

Quality of life improvement after one year follow up in patients with refractory angina pectoris treated with enhanced external counter pulsation

HEIDER HEMEED ABBAS¹, ALI YAHYA ABDULLAH², AHMED N. RAJEEB³, KHALID I. AMBER⁴, AHMED NASIR MACHCHI⁵

¹Department of Basic Medical Sciences, College of Medicine, Babylon University 1

²Consultant Interventional Cardiologist, Department of Medicine, College of Medicine, University of Kufa 2

³Consultant Interventional Cardiologist, Najaf Health Directorate, Najaf Center for Cardiac Surgery & Interventional Catheterization

⁴Consultant Interventional Cardiologist, Najaf Health Directorate, Najaf Center for Cardiac Surgery & Interventional Catheterization

⁵Najaf Health Directorate, Najaf Center for Cardiac Surgery & Interventional Catheterization

Correspondence to Dr. Heider Hemeed Abbas, E.mail: hhemeed@yahoo.com, Mobile: +9647802292151

ABSTRACT

Background:: Refractory angina is usually portrayed as a prolonged state (equal or more than 3 months in duration) considered by angina in the coronary vascular disorder setting, which cannot be regulated by a consolidation of ideal therapeutic treatment, surgical cardiac intervention, and where reversible cardiac ischemia has been stated to be the reason for the manifestation clinically.

Aim: Safety use enhanced external counter pulsation in treating refractory angina pectoris and short term outcome.

Method: Eighty eight (88) patients with refractory angina pectoris un respond to treatment and/or intervention or unfit for intervention or surgery have been enrolled in this prospective, single arm cohort clinical study, symptomatic angina despite medication and/or intervention, for all ECG, echocardiography study done to assess LV and valvular function, Doppler study for lower limb artery to assess if there is peripheral vascular disease, abdominal ultrasound done to exclude the presence of aortic abdominal aneurysm, then if patient eligible for EECP inclusion criteria refer for EECP unit.

Results: Over 12 month's period of the study, 88 persons were assessed including 26(30%) women and 62 (70%) men. The age range was 45 years to 80 years with the mean age range 61 years (SD ± 8.2).

We found statistically significant (p-value < 0.00001) change in symptom from CCS3 and CCS4 pre EECP to CCS1 and CCS2 post EECP. Also we observe that this change in CCS after EECP persist to 6 month and to lesser in 1 year but generally remain in CCS1 and CCS2 at end of 1 year which was also statistically significant (p-value < 0.00001) and we observe that not response appear in CCS4 and CCS3 patients where there improvement persist to the end of year.

Conclusion: EECP appear as safe effective therapy in selective patient with refractory angina not respond to medical and unfit for intervention or surgery. Response to EECP in well selected patient persist for 1 year

Keywords: EECP, Refractory angina pectoris, Quality of life.

INTRODUCTION

Refractory angina is usually portrayed as a prolonged state (equal or more than 3 months in duration) considered by angina in the coronary vascular disorder setting, which cannot be regulated by a consolidation of ideal therapeutic treatment, surgical cardiac intervention, and where reversible cardiac ischemia has been stated to be the reason for the manifestation clinically¹. The clinical load of refractory angina is developing as a result to the individual age and increased toleration of patients from coronary artery illness. The effective controlling of Refractory angina is often exceptionally puzzling.

Povsic et al. exhibited that refractory angina patients were extra habitually hospitalized, frequently subjecting diagnostic angiographic investigation with no revascularization². Attached with confirmation that refractory angina could not to be linked with all the execrable long-term mortality, newly discovered medication approximates aimed for improvement of manifestations and life quality in this exciting population of patients are desired³.

The coronary sinus reducer is a balloon catheter-mounted hourglass-shaped stent that has been shown to improve symptoms and quality of life in patients with refractory angina. Stenting of the coronary sinus to produce a stenosis and increase venous backpressure has gained traction recently as a means of improving perfusion by diverting blood to ischemic myocardium⁴.

In chronic angina, patients may be undergone for interventional revascularization to treat the chronic total occlusions. This mean arterial blood flow is frequently lengthy, actually testing and skilled professional operators required. It may be not without complexities, despite these need essentially decrement over time to ratio compatible to no chronic total occlusion percutaneous coronary intercession⁵.

External Enhanced Counter pulsation is non-invasive therapy include putting external compressive sleeves for the calves, upper and lower thighs followed by consecutively blowing up them with beginning them from distally to proximally with time of heart cycle. Transforming an impact resemble to that produced from an intra-aortic balloon pump, the sleeves are blow nearby beginning of diastole to increase venous return furthermore coronary

perfusion, and discharged in systole to diminish fundamental vascular opposition, improving cardiac workload and systemic perfusion. Therapy is done 1–2 hour sessions over a several weeks which approximate to 35 hours totally. The action mechanism by which counterpulsation has been exhibits to enhance the function of endothelium^{6,7} to diminish vascular stiffness^{8,9} and to flow of friction reserve and collateral blood flow^{10,11} as well as promotion of peripheral vascular extension caused by blood flow, and additionally influencing endothelial determined vasoactive factors by decreasing proinflammatory cytokines and induction turnover of nitric oxide⁹.

The Worldwide EECP tolerant Registry explored cardiac failure patients (who with ejection fraction equal or less than 35 percent) accompanied with refractory angina furthermore detected upgrades for angina population ($p < 0.001$), decreasing nitroglycerin utilization and life quality later termination of therapy. These impacts were preserved in a considerable ratio of patients after following up for three years^{12,13}

However, there is a bulk of studies of EECP have examined its using of EECP in cases of stable angina instead of refractory angina and, due to the intervention nature, EECP is restricted by a sum of contraindications which may include coagulation disorders with an international normal ratio of more than 2.5, severe chronic obstructive lung disease, cardiac arrhythmias, venous disease, severe peripheral arterial disease⁶.

However, EECP has been revealed reduction of hospitalization fees that will serve to encourage EECP adoption going forward.¹⁴ Equivalent to the progresses in cardiovascular carefulness, there is an growing of patients amount, mainly individuals with progressive coronary artery sickness, carry extreme manifestations caused by angina pectoris that not respond for ideal therapeutic treatment¹⁵ The modern treatments for refractory angina include medications (such as Ivabradine and Ranolazine), noninvasive treatment compromise enhanced external counterpulsation (EECP) and extracorporeal shockwave cure, invasive therapy, neuromodulation, and others^{16,17} As indicated nowadays scientific revisions, noninvasive EECP has been confirmed to be a hopeful therapy for angina relieve caused by firm coronary artery illnesses¹⁸.

EECP method, a noninvasive and nonpharmacological outpatient management, has been accepted by the Food and Drug Administration (FDA) in united states in patients with unstable or stable angina pectoris, congestive cardiac failure, cardiogenic trauma and intense myocardial infraction.¹⁹ Nowadays the EECP technique is utilized for angina patients unqualified for routine medical treatment who are not hopeful for further revascularization methods and those desired to suspend invasive therapy.

A lot of trials have confirmed that EECP lessened symptoms of angina by protracted total occlusions,^{20,21} advanced satisfaction of life quality^{21,22} improved exercise tolerance 21-24 and also increased the time to training provoked depression of ST-segment²³⁻²⁵ and to enhance perfusion of myocardium^{23,24}.

The instrument underlying the profit of EECP-derived is under assessment, which may be included the possible

mechanisms include endothelial function enhancement, improvement of collateralization, atherosclerosis declining, and peripheral “training impacts ” resemble for exercising¹⁹ The intense hemodynamic impact resulted shear pressure that may cause enhancement of production of powerful elements of vasodilatation which include nitric oxide and prostacyclin from endothelial cells. Several studies approved that there was increased quantity of nitric oxide and reduction the of brain natriuretic peptide and serum endothelin-1 concentration following EECP treatment^{24,26}.

Sessa et al.²⁷ established that prolonged practicing of exercise stimulates synthesis of nitric oxide gene expression and production of coronary nitric oxide in model of dogs. This procedure may have been started following EECP with enriching their training tolerance. Masuda et al. exhibited an increment in both resting furthermore post practice perfusion which may be enhance indirectly through creation preexist collaterals or opening new ones by expanded transmural stress gradients throughout EECP^{28,29}

EECP-enhanced promotions in periphery of endothelial function furthermore rigidity of arteries should lead to a important decrease in left ventricular after load and thusly, a decrease in oxygen gas needing of myocardial tissue. We have achieved 2 revisions exploring whether these EECP-induced decreases in after load of left ventricle are definitely connected with perfection in keys of myocardial oxygen request in coronary artery disorders patients with manifestations of chronic cardiac ischemia³⁰.

Aim of study: Safety use enhanced external counter pulsation in treating refractory angina pectoris and short term outcome.

PATIENT AND METHOD

Eighty eight patients with refractory angina pectoris un respond to treatment and/or intervention or unfit for intervention or surgery have been enrolled in this study, all these persons had been selected from those patients visit the cardiology consult department in Al-najaf cardiac center or from private clinic from the period January 2018 to January 2019, all patient's treated according do guidelines and refer to EECP according to it, from all patients agree to enter in this research counsel have been taken. For all patient's data collected about age, sex, blood pressure, laboratory finding of glucose, renal function, complete blood count have been done.

This patients includes 62 male and 26 female was involve in this prospective, single arm cohort clinical study, there age range from 45 to 80 year, symptomatic angina despite medication and/or intervention, for all ECG, echocardiography study done to assess LV and valvular function, Doppler study for lower limb artery to assess if there is peripheral vascular disease, abdominal ultrasound done to exclude the presence of aortic abdominal aneurysm, then if patient eligible for EECP inclusion criteria refer for EECP unit .

After end of all session all patients assess improvement according to change in Canadian cardiovascular society grading CCS pre and post EECP and on follow up 6 month and 1 year, at follow up by clinical visit or telephone attachment , 6 patients leave the research and 25 patients

miss contact and 3 patients die at period 2-8 months after end of session and 4 patients no tolerated session so stop prematurely at 4 session and excluded from data analysis and only 53 patient complete 1 year follow up.

Most patients have been diagnose with multi vessel diseased by angiography where significant coronary stenosis (> 70 %) in each vessel, most of our patents in this research have 3 vessel diseased with either unfit to intervention and / or surgery or un respond to it.

In EECP unit we have 20 EECP device (vasomedical, Inc., Westbury, New York) each one compose of an air compressor that attach to pneumatic cuffs and control by computer system, also each device have figure plethysmography for monitor systolic and diastolic pulse wave and transmitted to computer, the pneumatic cuff applied to lower limb and inflated sequentially during diastole with pressure 250-300 mmHg for few second by computer control which detect diastole by ECG or figure plethysmography monitor, each session duration 1 hour and most patient's should complete 30 session if tolerated , before assessment for response and the need for extension of session.

Inclusion criteria :Any patient with refractory angina pectoris unrespond to medication and / or intervention or unfit for intervention / surgery.

Exclusion criteria:

1. Severe peripheral vascular diseased
2. Abdominal aortic aneurysm
3. Severe aortic regurgitation
4. Uncontrolled hypertension
5. Uncontrolled congestive heart failure
6. Within 2 week from angiography from femoral rout
7. Thrombocytopenia and bleeding tendency
8. Deep vein thrombosis
9. Significant varicose vein

Statistical analysis: We use paired student t test and chi square test for both continuous variables and categorical variables, p value < 0.05 was regards as statistical significance.

We use mean, with stander deviation to describe categorical variables and t test for continuous variables as blood pressure before and after intervention. Calculations done by EXCEL Microsoft 2016 software.

RESULTS

Over 12 month's period of the study, 88 persons were assessed including 26(30%) women and 62 (70%) men. The age range was 45 years to 80 years with the mean age range 61 years (SD ± 8.2). Most patients treated with 30 session with 1 hour per session on average of 26 (SD ± 7) session with response rate at end of sessions 88.7% where response mean improvement of symptom and according to (CCS)change per and post EECP. We found statistically significant (p-value < 0.00001) change in symptom from CCS3 and CCS4 pre EECP to CCS1 and CCS2 post EECP as seen in figure 1.

Also we observe that this change in CCS after EECP persist to 6 month and to lesser in 1 year but generally remain in CCS1 and CCS2 at end of 1 year which was also statistically significant (p-value < 0.00001)and we observe that not response appear in CCS4 and CCS3 patients

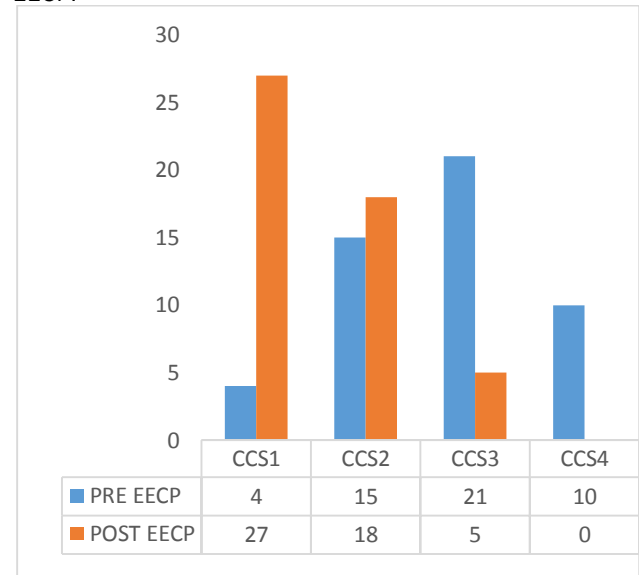
where there improvement persist to the end of year as seen in figure 2.

The response to EECP was not statistically (p-value = 0.185) affected by sex as seen in figure 3.

The smoking not statistically (p-value = 0.67) affect the response of patients to EECP (Fig. 4) The age appear as not statistically significant (p-value < 0.26) in response rate of patients to EECP (Fig.5). Hypertension appear to be non-effluence in response patients to EECP as it not statistically significant (p-value = 0.4) as seen in figure 6.

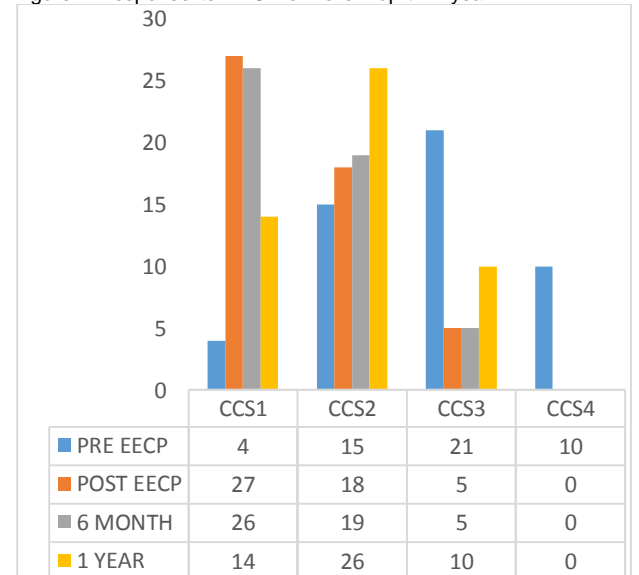
Surprisingly that diabetes observe as no influence in response to EECP as it not statistically significant (p-value = 0.12) as seen in figure 7.

Figure.1: Response in symptom as graded by CCS pre and post EECP.



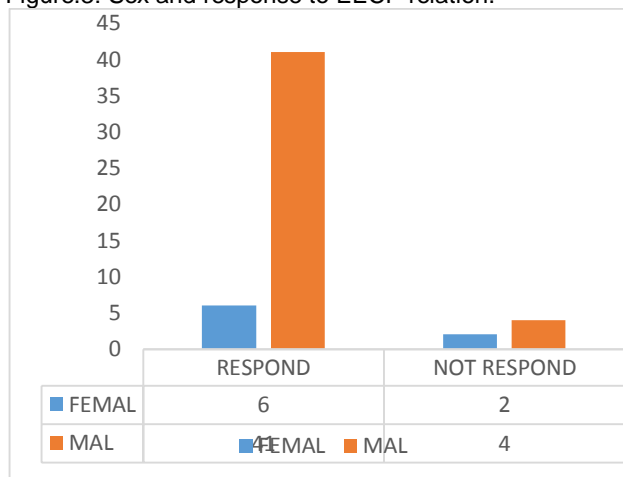
P-value < 0.00001

Figure.2 Response to EECP on follow up till 1 year.



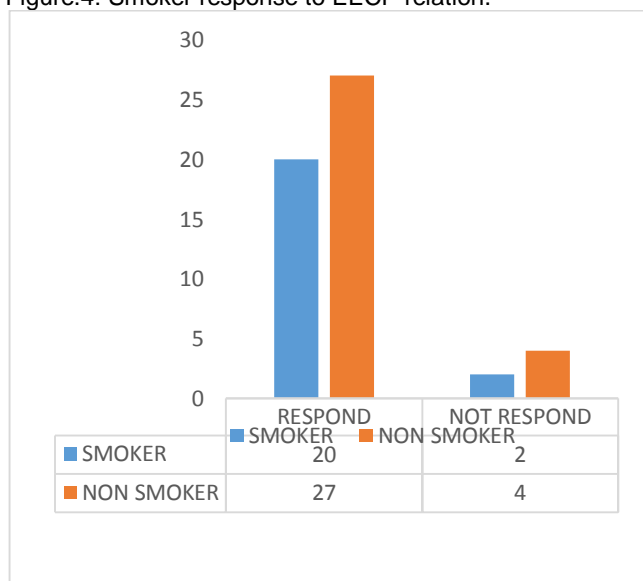
P-value < 0.00001

Figure.3: Sex and response to EECP relation.



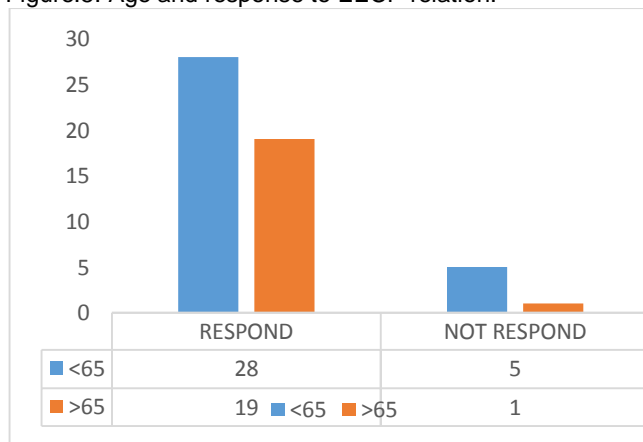
P-value = 0.185

Figure.4: Smoker response to EECP relation.



P-value = 0.67

Figure.5: Age and response to EECP relation.



P-value < 0.26

DISCUSSION

Most patients in this research have diffuse coronary disease confirmed by angiography some do intervention and other was beyond or unfit for it, so as they with refractory angina and unreasoned to medication they referred to EECP and in this research we found dramatic symptomatic response to this type of therapy specially that most patient was in CCS3 and CCS4 After the end of EECP sessions most patients improve in their symptom from CCS3 and CCS4 to CCS1 and CCS2 and this in concomitant with MUST-EECP³¹.

Also we observe that this improvement in symptom persist in follow up till the end of year of follow up in majority of patients and this in concomitant with other research 32-34 and most patients with CCS4 get response that no patient in 1 year follow up enter this stage as most patients remain in CCS2 and to lesser extend in CCS3 35, and that why we found dramatic improve in quality of life in our patients.

Decrease in symptom (CCS) may appear without increment in myocardial perfusion, and the initial advantage of this therapy can related to secondary action comparable to those of physical rehabilitation.³⁶ The mode of action of persist long-term benefits are multi-factorial and include refinement in the endothelial function, angiogenesis, exercise training effect, and neurohormonal modulation^{37,38}.

The International EECP Patient Registry (IEPR)³⁹ reported sustained improvement in angina and quality of life in the majority of patients over a 2-year period, an observational study has reported that the benefits may be sustained for 5 years⁴⁰.

In our research we observe that diabetic and nondiabetic patients show significant refinement in symptom and quality of life with after EECP therapy as observe by other research^{41,42}.

CONCLUSION

EECP appear as safe effective therapy in selective patient with refractory angina not respond to medical and unfit for intervention or surgery.

Response to EECP in well selected patient persist for 1 year

Limitation of study:

- 1.Larger number patient's research needed to confirm this research finding
- 2.Midterm to long term follow up needed to identify morbidity and mortality.
- 3.Compare with placebo or medical alone needed.

REFERENCE

1. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the 4e ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J* 2002;23:355–70. <https://doi.org/10.1053/euhj.2001.2706>; PMID: 11846493.
2. Povsic TJ, Broderick S, Anstrom KJ, et al. Predictors of longterm clinical endpoints in patients with refractory angina. *J Am Heart Assoc* 2015;e001287. Lawson WE, Hui JKC, Zheng ZS, Oster Z, Katz JP, Diggs P, Burger L, Cohn CD,

- Soroff HS, Cohn PE. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995;75:840-841.
3. Henry TD, Satran D, Hodges JS, et al. Long-term survival in patients with refractory angina. *Eur Heart J* 2013;34:2683–8. <https://doi.org/10.1093/eurheartj/eh1165>; PMID: 23671156.
 4. Beck CS, Leighninger DS. Scientific basis for the surgical treatment of coronary artery disease. *J Am Med Assoc* 1955;159:1264–71. <https://doi.org/10.1001/jama.1955.02960300008003>; PMID: 13271060.
 5. Werner GS, Hochadel M, Zeymer U, et al. Contemporary success and complication rates of percutaneous coronary intervention for chronic total coronary occlusions: results from the ALKK quality control registry of 2006. *Euro Intervention* 2010;6:361–6. <https://doi.org/10.4244/EIJV6I3A60>; PMID: 0884415.
 6. Manchanda A, Soran O. Enhanced external counterpulsation and future directions: step beyond medical management for patients with angina and heart failure. *J Am Coll Cardiol* 2007;50:1523–31. [tps://doi.org/10.1016/j.jacc.2007.07.024](https://doi.org/10.1016/j.jacc.2007.07.024); PMID: 17936150.
 7. 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;41:1761–8. [https://doi.org/10.1016/S0735-1097\(03\)00329-2](https://doi.org/10.1016/S0735-1097(03)00329-2); PMID: 12767662.
 8. 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;48:1208–14. <https://doi.org/10.1016/j.jacc.2006.04.094>; PMID: 16979007
 - Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five years follow-up study. *Clin Cardiol* 2000;23:254–258.
 9. Levenson J, Pernollet MG, Iliou MC, et al. Cyclic GMP release by acute enhanced external counterpulsation. *Am J Hypertens* 2006;19:867–72. <https://doi.org/10.1016/j.amjhyper.2006.01.003>; PMID: 16876689.
 10. Buschmann EE, Utz W, Pagonas N, et al. Improvement of fractional flow reserve & collateral flow by treatment with external counterpulsation (Art.Net.-2 Trial). *Eur J Clin Invest* 2009;39:866–75. <https://doi.org/10.1111/j.1365-2362.19572918>; PMID: 19572918.
 11. Gloekler S, Meier P, de Marchi SF, et al. Coronary collateral growth by external pulsation: a randomised controlled trial. *Heart* 2010;96:202–7. <https://doi.org/10.1136/hrt.2009.184507>; PMID: 19897461.
 12. Soran O, Kennard ED, Kfoury AG, Kelsey SF. IEPH 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. <https://doi.org/10.1016/j.amjcard.2005.07.122>;
 13. Loh PH, Cleland JGF, 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. *Clin Cardiol* 2008;31:159–64. <https://doi.org/10.1002/clc.20117>;
 14. Lawson WE, Hui JCK, Kennard ED, Linnemeier G. IEPH-II Investigators. Enhanced external counterpulsation is cost-effective in reducing hospital costs in refractory angina patients. *Clin Cardiol* 2015;38:344–9. <https://doi.org/10.1002/clc.22395>; PMID: 25962616.
 15. McGillion M, Arthur HM, Cook A, et al. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines. *Can J Cardiol*. England: 2012 Canadian Cardiovascular Society. Published by Elsevier Inc;2012:S20-S41.
 16. Henry TD, Satran D, Jolicoeur EM. Treatment of refractory angina in patients not suitable for revascularization. *Nat Rev Cardiol*. 2014;11:78–95.
 17. Manchanda A, Aggarwal A, Aggarwal N, et al. Management of refractory angina pectoris. *Cardiol J*. 2011;18:343–351.
 18. Montalescot G, Sechtem U, Achenbach S, et al. 2013 esc guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European society of cardiology. *Eur Heart J*. 2013;34:2949–3003.
 19. Soran O. Treatment options for refractory angina pectoris: enhanced external counterpulsation therapy. *Curr Treat Options Cardiovasc Med*. 2009;11:54–60.
 20. Michaels AD, Linnemeier G, Soran O, et al. Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the international eecp patient registry iepr). *Am J Cardiol*. 2004;93:461–464.
 21. Yavari M, Montazeri HR. Effects of enhanced external counterpulsation on anginal symptoms and improvements in objective measures of myocardial ischaemia. *Cardiovasc J Afr*. 2007;18:154–156.
 22. Kumar A, Aronow WS, Vadnerkar A, et al. 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. *Am J Ther*. 2009;16:116–118.
 23. Urano H, Ikeda H, Ueno T, et al. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. *J Am Coll Cardiol*. 2001;38:93–99 United States.
 24. 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 n-13-ammonia positron emission tomography. *Eur Heart J*. 2001;22:1451–1458.
 25. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (must-eeep): effect of eecp on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol*. 1999;33:1833–1840.
 26. Akhtar M, Wu G-F, Du Z-M, et al. Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. *Am J Cardiol*. 2006;98:28–30.
 27. Sessa WC, Pritchard K, Seyedi N, et al. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. *Circ Res*. 1994;74:349–353.
 28. Flynn MS, Kern MJ, Donohue TJ, et al. Alterations of coronary collateral blood flow velocity during intraaortic balloon pumping. *Am J Cardiol*. 1993;71:1451–1455.
 29. Kern MJ, Aguirre FV, Tatineni S, et al. Enhanced coronary blood flow velocity during intraaortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol*. 1993;21:359–368.
 30. Casey DP, Beck DT, Nichols WW, Conti CR, Choi CY, Khuddus MA, Braith RW. Effects of enhanced external counterpulsation on arterial stiffness and myocardial oxygen demand in patients with chronic angina pectoris. *The American journal of cardiology*. 2011; 07(10):1466–72. [PubMed: 21420062]
 31. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, Mckiernan T, Nesto RW. The multicenter study of enhanced external counter pulsation (MUST-EECP): effect of enhanced external counter pulsation on exercise-induced myocardial ischemia and angina episodes. *J Am Coll Cardiol* 1999;33:1833-1840.

32. Aroru RR, Chou TM, Jain D, Fleishman B, Crawford L, Mckiernan T, Nesto R, Ferrans CE, Keller S. Effects of enhanced external counter pulsation on health-related quality of life continue 12 months after treatment: a substudy of the multicenter study of enhanced external counter pulsation. *J Invest Med* 2002;50:25-32.
33. Lawson WE, Hui JKC, Zheng ZS, Oster Z, Katz JP, Diggs P, Burger L, Cohn CD, Soroff HS, Cohn PE. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995;75:840-841.
34. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counter pulsation: fiveyears follow-up study. *Clin Cardiol* 2000;23:254-258.
35. Pettersson T, Bondesson S, Cojocar D, Ohlsson O, Wackenfors A, Edvinsson L. One-year follow-up of patients with refractory angina pectoris treated with enhanced external counter pulsation. *BMC Cardiovasc Disord* 2006;6:28.
36. Michaels AD, Raisinghani A, Soran O, De lame PA, Lemaire ML, Kligfield P, Watson DD, Conti CR, Beller G. The effects of enhanced external counter pulsation on myocardial perfusion in patients with stable angina: a multicenter radionuclide study. *Am Heart J* 2005;150:1066-1073.
37. Masuda D, Nohara R, Hirai T, Kataoka K, Chen LG, Hosokawa R, Inubushi M, Tadamura E, Fujita M, Sasayama S. Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina; evaluation by(13)N-ammonia positron emission tomography. *Eur Heart J* 2001;22:1451-1458.
38. Bonetti PO, Holmes DR, Lerman A, Barsness GW, Jr. Enhanced external counterpulsation for ischemic heart disease: what's behind the curtain? *J Am Coll Cardiol* 2003;41:1918-1925.
39. Michael AD, Linnemeier G, Soran O, Kelsey SF, Kennard ED. Two-years out comes after enhanced external counter pulsation for stable angina pectoris (from the international EECPP patient Registry (IEPR)). *Am J Cardiol* 2004;93:461-464.
40. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counter pulsation: fiveyears follow-up study. *Clin Cardiol* 2000;23:254-258.
41. Urano H, Ikeda H, Ueno T, Matsumoto T, et al. Enhanced External Counter pulsation Improves Exercise Tolerance, Reduces ExerciseInduced Myocardial Ischemia and Improves Left Ventricular Diastolic Filling in Patients With Coronary Artery Disease. *J Am Coll Cardiol*, 2001; 37(1):93-99.
42. Feldman AM, Silver MA, Francis GS, et al. Enhanced External Counter pulsation Improves Exercise Tolerance in Patients with Chronic Heart Failure. *J Am Coll Cardiol*, 2006; 48(6):1199-1206.