

Effectiveness of enhanced external counter pulsation on clinical profile and health-related quality of life in patients with coronary heart disease: a systematic review

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Abstract

Introduction. *Enhanced External Counter Pulsation (EECP) is a non-invasive United States Food and Drug Administration (FDA) approved outpatient treatment option for the complex problem of angina, a common symptom of coronary heart disease. A systematic review of the literature searched to assess the effect of EECP on the clinical profile that comprised physiological measurements, biochemical assessments, cardiac clinical symptoms, physical functional status, and Health-Related Quality of Life (HRQoL) in Coronary Heart Disease (CHD) patients.*

Material and methods. *Total 258 EECP research articles from the early stage of EECP development to till date screened. Out of 258 EECP articles, total 60 articles (53 EECP articles for clinical profile and 7 article for HRQoL matched the inclusion criteria and other (n = 198) articles excluded due to irrelevant to study objectives.*

Results. *All enrolled studies showed a significant improvement in angina pectoris and HRQoL with reduction of nitroglycerine use and exercise tolerance. There are several gaps in research has been found for further research to evaluate the EECP effectiveness on Body Mass Index (BMI), Heart Rate, Cholesterol, Triglyceride, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), HbA1C, SpO₂, Vo₂max level with a comparative assessment of cardiac and non-cardiac metabolic markers including blood glucose.*

Conclusions. *There is further need of multi-centric randomize controlled trial studies to evaluate the effect of EECP on obese, diabetic, hypertension and other metabolic disease patients and more research required for further modifications in EECP device to cure, prevent and treat chronic diseases by the non-invasive procedure.*

Key words: enhanced external counter pulsation, angina pectoris, health-related quality of life, coronary heart disease

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Introduction

Cardiovascular disease, especially Coronary Heart disease (CHD) is the number one killer and foremost

cause of deaths around the world [1]. Angina pectoris, the prime symptom of coronary heart disease ranked first among causes of mortality [2]. The current non-pharmacological and non-invasive therapy available

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for chronic stable angina (a typical symptom of coronary heart disease) and heart failure is Enhanced External Counter Pulsation (EECP). EECP is USA-FDA approved therapy for coronary heart disease patient [3]. EECP, an electro-mechanical system is a registered trademark of Vasomedical, Inc, New York, USA and PSK (Chinese Company) is the exclusive distributor of Vasomedical's devices all over the world [4–8]. CHD patients usually undergo EECP treatment of 35 consecutive 1-hour sessions over 5–7 weeks. Treatment patient is continuously monitored for cardiac outputs, heart rate and spo2 using ECG and finger plethysmogram, which are connected to the EECP device [9–11]. This study designed to evaluate the effect of EECP in Clinical profile and HRQoL in CHD patients.

Material and methods

Searching methods

A systemic review of the literature of EECP on clinical profile and HRQoL in coronary heart disease patients was search through PubMed, Medline, Vasomedical EECP manufacturer web-link, and Google scholar sources. Searching for the articles done as per the inclusion and exclusion criteria of the study and the studies summarized in Figure 1.

Inclusion criteria

EECP article of Randomized Control Trial (RCT), case studies, prospective and retrospective studies on clinical profile and HRQoL in coronary heart disease patients were included.

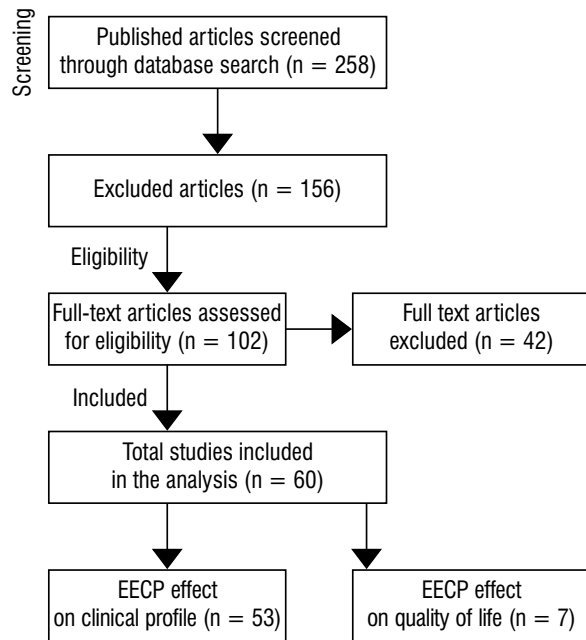


Figure 1. Flowchart of screened and included studies

Exclusion criteria

Heart Failure studies, Non-cardiac EECP studies with RCT, Case studies, Prospective and Retrospective and reviews of EECP papers excluded from the study.

Quality assessment

Study quality was assessed through two authors independently. Newcastle-Ottawa scale (NOS) was used to assess the quality of studies. Detail of assessment is given in Tables 1, 2.

Table 1. Newcastle-Ottawa scale in the assessment of clinical profile included studies

Study	Is the case definition adequate? (one point)	Representativeness of cases (one point)	Selection of controls (one point)	Definition of controls (one point)	Assessment of outcome (one point)	Adequacy of cohort follow-up (one point)	Was follow-up long enough for outcomes to occur? (one point)	Comparability of cases and controls on basis of design or analysis (two points)	Total score (nine points)
Lawson et al. 1992								2	9
Sjukri et al. 1995								2	9
Arora et al. 1999								2	9
Lawson et al. 2000								2	9
Lawson et al. 2000								2	9
Urano et al. 2001								2	9
Stys et al. 2001								2	9
Barsness et al. 2001								2	9
Springer S et al. 2001								2	9
Lakshmi et al. 2002								2	9
Stys et al. 2002								2	9
Michaels et al. 2002							0	2	8

Table 1. cont. Newcastle-Ottawa scale in the assessment of clinical profile included studies

Study	Is the case definition adequate? (one point)	Representativeness of cases (one point)	Selection of controls (one point)	Definition of controls (one point)	Assessment of outcome (one point)	Adequacy of cohort follow-up (one point)	Was follow-up long enough for outcomes to occur? (one point)	Comparability of cases and controls on basis of design or analysis (two points)	Total score (nine points)
Soran et al. 2002								2	9
Fitzgerald et al. 2003								2	9
Bonetti et al. 2003								2	9
Schechter et al. 2003								2	9
Tartaglia et al. 2003								2	9
Werner et al. 2003								2	9
Lawson et al. 2003								2	9
Linnemeier et al. 2003								2	9
Linnemeier et al. 2003								2	9
Bagger et al. 2004							0	2	8
Michaels et al. 2004								2	9
Lawson et al. 2004								2	9
Masuda et al. 2004								2	9
Henrikson et al. 2004								2	9
Taguchi et al. 2004								2	9
Lawson et al. 2005								2	9
Michaels et al. 2005								2	9
Arora et al. 2005								2	9
McCullough et al. 2006								2	9
Soran et al. 2006								2	9
Akhtar et al. 2006								2	9
Nichols et al. 2006								2	9
Lawson et al. 2006								2	9
Novo et al. 2006								2	9
Loh et al. 2006								2	9
Arora et al. 2007								2	9
Michaels et al. 2007								2	9
McCullough et al. 2007								2	9
Yavari et al. 2007								2	9
Loh et al. 2008								2	9
Erdling et al. 2008								2	9
Buschmann et al. 2009								2	9
Esmailzadeh et al. 2009								2	9
Soran et al. 2012								2	9
Eslamian et al. 2013								2	9
Bozorgi et al. 2014								2	9
Beck et al. 2014								2	9
Tabary et al. 2015								2	9
Subramanian et al. 2016							0	2	8
Beck et al. 2016								2	9

Table 2. Newcastle-Ottawa scale health related quality assessment of included studies

Study	Is the case definition adequate? (one point)	Representativeness of cases (one point)	Selection of controls (one point)	Definition of controls (one point)	Assessment of outcome (one point)	Adequacy of cohort follow-up (one point)	Was follow-up long enough for outcomes to occur? (one point)	Comparability of cases and controls on basis of design or analysis (two points)	Total score (nine points)
Arora et al. 2002								2	9
Kumar et al. 2009								2	9
Wu et al. 2012							0	2	8
Ziaeirad et al. 2012								2	9
Jorgensen et al. 2013								2	9
May et al. 2015							0	2	8
Shakouri 2015								2	9

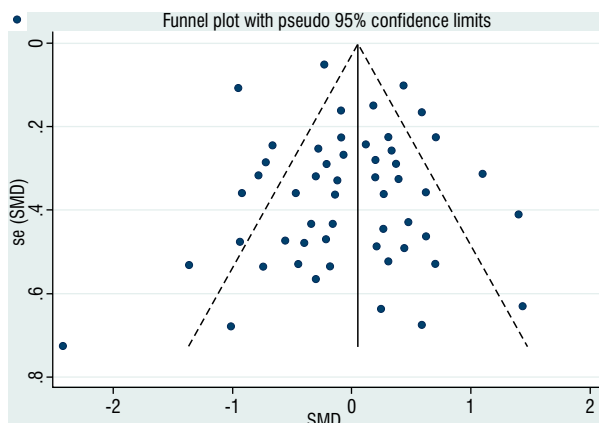


Figure 2. Funnel plot of included studies in clinical profile — EECP

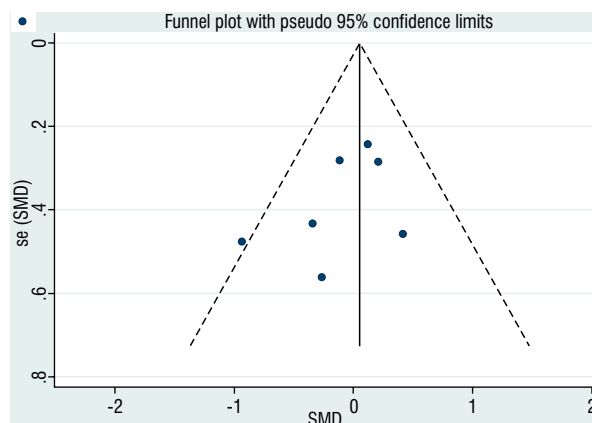


Figure 3. Funnel plot of included studies in HRQoL — EECP

Statistical analysis

Statistical analyses were performed using RevMan 5.0 (Cochrane Collaboration). A random-effects model was used with weighted mean difference (WMD) in clinical profile and HRQoL from pre-EECP to post-EECP. Bias in studies was assessed through visual inspection of the funnel plot as well as Begg’s and Egger’s testing. Detail of analysis is given in Figures 2 to 5.

EFFECT OF EECP ON CLINICAL PROFILE IN CORONARY HEART DISEASE PATIENTS

Lawson et al. [12] conducted a study on 18 patients with chronic angina treated with an improved system of enhanced external counter pulsation (EECP) and found that all patients improved in angina symptoms and generally decreased anti-angina medications. A decrease in myocardial ischemia observed in 67% patients and 89% of patients were symptom-free. Sjukri et al. [13] carried out a study on 201 coronary heart disease

patients. The results of the study showed significant improvement in coronary perfusion by 86.8% and exercise tolerance by 94.2%. Arora et al. [14] performed a multi centric prospective randomized control study to assess the safety and efficacy of enhanced external counterpulsation (EECP). A significant improvement in angina severity and exercise tolerance and timing was reported. EECP showed well tolerated and safe therapy for CHD patients. Lawson et al. [15] carried out a study on 33 patients to evaluate the effect of EECP on long-term prognosis in CHD patients. The study suggests that particularly for the majority of patients demonstrating improvement by 64% in radionuclide stress perfusion post-treatment and EECP may be an effective long-term therapy. Lawson et al. [16] conducted a cohort study in 2,289 CHD patients to evaluate EECP safety and efficacy. EECP was found to be safe and well-tolerated therapy with improvement in angina class by 74% with significant p-value ($p < 0.001$). Urano et al. [17] performed a study on 512 CHD patients to examined EECP efficacy in myocardial ischemia, exercise tolerance and cardiac

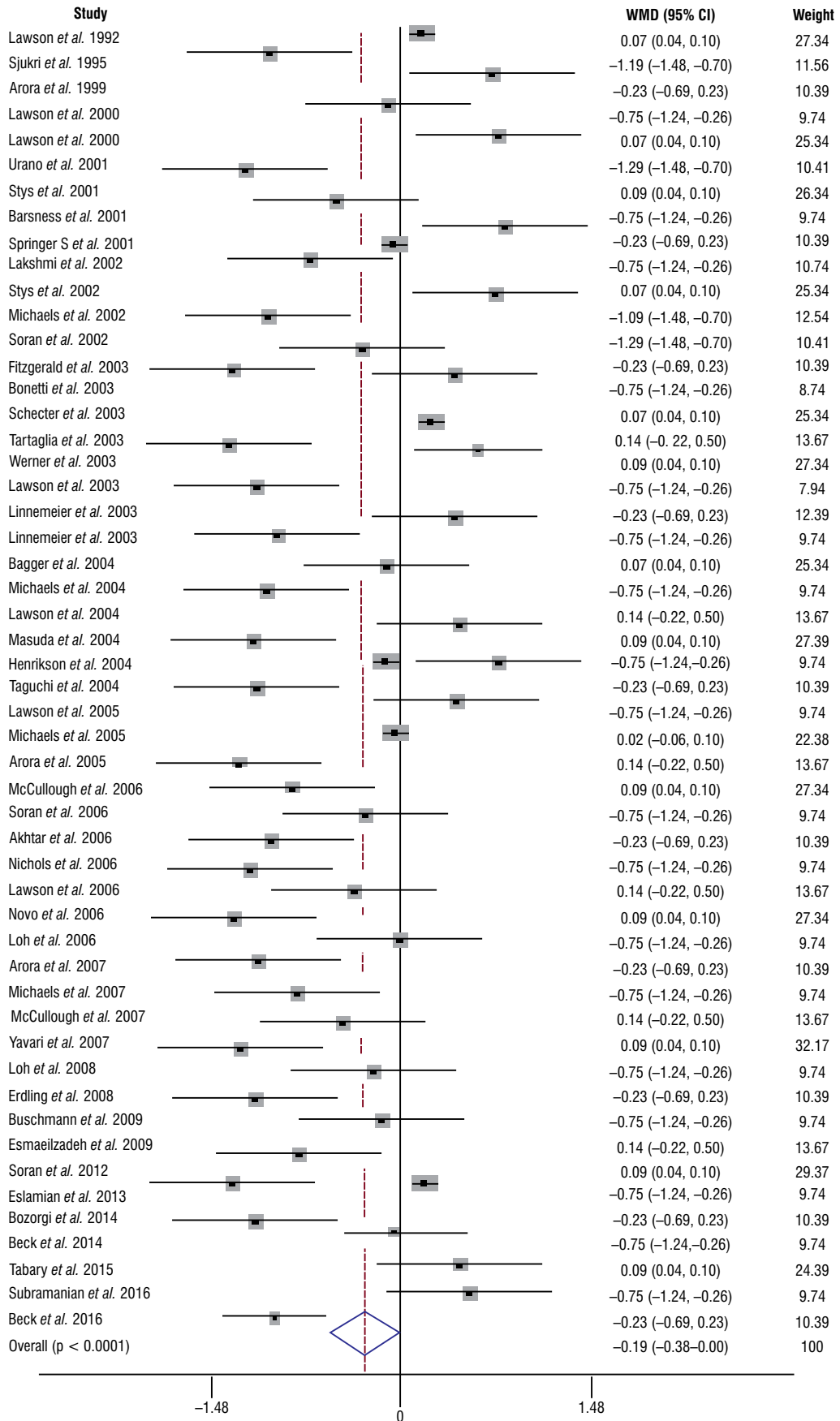


Figure 4. Forest plot of weighted mean differences in clinical profile in pre- and post-EECF

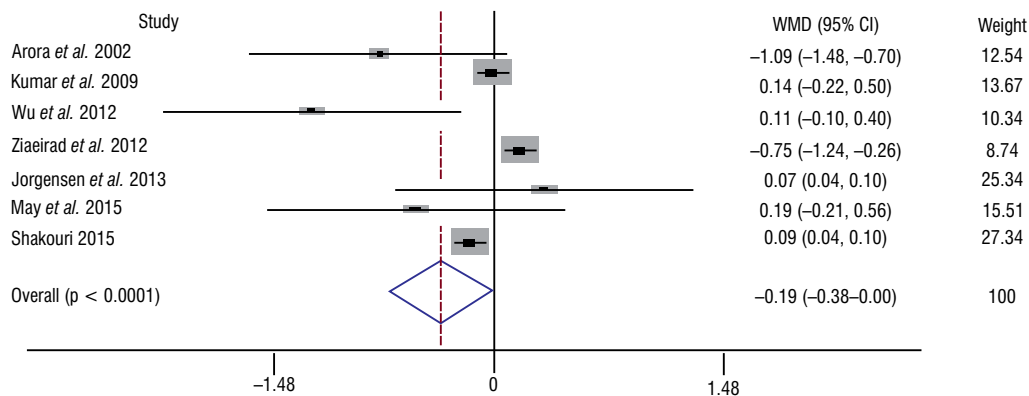


Figure 5. Forest plot of weighted mean differences in HRQoL in pre- and post-EECP

function. The result of the study reveals the improvement in exercise test parameters reduced myocardial ischemia by thallium scintigraphy in association with improved LV diastolic filling in patients with stable CAD. Stys *et al.* [18] carried out a clinical registry of 37 centers with the enrollment of 395 chronic stable angina patients to examine the relation of the ER to post treatment improvement in Canadian Cardiovascular Society (CCS) angina class. After EECp, CCS improved by at least 1 class in 88% of patients, 87% of men and 92% of women. EECp is effective in improving CCS in chronic stable angina patients. Barsness *et al.* [19] performed a study on 1246 CHD patients to determine whether EECp is a safe and effective treatment for patients with angina pectoris. The results demonstrated significant improvement in angina and reduction in nitroglycerine anti-angina drugs by 61.7%. Springer *et al.* [20] conducted a study on 28 CHD patients to assess psychological function and well-being status and observed significant improvement in psychological and well-being status. Lakshmi *et al.* [21] carried out a study on 2486 patients those were enrolled in the IEPp. The study revealed a significant improvement in angina class in patients whose DA ratio was increased and results sustained for 6 months. Stys *et al.* [22] performed a study on 175 CHD patients and found a significant improvement in angina class in 85% of patients. This study results showed the EECp effectiveness in improving stress myocardial perfusion with exercise tolerance in CAD patients.

Michaels *et al.* [23] conducted a study on 10 CHD patients and found the significant improvement in diastolic and mean pressures with reduction of systolic pressure in the central aorta and the coronary artery of CAD patients. The study concludes that EECp may serve as a potential mechanical assistant device for CAD patients. Holubkov *et al.* [24] carried out a study on 771 CHD patients treated with EECp and the results of this study conclude that EECp may be a safe treatment option for

CAD patients. Soran *et al.* [25] performed a study on 1402 CHD patients and the results showed that angina decreased by at least one class in 67% of patients with LV dysfunction just after completion of EECp treatment. Fitzgerald *et al.* [26] conducted a cohort study on 4669 CHD patients and found decreased angina episodes and nitroglycerin use and 74.8% reduction in Canadian Cardiovascular Society (CCS) functional class and improvement in angina sustained for 6 months. Bonetti *et al.* [27] performed a study on 23 CHD patients to examine the effect of enhanced external counter pulsation (EECP) on endothelial function and found that 70% patients get symptomatic relief by EECp treatment. The author revealed that significant improvement in endothelial function by EECp may benefit to the clinical status of CHD patients.

Schechter *et al.* [28] carried out a study of 20 CHD patients to investigate the influence of short-term external counterpulsation (ECP) therapy on flow-mediated dilation (FMD) in patients with coronary artery disease (CAD). The author revealed that external counter pulsation may improve vascular endothelial function and refractory angina pectoris in CHD patients. Tartaglia *et al.* [29] conducted a study on 25 CHD patients to determine the effect of EECp on exercise capacity and myocardial perfusion by comparing results of maximal exercise radionuclide testing pre- and post-EECP treatment. A significant improvement in treadmill times has been reported and radionuclide perfusion scores also showed a significant reduction in ischemic segments. Werner *et al.* [30] performed a study on 48 CHD patients and weekly angina episodes were reduced by 48%, nitroglycerin puffs were reduced by 51%, work capacity was improved by 22%. Study validates the reduction of angina with significant improvement of work capacity after EECp.

Lawson *et al.* [31] carried out a study on 4592 CHD patients and his collected data from international enhanced external counter pulsation (EECP) patient regis-

try showed significant improvement in angina by 73% in at least 1 class and 2 classes by 35.2% and 3 classes by 17.3%. The mean angina episodes per week decrease to 2.5 per week after EECP treatment and nitroglycerine uses per week after EECP was 2.5 times per week and improvement in functional status also observed in the study. Linnemeier *et al.* [32] conducted a study on 3037 CHD patients to determine whether enhanced external counterpulsation is a safe and effective treatment for angina in octogenarians. At 6-month follow-up, 81% of patients sustained angina improvement. This study concludes that enhanced external counterpulsation is effective and well tolerable non-invasive treatment. Linnemeier *et al.* [33] performed another study on 1532 IEPR patients. The author demonstrated that after 1 year, maintenance of angina rate was reduced in 86% of patients with diabetes. This study also suggests that in diabetes patients, EECP can be a safe, effective, well-tolerated treatment option for the relief of angina. Bagger *et al.* [34] carried out a study on 23 patients with angina pectoris with positive dobutamine stress echocardiogram. This study was done to evaluate EECP effectiveness on dobutamine stress-induced wall motion score among angina patients. The reduction in dobutamine-induced wall motion abnormalities after EECP therapy was reported.

Michaels *et al.* [35] conducted the long-term outcomes of enhanced external counterpulsation in 1097 CHD patients to relieve angina and improving the quality of life in a large cohort of patients with chronic angina pectoris. 73% patients had a reduction by at least 1 angina class at the end of treatment, and 50% reported an improvement in the quality-of-life assessment after enhanced external counterpulsation was; these results were sustained at 2-year follow-up. Lawson *et al.* [36] performed a study on 2861 CHD patients to examine the safety and effectiveness of EECP therapy. Post-EECP, patients had improved their CCS angina by at least one class. At 6-month follow-up, the CCS-class improved reduction in angina episodes and nitroglycerin use. Enhanced external counterpulsation was proved an effective therapy in relieving angina in patient's angina patients. Masuda *et al.* [37] carried out a study on total 18 CHD patients. Out of 18 patients, 11 were treated with EECP and 7 were treated 5000 IU heparin pretreatment along with EECP. The study was done to evaluate EECP and intravenous heparin injection therapy effectiveness in angina pectoris patients and the results of the study showed significant improvement in exercise capacity and oxygen metabolism of coronary heart disease patients treated with combination therapy of EECP and heparin.

Henrikson *et al.* [38] conducted a study on 28 CHD patients and found that post EECP most patients (82%)

had at least one full class improvement in their angina pattern. EECP remains an effective treatment for severe CAD. Taguchi *et al.* [39] performed study on 24 patients with myocardial infarction. This study was done to assess the haemodynamic effects of EECP and its mechanism with special reference to neurohumoral factors. The finding of this study suggests that an increase in ANP without an increase in BNP is an important mechanism for the effects of EECP therapy. Lawson *et al.* [40] carried out a study on 2007 CHD patients and demonstrated the angina reduction by 83% at least one CCS angina class and improvement in weekly angina episodes and their frequency of nitroglycerine use decreased with improvement in well-being status by 63%. Michaels *et al.* [41] conducted a study on 1192 CHD patients to assess the frequency, efficacy, predictors, and long-term success of repeat enhanced external counter pulsation (EECP) therapy in relieving angina in a large cohort of angina patients. After 2 years of EECP therapy, 70% of patients reported the significant decrease in angina and nitroglycerine consumption. Arora *et al.* [42] performed a study on 30 patients with stable angina pectoris having class II-IV. This study was done to assess the effect of EECP on vascular cell release of coagulation factors. The author reveals that EECP may not play a significant role in controlling coagulation factors in CHD patients.

McCullough *et al.* [43] carried out a study on 2730 obese heart patients to evaluate the association of baseline body mass index (BMI) on the outcomes of enhanced external counterpulsation (EECP) therapy for chronic stable angina. A greater reduction in weekly angina episodes from baseline to follow up observed and study conclude that reduction of angina is directly proportional to BMI value. Akhtar *et al.* [44] conducted a study on 13 CHD patients to evaluate the effect of EECP treatment on plasma nitric oxide and endothelin-1 level. This study concludes that EECP may increase nitric oxide and decreases endothelin-1 levels.

Soran *et al.* [45] carried out a cohort study on 363 CHD patients and post EECP treatment, there was a significant decrease in severity of angina class ($p < 0.001$), and 72% patients were improved from severe angina and 52% of patients discontinued nitroglycerin use. At 2 years of follow up 55%, patients showed improvement in angina and prove that EECP is effective and durable therapy approach for CAD patients and 52% CHD patients discontinued nitroglycerin use. Nichols *et al.* [46] performed a study on 20 angina patients to prove the hypothesis of arterial properties and wave reflection characteristics favourably altered after EECP. The study revealed that EECP treatment may reduce arterial stiffness and can improve wave reflection characteristics in patients with angina.

Lawson *et al.* [47] conducted a study on 1458 CHD patients and found that EECP significantly reduced angina frequency, nitroglycerin use. Significant improvements in angina by 70–74% with reduction of nitroglycerine use by 52% with better well-being persist until 2 years of follow up. Novo *et al.* [48] carried out a study on 25 CHD patients to evaluate the efficacy of EECP on clinical symptoms, myocardial ischemia and cardiac perfusion in intractable angina patients. 84 per cent of patients showed an increment in at least one functional angina class and reduced inducible ischemia and maximal benefits observed in patients with worst systolic failure had been observed.

Loh *et al.* [49] did a study on 58 CHD patients to assess EECP immediate and long-term effectiveness in chronic stable refractory angina patients. This study results showed that angina improved at least one class CCS angina improvement by 78% after 1 year and increase exercise capacity with the reduction in nitroglycerine use. Arora *et al.* [50] conducted a study on 11 CHD patients to assess the effect of EECP on myocardial perfusion. In this study no significant effect on myocardial perfusion seen due to very less sample size and highly variable clinical responses. Michaels *et al.* [51] performed a study on 27 patients and significant improvement in heart rate variability in diabetic CHD patients and associated with reduced mortality rate had been reported. McCullough *et al.* [52] did a study on 902 patients from the IEPR. This study was done to evaluate the degree of residual angina on the clinical outcomes of EECP and conclude that residual high-grade angina pectoris occurs after post EECP in those patients who had the history of severe angina and multi-vessel disease.

Yavari *et al.* [53] conducted a study on 67 CHD patients to assess EECP efficacy in relieving angina and improving myocardial ischemia. The results of this study conclude that EECP is safe, effective and well-tolerated therapy for angina pectoris treatment. Loh *et al.* [54] did a study on 1477 CHD patients to evaluate EECP effectiveness. Immediately after EECP, angina reduction has been seen with $p < 0.001$. The improvement in CCS class was improved by at least 1 class in 78% of the patients and by at least 2 classes in 38% and sustained in 74% of the patients during follow-up for 3 years. Erdling *et al.* [55] carried out a study on 86 CHD patients and conclude that after EECP treatment 79% of patients showed improvement in CCS class immediately and 61.5% of patients sustained these benefits till 12 months and 29% at 2 years follow up. The author concludes that EECP is safe & effective for CAD with angina pectoris patients and patients with CCS angina class III & IV reported maximum improvement. Buschmann *et al.* [56] conducted a study on 23 CHD patients and found

improvement in CCS and NYHA class in CAD patients with significant improvement in pressure derived collateral flow index and fractional flow, which also increased. Esmailzadeh *et al.* [57] performed a study on 20 CHD patients to assess the effects of EECP on cardiac functions and found a reduction in NYHA angina class. Significant improvement was observed in LV systolic, diastolic function in angina patient. Soran *et al.* [58] conducted a study on 2072 patients and treated with EECP. Significant reduction by 76–84% in the severity of angina in CAD patients at 1 year of follow up was reported and both US and turkey group got good results. Eslamian *et al.* [59] performed a study on 50 CHD patients to assess Enhanced External Counter Pulsation (EECP) effectiveness on clinical symptoms, echocardiographic measurements, and perfusion scan parameters and exercise tolerancetest. A significant improvement was observed in angina severity and well-being status. Bozorgi *et al.* [60] did a study on 20 CHD patients with refractory angina. A significant reduction in angina classes III and IV was reported with sustained results for 6 months. The author concludes that EECP decreased symptoms and increased total exercise time and sustained these results for 6 months.

Beck *et al.* [61] conducted a study on 24 CHD patients and significant improvement in plasma level of nitrates, improved peak VO₂, and reduced LV function with significant improvement in peripheral vascular function and functional capacity had been reported. Tabary *et al.* [62] performed a study on 48 CHD patients to assess clinical and para-clinical effects of enhanced external counterpulsation (EECP) effectiveness. Significant improvement in hemoglobin, LVEF, diastolic and systolic B.P, Chest pain, dyspnea and improvement in clinical conditions had been reported. Subramanian *et al.* [63] did a study on 72 CHD patients and found significant improvement in central systolic pressure, brachial systolic pressure, aortic pulse pressure, and augmentation pressure and augmentation index. Beck *et al.* [64] conducted the study on 17 CHD patients. The author concludes that EECP may be useful as an adjuvant therapy for improving functional classification and improve central blood pressure, aortic pulse pressure, wasted left ventricular energy, and myocardial oxygen demand in CHD patients.

EFFECT OF EECP ON HR-QoL IN CORONARY HEART DISEASE PATIENTS

Arora *et al.* [65] conducted a study to assess EECP effectiveness on HRQoL. A significant improvement in HRQoL was observed at 12 months of follow up. The result shows improvements in HRQoL changes after EECP treatment. Kumar *et al.* [66] did a prospective

study and found that EECP significantly improved angina symptoms, dyspnea on exertion, and quality of life after 35 days of treatment and at 1 year follow up. EECP also improved the 6-minute walking capacity. Wu *et al.* [67] performed a study to evaluate EECP after six months regarding physical capacity and HRQoL in patients with refractory AP. Patients enhanced walking distance on average by 29 m after EECP. CCS class also improved and persisted at six months follow-up. HRQoL improved significantly and the effects maintained at follow-up after the treatment.

Ziaeirad *et al.* [68] did a quasi-experimental study on 64 patients to evaluate the QoL of patients with angina pectoris after treatment with enhanced external counterpulsation. The author reveals that EECP is an

effective noninvasive method in treating patients with angina pectoris and in developing their HRQoL. Jorgensen *et al.* [69] conducted a special case study of the 43-year-old woman who had 15 hospital admissions in six years due to angina. The case study proves the EECP effectiveness towards angina recovery and significant improvement in HRQoL. May *et al.* [70] performed a study to assess the effect of EECP on QoL and exercise capacity in CAD patients. Author of this concludes that quality of life and exercise capacity was improved after EECP. Shakouri *et al.* [71] conducted a study to investigate the effect of EECP on plasma nitric oxide (NO) and HRQoL in CAD patients. The author revealed that HRQoL and NO level increased after EECP treatment in CHD patients. Summary of studies given in Tables 3, 4.

Table 3. EECP effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Lawson <i>et al.</i> [12]	1992	Efficacy of enhanced external counterpulsation in the treatment of angina pectoris	18	Myocardial ischemia 67% decrease, exercise duration increased, reduction in anti-anginal medicines and 89% patients were symptom-free
Sjukri <i>et al.</i> [13]	1995	EECP in the treatment and rehabilitation of coronary patients in Indonesia	201	Exercise tolerance 94.2%, improvement in CCS angina class
Arora <i>et al.</i> [14]	1999	The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes	139	Exercise duration increase, angina severity reduced, extends times to exercise-induced ischemia, Nitroglycerine usage decrease
Lawson <i>et al.</i> [15]	2000	Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study	33	Improvement in stress perfusion after EECP, 64% did not suffer any major adverse cardiovascular event due to the effect of EECP at 5 year of study follow up
Lawson <i>et al.</i> [16]	2000	Treatment benefit in the enhanced external counterpulsation consortium	2289	74% angina pectoris patients improved in CCS angina class III & IV with significant p-value ($p < 0.001$)
Urano <i>et al.</i> [17]	2001	Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia, and improves left ventricular diastolic filling in patients with coronary artery disease	512	Improvement in Exercise duration and tolerance with improvement in LV function. Improvement in diastolic filling and diastolic function
Stys <i>et al.</i> [18]	2001	Acute hemodynamic effects and angina improvement with enhanced external counterpulsation	395	CCS angina class improvement by at least I class in 88% of patients
Barsness <i>et al.</i> [19]	2001	The International EECP Patient Registry (IEPR): design, methods, baseline characteristics and acute results	1246	Decrease in at least I anginal class by 81% and mean change decrease in anginal episodes per week (6.4 ± 12.6) with reduction of nitroglycerine use by 61.7%
Springer <i>et al.</i> [20]	2001	Psychosocial effects of EECP in the angina patient: A second study	28	Improvement in physical functioning and mental health with special reference to stress and QoL

Table 3. cont. EECP effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Lakshmi <i>et al.</i> [21]	2002	Relation of the Pattern of Diastolic Augmentation During a Course of Enhanced External Counterpulsation (EECP) to Clinical Benefit (from the International EECP Patient Registry [IEPR])	2486	At 6 months of follow up, the patients showed a higher reduction in angina class who had the greatest increase in the DA ratio as compared to those who had a decrease in the DA ratio
Stys <i>et al.</i> [22]	2002	Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris	175	85% angina improvement, improvement in stress myocardial perfusion and maximize exercise functions
Michaels <i>et al.</i> [23]	2002	Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation	10	Diastolic BP increase, Systolic B.P decrease and increment in coronary flow by 28% during EECP treatment
Holubkov <i>et al.</i> [24]	2002	Comparison of patients undergoing enhanced external counterpulsation and percutaneous coronary intervention for stable angina pectoris	771	Angina improvement in CCS class higher who received EECP therapy as compared to PCI group
Soran <i>et al.</i> [25]	2002	Enhanced external counterpulsation as treatment for chronic angina in patients with left ventricular dysfunction: a report from the International EECP Patient Registry (IEPR)	1402	Improvement in angina at least one class in 67% of patients with LV dysfunction 70.6% after 6 months of follow up
Fitzgerald <i>et al.</i> [26]	2003	Enhanced external counterpulsation as initial revascularization treatment for angina refractory to medical therapy	4,669	The decrease in anginal episode per week with significant value $p < 0.001$, reduced nitroglycerine uses and CCS angina class reduction in 74.8 patients
Bonetti <i>et al.</i> [27]	2003	Enhanced external counterpulsation improves endothelial function in patients with symptomatic CAD	23	Enhanced peripheral endothelial function immediately after EECP treatment with a contribution to the clinical benefit of EECP
Schechter <i>et al.</i> [28]	2003	External counterpulsation therapy improves endothelial function in patients with refractory angina pectoris	20	Significant improvement in angina class ($p < 0.001$), nitrate consumption decrease ($p < 0.001$) with improvement in endothelial functions
Tartaglia <i>et al.</i> [29]	2003	Exercise capability and myocardial perfusion in chronic angina patients treated with enhanced external counterpulsation	25	96% patients improved by at least one functional angina class and exercise duration increased in treadmill exercise testing and reduction in ischemic segments
Werner <i>et al.</i> [30]	2003	Practicability and limitations of enhanced external counterpulsation as an additional treatment for angina	48	Anginal episode reduced by 48%, Nitroglycerine reduction by 51% and work capacity increase by 22%

Table 3. cont. EECF effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Lawson <i>et al.</i> [31]	2003	Analysis of baseline factors associated with a reduction in chest pain in patients with angina pectoris treated by enhanced external counterpulsation	4592	Significant improvement in angina by 73% in at least 1 class and 2 classes by 35.2% and 3 classes by 17.3%. Mean angina episodes per week decrease to 2.5 per week after EECF treatment and nitroglycerine uses per week after EECF was 2.5 times per week and improvement in functional status also observed
Linnemeier <i>et al.</i> [32]	2003	Enhanced external counterpulsation in the management of angina in the elderly	3037	Angina improvement in 81% at 6 months with a reduction in nitroglycerine use and improvement in well-being status with decrease rate of cardiac hospitalization has been observed
Linnemeier <i>et al.</i> [33]	2003	Enhanced External Counterpulsation for the relief of angina in patients with diabetes: safety, efficacy and 1- year clinical outcomes	1532	Significant improvement in CCS angina class by 69% in diabetes mellitus immediately after EECF and 86% at 1 year follow up, reduction in nitroglycerine use and improvement in well-being status has been observed and confirm that EECF is safe, effective and well tolerable treatment
Bagger <i>et al.</i> [34]	2004	Effect of enhanced external counterpulsation on dobutamine-induced left ventricular wall motion abnormalities in severe chronic angina pectoris	23	Reduction in dobutamine-induced wall motion abnormalities observed after EECF treatment
Michaels <i>et al.</i> [35]	2004	Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the International EECF patient registry [IEPR])	1097	Significant improvement by 73% angina improvement, 50% improvement in well-being of CAD patients at 2 years of follow up
Lawson <i>et al.</i> [36]	2004	The effectiveness of enhanced external counterpulsation in patients with left main disease and angina.	2861	Significant improvement in angina pectoris and reduction in nitroglycerine use and reduction in weekly angina episodes observed
Masuda <i>et al.</i> [37]	2004	Improvement of oxygen metabolism in ischemic myocardium as a result of enhanced external counterpulsation with heparin pretreatment for patients with stable angina	18	Significant improvement in exercise capacity and oxygen metabolism of CHD patients treated with EECF and intravenous heparin infusion combined therapy was observed
Henrikson <i>et al.</i> [38]	2004	Enhanced external counterpulsation therapy: significant clinical improvement without electrophysiologic remodelling	28	Significant improvement in angina by 82% and effective treatment for CAD patients
Taguchi <i>et al.</i> [39]	2004	Effects of enhanced external counterpulsation on hemodynamics and its mechanism relation to neurohumoral factors	24	Study concludes that increments in ANP without enhancement in BNP was an important mechanism for EECF effectiveness
Lawson <i>et al.</i> [40]	2005	Predictors of benefit in angina patients one year after completing enhanced external counterpulsation: initial responders to treatment versus non responders	2,007	Angina reduced by at least 83% immediately, and improvement in weekly anginal episodes, the frequency of nitroglycerine use decreased and well-being status improved by 63%

Table 3. cont. EECP effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Michaels <i>et al.</i> [41]	2005	Frequency and efficacy of repeat enhanced external counterpulsation for stable angina pectoris (from the International EECP Patient Registry)	1192	After EECP treatment 86% reported decrease in angina CCS class by at least one and 57% patients discontinued nitroglycerine use After 2 years 70% patients reported significant decrease in angina and nitroglycerine consumption
Arora <i>et al.</i> [42]	2005	Effects of enhanced counterpulsation on vascular cell release of coagulation factors	30	The study suggests that EECP may not play a vital role in controlling coagulation factors in coronary heart disease patients, further research required
McCullough <i>et al.</i> [43]	2006	Impact of body mass index on outcomes of enhanced external counterpulsation therapy	2730	Changes in angina and duke activity status have been observed in all BMI patients. Greater reduction of angina is directly proportional to BMI value
Soran <i>et al.</i> [44]	2006	Two-year outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the International EECP Patient Registry)	363	At 2 years of follow up 55% of patients showed improvement in angina and prove that EECP is effective and durable therapy approach for CAD patients and 52% CHD patients discontinued nitroglycerin use
Akhtar <i>et al.</i> [45]	2006	Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels	13	EECP increases nitric oxide and decreases endothelin-1 level and changes sustained for 3 months in CHD patients
Nichols <i>et al.</i> [46]	2006	Enhanced external counterpulsation treatment improves arterial wall properties and wave reflection characteristics in patients with refractory angina	20	The study suggests that EECP can reduce arterial stiffness and may improve wave reflection characteristics in CHD patients and these changes decrease left ventricular afterload, myocardial oxygen demand and can reduce anginal episodes
Lawson <i>et al.</i> [47]	2006	Two-year outcomes in patients with mild refractory angina treated with enhanced external counterpulsation	1458	Improvement in angina by 70–74% with reduction of nitroglycerine use by 52% with better well-being persist till 2 years of follow up
Novo <i>et al.</i> [48]	2006	Enhanced external counterpulsation for treatment of refractory angina pectoris	25	Significant improvement in angina by 84% and reduced inducible ischemia and maximal benefits observed in patients with the worst systolic failure
Loh <i>et al.</i> [49]	2006	The immediate and long-term outcome of enhanced external counterpulsation in treatment of chronic stable refractory angina	58	At least one class CCS angina improvement by 78% after 1 year and increase exercise capacity with a reduction in nitroglycerine use
Arora <i>et al.</i> [50]	2007	Effect of enhanced external counterpulsation on myocardial perfusion in patients with stable angina: A multicenter radionuclide study	11	No significant effect on myocardial perfusion has been observed due to very less number of sample size and highly variable clinical responses and study suggest for further research to assess EECP effectiveness on myocardial perfusion
Michaels <i>et al.</i> [51]	2007	The effects of enhanced external counterpulsation on time- and frequency-domain measures of heart rate variability	27	Improvement in heart rate variability in diabetic CHD patients and associated with reduced with reduced mortality rate

Table 3. cont. EECP effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
McCullough [52]	2007	Residual high-grade angina after enhanced external counterpulsation therapy	902	The researcher observed high residual grade angina after EECP in those patients who had severe angina and multivessel diseases
Yavari <i>et al.</i> [53]	2007	Effects of enhanced external counterpulsation on anginal symptoms and improvements in objective measures of myocardial ischaemia	67	The study concludes that EECP is a safe, well tolerated and effective non-invasive therapy for CHD patients
Loh <i>et al.</i> [54]	2008	Enhanced external counterpulsation in the treatment of chronic refractory angina: a long-term follow-up outcome from the International Enhanced External Counterpulsation Patient Registry	1477	After 1-year EECP treatment 78% patients reported reduction in CCS angina class and 74% of patients sustained improvement at 3-years follow
Erdling <i>et al.</i> [55]	2008	Enhanced external counterpulsation in treatment of refractory angina pectoris: two-year outcome and baseline factors associated with treatment failure	86	After EECP treatment 79% of patients showed improvement in CCS class immediately and 61.5% of patients sustained these benefits till 12 months and 29% at 2 years follow up and study conclude that EECP is safe & effective for CAD with angina pectoris patients and patients with CCS angina class III & IV reported maximum improvement
Buschmann <i>et al.</i> [56]	2009	Improvement of fractional flow reserve and collateral flow by treatment with external counterpulsation.	23	Improvement in CCS and NYHA class in CAD patients with significant improvement in pressure derived collateral flow index and fractional flow also increased
Esmailzadeh <i>et al.</i> [57]	2009	Evaluation of left ventricular systolic and diastolic regional function after enhanced external counterpulsation therapy using strain rate imaging	20	Reduction in NYHA angina class & improvement in LV systolic and diastolic function in patients with chronic angina with increment in LVEF from 40.25–46.25% with significant p-value ($p < 0.001$)
Soran <i>et al.</i> [58]	2012	Comparison of long-term clinical outcomes, event-free survival rates of patients undergoing enhanced external counterpulsation for coronary artery disease in the united states and turkey	2072	Significant reduction in the severity of angina in CAD patients at 1-year of follow up
Eslamian <i>et al.</i> [59]	2013	Therapeutic effects of enhanced external counterpulsation on clinical symptoms, echocardiographic measurements, perfusion scan parameters and exercise tolerance test in CAD patients with refractory angina	50	Significant improvement in angina severity ($p < 0.001$), wellbeing status and ischemia severity ($p = 0.044$) and demonstrated useful safe and effective treatment method for angina pectoris in CHD patients
Bozorgi <i>et al.</i> [60]	2014	Effect of enhanced external counterpulsation (EECP) on exercise time duration and functional capacity in patients with refractory angina pectoris	20	Significant reduction in the severity of angina and physical functioning sustained for 6 months

Table 3. cont. EECP effectiveness on clinical profile in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Beck <i>et al.</i> [61]	2014	Enhanced external counterpulsation improves endothelial function and exercise capacity in patients with ischaemic left ventricular dysfunction	24	Significant improvement in plasma level of nitrates and improved peak VO ₂ and reduce LV function with significant improvement in peripheral vascular function and functional capacity
Tabary <i>et al.</i> [62]	2015	The assessment of the clinical and paraclinical effects of enhanced external counterpulsation therapy in patients with coronary artery disease	48	Improvement in Hemoglobin, LVEF, Diastolic and systolic B.P, Chest pain, dyspnea and improve clinical conditions
Subramanian <i>et al.</i> [63]	2016	Effect of enhanced external counterpulsation treatment on aortic blood pressure, arterial stiffness and ejection fraction in patients with coronary artery disease	72	Central B.P significantly decrease with improvement in LV function in CAD patients
Beck <i>et al.</i> [64]	2016	Enhanced external counterpulsation reduces indices of central blood pressure and myocardial oxygen demand in patients with left ventricular dysfunction	17	EECP worked as adjuvant therapy and improvement in functional status, central B.P and myocardial oxygen demand in CAD patients

Table 4. EECP effectiveness on health-related the quality of life in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Arora <i>et al.</i> [65]	2002	Effects of enhanced external counterpulsation on health-related quality of life continue 12 months after treatment: a substudy of the multicenter study of enhanced external counterpulsation	139	Significant improvement in Health-related QoL in patients who had active EECP as compare to those having inactive EECP in all HR-QoL parameters ($p < 0.05$)
Kumar <i>et al.</i> [66]	2009	Effect of enhanced external counterpulsation on clinical symptoms, quality of life, 6-minute walking distance, and echocardiographic measurements of left ventricular systolic and diastolic function after 35 days of treatment and at 1-year follow up in 47 patients with chronic refractory angina pectoris	47	Significant improvement in QoL and walking capacity
Wu <i>et al.</i> [67]	2012	Enhanced external counterpulsation in patients with refractory angina pectoris: a pilot study with six months follow-up regarding physical capacity and health-related quality of life	34	Improvement in physical and functional capacity with HR-QoL improvement
Ziaeirad <i>et al.</i> [68]	2012	The effects of enhanced external counterpulsation on health-related quality of life in patients with angina pectoris	64	Angina & QoL improvement

Table 4. cont. EECP effectiveness on health-related the fuality of life in coronary heart disease patients

Author	Study (year)	Title of study	Sample size	Findings & conclusion
Jorgensen et al. [69]	2013	Improvement of angina, quality of life, and working capacity after enhanced external counterpulsation	One special case	QoL & Angina improvement
May et al. [70]	2015	Enhanced external counterpulsation — effect on angina pectoris, QoL and exercise capacity after 1 year	50	Improvement in exercise capacity with generic and disease specific QoL improvement
Shakouri [71]	2015	Effect of enhanced external counterpulsation and cardiac rehabilitation on quality of life, plasma nitric oxide, endothelin and high sensitive crp in patients with coronary artery disease: a pilot study	42	Mean change in quality of life and endothelial functioning has been observed in CAD patients

Discussion

Above discussed EECP studies validates the significant improvement in CCS and NYHA angina classification, angina episodes, left ventricle ejection fraction functioning, exercise tolerance and HRQoL with reduction of nitroglycerine use & decrease hospitalization rate in coronary heart disease patients. EECP used for angina and heart failure for the past two decades, but still, more research required filling the gaps in research. There are very few or rare study conducted to assess EECP effectiveness on BMI, Heart Rate, Cholesterol, Triglyceride, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), HbA1C, SpO₂, Vo₂max, 12-minute walk or run test and comparative prospective randomized trials on cardiac and non-cardiac metabolic markers.

Conclusion

Further clinical research is required to evaluate EECP effectiveness on obese, diabetic, hypertension and other metabolic disease patients with CHD and multi-centric randomized controlled trials are required for further modifications in EECP device to cure, prevent, and treat chronic diseases such as obesity, hypertension, diabetes, and neurological disorders by the non-invasive procedure.

Conflict of interest

None.

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