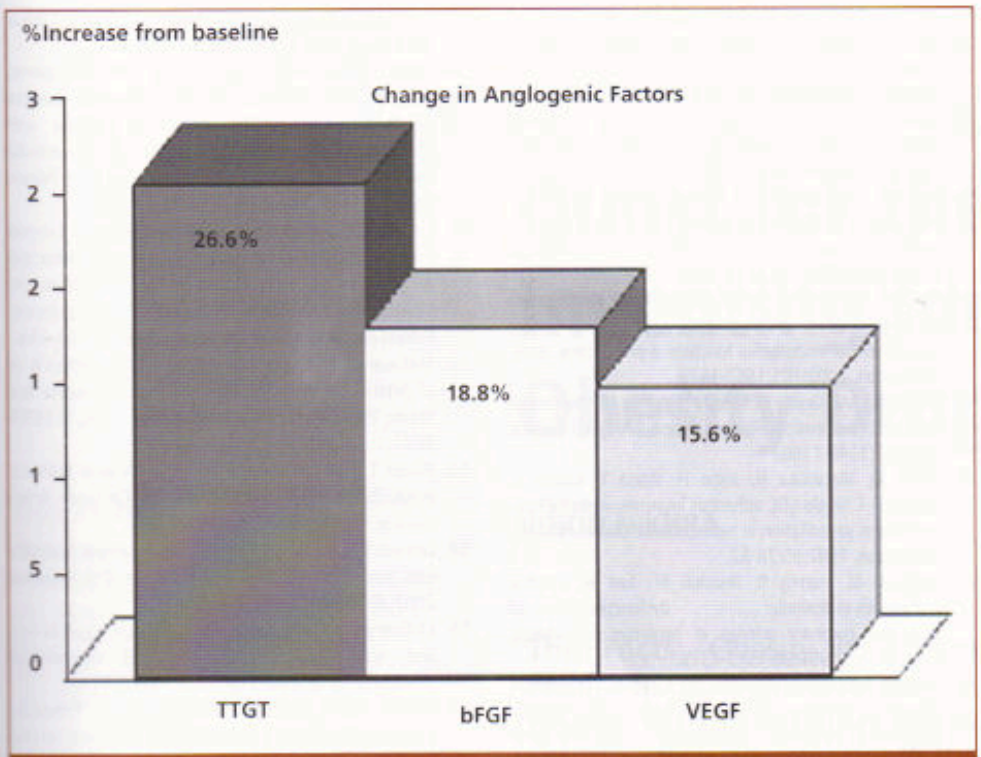


Figure 5. Percentage change of angiogenic factors in blood sample after 35 sessions of EECP

the level achieved by exercise training.[60] Surprisingly, this was achieved without any lifestyle modification[61] or weight reduction. Further, a 31% decline was seen in homeostasis model assessment of insulin resistance (HOMA-IR) value a marker of insulin sensitivity. EECP has been previously shown to improve myocardial perfusion by recruiting the dormant collaterals and by stimulating angiogenesis, mediated through increase in vascular endothelial growth factor (VEGF -15.6%), hepatocyte growth factor (HGF-26.6%), and basic fibroblast growth factor (b FGF -18.8%) (Figure 5).[62]

Current review shows the overall clinical benefits correlate well with improving endothelial function and decreasing arterial stiffness thereby reducing left ventricular load and myocardial oxygen demand. The cardiovascular effect of EECP is mediated both through central increase in supply and peripheral decrease in demand.

CONCLUSION

Enhanced external counter pulsation therapy has many cardiovascular protective actions similar to moderate to intense aerobic exercise. The rapid repetitive, inflation and deflation causes cyclic strain and stretch effect in central and peripheral arteries resulting in recruitment of progenitor cells from its reserve and mediating endothelial cell repair. The shear stress caused due to increased flow velocity and pressure results in improving the endothelial function by increasing nitric oxide (NO) level by up regulating the expression of NO synthase and decreasing endothelin (ET-1) level. This improved endothelial function may be responsible for increase plasma VEGF concentration and leads to increased coronary blood flow. EECP not only improve symptoms and quality of life in patient with coronary artery disease but has shown to protect and repair the vascular damages. This mechanism of action may possibly arrest or decrease the progress of atherosclerotic disease progression. This shows EECP therapy rather than to treat end stage coronary artery disease, may be used as vascular protective treatment for patient with endothelial dysfunction.

REFERENCES

1. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet. 1997;350:461-468.
2. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol. 2003;42:1161-1170.
3. Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004;43:1743-1751.
4. Boden WE, O'Rourke RA, Teo KK, et al. Optimal Medical Therapy with or without PCI for stable coronary disease. N.Engl J Med. 2007;356:1503-1516.
5. Frye RL, August P, Brooks MM, et al. BARI 2D Study Group: A Randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009;360:2503-2515.
6. Hueb W, Lopes N, Bernard J, et al. Ten-Year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): A Randomized Controlled Clinical Trail of 3 therapeutic strategies for Multivessel Coronary Artery Disease. Circulation. 2010;122:949-957.
7. Lawson W, Hui JK, Soroff HS, et al. Efficacy of Enhanced External Counterpulsation in the treatment of Angina Pectoris. Am J Cardiol. 1992;70:859-862.
8. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol. 1999;33:1833-1840.
9. Feldman AM, Marc A. Silver MA, et al. Varricchione T for the PEECH Investigators. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1198-205.
10. Abbottsmith CW, Chung ES, Varricchione T, et al. Feldman AM; Prospective Evaluation of EECP in Congestive Heart failure (PEECH) Investigators. Enhanced external counterpulsation improves exercise duration and peak oxygen consumption in older patients with heart fail: a subgroup analysis of the PEECH Trial. Congest Heart Fail. 2006;12:307-311.
11. Lawson WE, Hui JCK, Soroff HS, et al. Efficacy of Enhanced External Counterpulsation in the Treatment of Angina Pectoris. Am J Cardio.1992;70:859-862.
12. Stys TP, Lawson WE, Hui JC, et al. Effects of enhanced external counterpulsation on stress radionudide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardio.l 2002;89:822-824.
13. Tartaglia J, Stenerson R, Charney S, et al. Exercise capability and myocardial perfusion in chronic angina patients treated with enhanced external Counterpulsation. Clin Cardiol. 2003;26:287-290.
14. Stys T, Lawson WE, Hui JCK, Lang G, Liuzzo J, Cohn PF. Acute Hemodynamic Effects and Angina Improvement with Enhanced External Counterpulsation. Angiology. 2001;52:653-658.
15. Krishnamurthy S, Simandl S, Lawson WE, et al. Maximizing the Hemodynamic Benefit of Enhanced External Counterpulsation. Clinical Cardiology. 1998;21:649-653.
16. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. Circulation 2002;106:1237-1242.
17. Niebauer J, Cooke JP. Cardiovascular effects of exercise: role of endothelial shear stress. J Am Coll Cardiol. 1996;28:1652-1660.
18. Shantsila E, Watson T, Lip GY. Endothelial progenitor cells in cardiovascular disorders. J Am Coll Cardiol. 2007;49:741-752.

19. Gurovich AB, RW. Three –dimension blood flow classification scheme better describes NO-mediated arterial vasodilation. (Abstract) Med Sci Sports Exerc. 42:7,2011.
20. Werner D, Michalk F, Hink B, et al. Impact of Enhanced External Counterpulsation on peripheral circulation. Angiology. 2007;58;185.
21. Haskell WL. Cardiovascular complications during exercise training of cardiac patients. Circulation. 1978;57:920-924.
22. Van Camp SP, Peterson RA. Cardiovascular complications of outpatient cardiac rehabilitation programs. JAMA. 1986;256:1160–1163.
23. Digenio AG, Sim JG, Dowdeswell RJ, Morris R. Exercise-related cardiac arrest in cardiac rehabilitation: the Johannesburg experience. S Afr Med J. 1991;79:188-191.
24. Lawson WE, Hui JC, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology. 1996;87:271-275.
25. Gloekler S, Meier P, de Marchi SF, et al. Coronary Collateral Growth by External Counterpulsation: a randomised controlled trail. Heart. 2010;96:202-207.
26. Buschmann EE, Utz W, Pagonas N, et al. Improvement of fractional flow reserve and collateral flow by treatment with external counterpulsation (Art.Net.-2 Trial) European Journal of Clinical Investigation. 2008/2009;39(10):866-875.
27. Campbell AR, Satran D, Zenovich AG, Campbell KM, Espel JC, Arndt TL, Poulose AK, Boisjolie CR, Juusola K, Bart BA, Henry TD. Enhanced external counterpulsation improves systolic blood pressure in patients with refractory angina. Am Heart J 2008;156:1217-22.
28. Werner N, Nickenig G. Clinical and therapeutical implications of EPC biology in atherosclerosis.J Cell Mol Med. 2006;10:318-332.
29. Fadini GP, de Kreutzenberg S, Agostini C, et al. Low CD34+ cell count and metabolic syndrome synergistically increase the risk of adverse outcomes. Atherosclerosis. 2009;207:213-219.
30. Vasa M, Fichtlscherer S, Aicher A, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors forcoronary artery disease. Circ Res. 2001;89:E1-7.
31. Hristov M, Erl W, Weber PC. Endothelial progenitor cells: mobilization, differentiation,and homing. Arterioscler Thromb Vasc Biol. 2003;23:1185-1189.
32. Rehman J, Li J, Parvathaneni L, et al. Exercise acutely increases circulating endothelial progenitor cells and monocyste-/macrophage-derived angiogenic cells. J Am Coll Cardiol. 2004;43:2314-2318.
33. Laufs U, Werner N, Link A, et al. Physical training increases endothelial progenitor cells,inhibits neointima formation and enhances angiogensis. Circulation. 2004;109:220-226.
34. Barsheshet A, Hod H, Shechter M, et al. The Effects of External Counter Pulsation Therapy on Circulating Endothelial Progenitor Cells in Patients with Angina Pectoris. Cardiology. 2008;110:160-166.
35. Kiernan TJ, Boilson BA, Tesmer L, et al. Effect of enhanced external counterpulsation on circulating CD34+ progenitor cell subsets, Int J cadiol. 2011;153:202-206.
36. Jewell CW, Houck PD, Watson LE, et al. Enhanced External Counterpulsation is a regenerative therapy. Frontier in Bioscience. 2010;E2:111-121.
37. Heitzer T, Schlinzig T, Krohn K, et el. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation. 2001;104:2673-2678.
38. Gokce N, Keaney JF Jr, Hunter LM, et al. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. Circulation. 2002;105:1567-1572.
39. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelialdysfunction. J Am Coll Cardiol. 2003;42:1149-1160.
40. Tamai O, Matsuoka H, Itabe H, Wada Y, Kohno K, Imaizumi T. Single LDL apheresis improves endothelium-dependent vasodilation in hypercholesterolemic humans. Circulation. 1997;95:76-82.
41. Solzbach U, Hornig B, Jeserich M, Just H. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulationn. 1997;96:1513-1519.
42. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: The TREND study. Circulation. 1996;94:258-265.
43. Lieberman EH, Gerhard MD, Uehata A, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. Ann Intern Med. 1994;121:936-941.
44. Clarkson P, Adams MR, Powe AJ, et al. Oral l-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. J Clin Invest. 1996;97:1989-1994.
45. Akhtar M, Wu GF, Du ZM, Zheng ZS, Michaels AD. Effect of External Counterpulsation on Plasma Nitric Oxide and Endothelin-1 Levels. Am J Cardiol. 2006;98:28-30.
46. Masuda D, Nohara R, Hirai T, et al. Enhanced External Counterpulsation Improved Myocardial Perfusion and Coronary Flow Reserve in Patients with Chronic Stable Angina; Evaluation by 13N-Ammonia Positron Emission Tomography. European Heart Journal. 2001;22:1451-1458.
47. Zhang Y, He X, Chen X, et al. Enhanced External Counterpulsation Inhibits Intimal Hyperplasia by Modifying Shear Stress Responsive Gene Expression in Hypercholesterolemic Pigs. Circulation. 2007;116:526-534.
48. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced External Counterpulsation Improves Endothelial Function in Patients with Symptomatic Coronary Artery Disease. J AM Coll Cardiol. 2003;41:1761-1768.
49. Lawson WE, Hui JCK, Cohn PF. Long-Term Prognosis of Patients with Angina Treated with Enhanced External Counterpulsation: Five-Year Follow-Up Study Clinical Cardiology. 2000;23:254-258.
50. Soran O, Kennard ED, Kfoury AG, et al. IEPR Investigators. Two-Year Clinical Outcomes After Enhanced External Counterpulsation (EECP) Therapy in Patients with Refractory Angina Pectoris and Left Ventricular Dysfunction (Report from The International EECP Patient Registry). Am J Cardiol. 2006;97:17-20.
51. Loh PH, Cleland JG, Louis AA, et al. Enhanced External Counterpulsation in the Treatment of Chronic Refractory Angina: A Long-term Follow-up Outcome from the International Enhanced External Counterpulsation Patient Registry. Clinical Cardiology. 2008;31:159-164.
52. Mattace-Raso FUS, van der Cammen TJM, Hofman A, et al. Arterial Stiffness and Risk of Coronary Disease and Stroke, The Rotterdam study, Circulation. 2006;113:657-663
53. Weber T, Auer J, O'Rourke MF, et al. Arterial Stiffness, Wave Refleactions, and the Risk of Coronary Artery Disease. Circulation. 2004;109:184-198.
54. Laurent S. Bontonyrie P. Arterial stiffness, a new surrogate end point for cardiovascular disease ? J Nephrol. 2007;20:S45-50.
55. McEniery CM, Wilkinson IB, Avolio AP. Age, hypertension and arterial function. Clinical and experimental pharmacology & physiology. 2007;34:665-671.
56. Nichols WW, Estrada JC, Braith RW, et al. Enhanced external counterpulsation treatment improves arterial wall properties and wave reflection characteristics in patients with refractory angina. J Am Coll Cardiol. 2006;48:1209-1215.
57. Casey DP, Beck DT, Nichols WW, et al. Effects of Enhanced External Counterpulsation on Arterial Stiffness and Myocardial oxygen Demand in Patients with Chronic Angina Pectoris. Am J Cardiol. 2011; 107:1466-1472.
58. Levenson J, Simon A, Megnien JL, et al. Effects of enhanced external counterpulsation on carotid circulation in patients with coronary artery disease. Cardiology. 2007;108:104-110.
59. Martin JS, Beck DT, Arnanda JM Jr, Braith RW. Enhanced external counterpulsation improves peripheral artery function and glucose tolerance in subject with abnormal glucose tolerance. J Appl Physiol. 2012;112:868-876.
60. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, 532 Roubenoff R, Tucker KL, and Nelson ME. A randomized controlled trial of resistance 533 exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes care. 2002;534:2335-2341.
61. Uusitupa MI. Early lifestyle intervention in patients with non-insulin-dependent diabetes 613 mellitus and impaired glucose tolerance. Annals of medicine. 1996;28:445-449.
62. Masuda D, Nohara R, Kataoka K, Hosokawa R, Kanbara N, Fujita M.Enhanced External Counterpulsation Promotes Angiogenesis Factors in Patients with Chronic Stable Angina. Circulation. 2001;104 (17 Suppl II):444.