Original Article

Echocardiographic Characteristics Including Tissue Doppler Imaging After Enhanced External Counterpulsation Therapy

Majid Maleki, MD[1], Gilda Estahbanaty, MD[1*], Niloufar Samiei, MD[1],
Fereidoon Noohi, MD[1], Ahmad Mohebi, MD[1], Zahra ojaghi, MD[1],
Maryam Esmaeilzadeh, MD[1], Anita Sadeghpour, MD[1],
Ozlem Soran, MD, MPH, FACC, FESC[2]

[1]Shahid Radjaie Cardiovascular Center, Iran University of Medical Sciences, Tehran, Iran.
[2]Cardiovascular Institute, University of Pittsburgh, USA

Abstract

Background: The aim of this study was to echocardiographically assess the effects of EECP (Enhanced External Counterpulsation Therapy) therapy on systolic and diastolic cardiac function.

Methods: LVEF (left ventricular ejection fraction), ESV (end-systolic volume), EDV (end-diastolic volume), Sm (myocardial systolic wave), Ea (myocardial early diastolic wave), Vp (propagation velocity), E/Ea (peak early diastolic transmitral flow velocity/Ea), E/Vp and diastolic function grade were studied in twenty-five patients before and after 35 hours of EECP.

Results: EECP reduced ESV and EDV and increased EF significantly (p=0.018, 0.013, 0.002, respectively) in patients with baseline LVEF ≤ 50%, but not in patients with baseline LVEF>50%. Patients with E/Ea ≥ 14 had a significant reduction in EDV and ESV (p=0.038 and 0.32, respectively) and an increase in LVEF (p=0.007) after EECP, whereas patients with baseline E/Ea<14 had no significant change in these parameters. Similarly, EECP significantly improved ESV, EDV and LVEF (p=0.014, 0.032, 0.027 respectively) in patients with grades II and III of diastolic dysfunction (decreased compliance) at baseline, but not in patients with normal diastolic function or grade I diastolic dysfunction (impaired relaxation). Patients with Ea<7 cm/sec prior to EECP showed significant improvement in EDV, ESV and LVEF after therapy (p=0.024, 0.015, 0.001), while patients with Ea ≥ 7cm/sec showed no significant change. Similarly, patients with Sm<7cm/sec prior to EECP showed significant improvement in EDV, ESV and LVEF after EECP (p=0.016, 0.017, 0.006), while patients with Sm ≥ 7cm/sec did not.

Conclusion: These results provide new insight into the hemodynamic effectiveness and potential clinical applications of EECP.

Introduction

Enhanced External Counterpulsation Therapy (EECP) has been studied for 45 years as a noninvasive method for the

*Corresponding Author: **Gilda Estahbanaty,** fellow of echocardiography, Iran Medical University, Shahid-Radjaie Cardiovascular Center. Valiye asr Street, Tehran, Iran. 15745/747. Tel: +98 21 23922930. Fax: +98 21 22055594. E-mail: gildaestahbanaty@yahoo.fr.*

treatment of ischemic heart disease.1,2 Recently, EECP has been used successfully as therapy for patients with chronic stable angina inadequately controlled with medication and unsuitable for PCI (percutaneous coronary intervention) or CABG (coronary artery bypass graft surgery).3-5 EECP increases time to exercise-induced ischemia, reduces angina frequency and nitroglycerin use, and improves Canadian Cardiovascular Society classification (CCS) and quality of life.3,4,6-9 It has been reported that up to 15% of patients with angina meet the criteria for refractory angina.10

Although EECP is known to decrease symptoms in patients with angina, its role in patients with heart failure has only recently been investigated. Recent studies suggest EECP increases exercise capacity by increasing peak oxygen uptake and exercise duration and improving functional status and quality of life in patients with heart failure. With the help of these studies, FDA cleared the EECP therapy for treatment of heart failure in 2002.11-16

EECP is associated with an immediate and long-lasting increase in the blood flow of coronary arterial circulation,17,18 increasing endothelial shear stress19 and enhancing endothelial function by stimulating the release of the vasodilatory mediator nitric oxide and reducing the release of vasocontractile endothelin-1.20-22 Also, EECP stimulates collateral blood vessel development not only by increasing the release of angiogenesis factors such as vascular endothelial growth factor,23,24 basic fibroblast growth factor, and hepatocyte growth factor,20,24 but also by increasing monocyte chemoattractant protein 1 (a proinflammatory cytokine).

The present study sought to evaluate the effects of EECP on the echocardiographic parameters of systolic and diastolic function before and after a 35-hour course of EECP.

Study population

Twenty-five consecutive patients with refractory chronic, stable angina met the following inclusion criteria: (1) age>18 years; (2) symptoms of angina consistent with Canadian Cardiovascular Society classification II or III; (3) angiographically proven CAD; and (4) deemed a poor candidate for PCI or CABG.

Patients were excluded if they had any of the following: (1) unstable angina; (2) myocardial infarction in the preceding 6 weeks; (3) LV ejection fraction <25%; (4) significant valvular disease; (5) overt heart failure; (6) left main lesion>50%; (7) blood pressure >180/100mmHg; (8) a permanent pacemaker or ICD (Internal Cardiac Defibrillator); (9) AF (Atrial Fibrillation) rhythm or frequent PVC (Premature Ventricular Contraction) that interfered with EECP triggering; (10) severe peripheral vascular disease, phlebitis or deep vein thrombosis; and (11) bleeding diathesis or warfarin use with INR > 2.0.

Medication usage remained unchanged during this study and patients underwent echocardiography before and after EECP therapy.

Methods

EECP

All patients were treated with an EECP therapy system (Vasomedical, Inc., Westbury, New York), comprised of an air compressor, computer console, treatment table and an integrated cuff set with three pairs of pneumatic cuffs. Before treatment, the cuffs are wrapped around the calves and the lower and upper thighs of the patient, and ECG leads are placed. In synchrony with the patient's cardiac cycle, the EECP system inflates the cuffs with air in rapid sequence from the calves to the buttocks in early diastole, compressing blood vessels in the lower extremities and displacing venous and arterial blood towards the heart. At the end of diastole, the compressed air is released from all the cuffs simultaneously to rapidly remove the externally applied pressure and allow the vessels to reconform. Inflation increases diastolic blood pressure (diastolic augmentation) and venous return during diastole, while deflation reduces vascular impedance and cardiac workload during the subsequent systole. The EECP was applied in 35 hours divided into 60-minute sessions five days per week. During each session, the change in the patients' blood pressure wave was monitored by finger plethysmography. A cuff pressure of approximately 0.04 Pascal was applied so that the ratio of plethysmographically-measured diastolic peak pressure to systolic peak pressure was 1.5 times or higher.

Echocardiography

Standard echocardiography examinations were carried out in accordance with the recommendations of the American Society of echocardiography using a digital ultrasound machine (Vivid 3, GE Medical Systems, Inc.) with the patient in the left, lateral decubitus position. A variable frequency phased-array transducer (2.5-3.5-4.0MHZ) was used for two-dimensional, M-mode and Doppler imaging. All measurements were analyzed using the average of ≥3 cardiac cycles. Two-dimensional (2D) measurements of left ventricular (LV) volume were obtained from the apical 4-chamber view at end-diastole and end-systole, and left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method.

Pulsed Doppler assessment of LV inflow was performed in the apical 4-chamber view with the sample volume placed at the level of the valve tips. The following measurements of global LV diastolic function were determined: peak velocity of the of E and A waves and the E/A ratio; deceleration time of the E wave (msec); and isovolumic relaxation time (msec), measured as the time interval occurring between the end of systolic output flow and transmittal E-wave onset by placing pulsed Doppler sample volume between the outflow tract and the mitral valve.

Pulsed Doppler myocardial imaging

Pulsed doppler myocardial imaging (DMI) was performed by spectral pulsed Doppler signal filters by adjusting the Nyquist limit within 15-20 cm/sec (close to myocardial velocities) and using minimal optimal gain. In the apical 4-chamber view, a 3.5-mm pulsed Doppler sample volume was placed on the basal septum of the LV at the level of mitral annulus. Myocardial systolic wave (Sm) and early diastolic wave (Ea) were measured.

Diastolic function grading

Normal LV diastolic function was diagnosed if the peak early diastolic transmitral flow velocity (E)/peak late diastolic transmitral flow velocity (A) ratio was between 0.75 and 1.5 and the E/Ea ratio was <10. Mild LV diastolic dysfunction was diagnosed if the E/A ratio was <0.75 regardless of the E/Ea ratio. Moderate LV diastolic dysfunction was diagnosed if the E/A ratio was between 0.75 and 1.50 and the mitral E/ peak early diastolic myocardial velocity (Ea) ratio was >10. Severe LV diastolic dysfunction was diagnosed if the E/A ratio was >1.5 and the E/Ea ratio was >10.

Color Doppler M-mode imaging

Mitral inflow propagation velocity was evaluated from the apical 4-chamber view using color flow imaging to place a color M-mode cursor parallel to mitral inflow in the center of the flow stream. The aliasing velocity of 0.5 to 0.7 m/sec and signal was recorded at a fast sweep speed (100-200 mm/sec). The slope of the first aliasing velocity from the mitral valve to LV was measured.

Statistical analysis

All values were expressed as mean±SD. The paired t-test method was used to compare pre-treatment with post-treatment values and statistical significance was determined at a level of $p < 0.05$.

Results

Twenty-five consecutive patients presenting for EECP therapy were enrolled in this study. Mean age of the patients was 57.8±9 years (range: 42 to 82 years) and eighteen were men (72%). Eighteen patients (72%) had three vessels and six patients (24%) had two-vessel disease, one patient (4%) had single vessel disease. Sixteen patients had history of CABGS (64%) (Table 1).

Table 1. Baseline characteristics

Mean age, range (years)	57.8, 42-82
Gender (men / women)	18
Coronary artery disease factors and revascularization status	
3VD	18(72%)
2VD	6(24%)
1VD	1(4%)
Left ventricular ejection fraction	
EF>50%	12(48%)
EF=31%-50%	8(32%)
EF<31%	5(20%)
Prior PCI	2(8 %)
Prior CABG surgery	16(64%)
Angina CCS class	
I	5 (20%)
II	13 (52 %)
III	7 (28 %)
IV	0

CAD, Coronary artery disease; CABG, Coronary artery bypass grafting; PCI, Percutaneous coronary intervention; CCS, Canadian cardiovascular society classification

Mean baseline end-diastolic volume (EDV) was 125.08±67.5 ml and end-systolic volume (ESV) was 73.6±60 ml, both of which reduced significantly after EECP therapy to 105±58.4 ml and 59.8±47.2 ml, respectively (both p<0.01). Mean LVEF was 46%±12.6% at baseline, which increased significantly to 51.5%±12% (p<0.01). Mean baseline Ea and Sm were 10±5.7 cm/sec and 9±5.44 cm/sec, respectively, and showed no significant change after EECP. Mean propagation velocity, E/Ea, and E/Vp before treatment were 42.40±13.79, 15.6±7.46, 2.05±0.90, respectively, and showed no change after EECP therapy. Mean diastolic function grade was 2.24±1.26 pre-treatment, and exhibited no significant change after therapy (Table 2).

Table 2 Changes in left ventricular function after EECP*

	Pre-EECP	Post-EECP	P value
LVEF (%)	46±12.6	51.5±12	<0.01
LVEDV (ml)	125.08±67.5	105±58.4	<0.01
LVESV (ml)	73.6±60	59.8±47.2	<0.01

*Data are stated as mean±SD
EECP, Enhanced external counterpulsation; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume

In a secondary set of analyses, patients were divided according to whether their baseline values fell above or below prespecified thresholds. EECP reduced ESV and EDV while it increased LVEF significantly (p=0.018, 0.013, 0.002, respectively) in patients with baseline LVEF≤50%. There was no such change in those with baseline LVEF>50%.

Patients with E/Ea<14, who were expected to have low left atrial pressure, had no improvement in EDV, ESV, and LVEF after EECP treatment, whereas those with E/Ea ≥14, who were expected to have elevated LAP, had a significant reduction in EDV and ESV (p=0.038 and p=0.032, respectively) and an increase in LVEF (p=0.007). Similarly, patients with normal diastolic function or mild diastolic dysfunction (impaired relaxation) had no significant change in EDV, ESV, and LVEF after EECP treatment, while patients with moderate to severe diastolic dysfunction (decreased LV compliance) had significantly improved ESV, EDV, and LVEF (p=0.014,0.032,0.027 respectively).

Patients with Ea<7 cm/sec prior to EECP showed a significant improvement in EDV, ESV, and LVEF after therapy (p=0.024, 0.015, 0.001), while those with Ea≥7cm/sec exhibited no significant change. Similarly, patients with baseline Sm<7cm/sec showed a significant improvement in EDV, ESV, LVEF after EECP (p=0.016, 0.017, 0.006), while those with Sm≥7cm/sec showed no significant change after EECP.

Discussion

The present study is one of the first echocardiographic studies of patients treated with EECP for chronic stable refractory angina pectoris focusing on tissue Doppler imaging. Findings in this study demonstrated that EECP significantly increases LVEF and decreases EDV and ESV. Therefore, systolic function and LV volumes improve after EECP therapy.

Urano et al. reported that EECP treatment improved not only LV dilation, but also myocardial blood flow.22 EECP treatment is also associated with an immediate increase in blood flow in multiple vascular beds, including the coronary arterial circulation.16 As a result, EECP increases endothelial shear stress by increasing blood flow,10 which enhances endothelial function7 by stimulating the release of vasodilatory mediator nitric oxide and reducing the release of vasocontractile endothelin-1.19,20,23 These changes are progressive during the course of therapy24 and serve to explains improved coronary perfusion and vasodilation after EECP.

The result of this study shows no significant change in diastolic function parameters such as Ea, propagation velocity, E/Ea, E/Vp, and diastolic function grade. Similarly, in a recent study, no significant change in fractional shortening and diastolic function was observed. There was a reduction

in the area of inducible ischemia at dobutamine stress echocardiography after EECP; nevertheless, perhaps due to a small sample size, it was not significantly different.25

It was noted that the patients with lower LVEF (≤50%) and Sm velocity of the septal annulus (<7cm/sec) had more significant changes in LVEF, EDV, and ESV than the patients with higher E/Ea (≥14) and lower Ea velocity of septal annulus (<7cm/sec). Therefore, in our study the patients with more advanced systolic and diastolic dysfunction, and higher LV end diastolic pressure and left atrial pressure, had more improvement in LVEF, EDV, and ESV, which is in accordance with results reported by Novo et al. regarding a trend that patients who benefited most were those with worse systolic function and severely compromised segmental kinesis.25

Results from this study provide new insight into the hemodynamic effects of EECP therapy in patients with coronary artery disease and either preserved or impaired left ventricular function. Effects of this safe, noninvasive therapy in individual patients can be more readily anticipated and clinical application of EECP may hold the promise of being more specifically prescribed in the near future.

Acknowledgement

References

1.   Denis C, Moreno JR, Hall DP, Crosz C, Ross SM, Wesolowski SA, Senning A. Studies on external counterpulsation as a potential measure for acute left heart failure. Trans Am Soc Artif Int Organs 1963;9:186 –191.

2.   Soroff HS, Hui J, Giron F. Current status of external counterpulsation. Crit Care Clin 1986;2:277– 295.

3.   Lawson WE, Hui JCK, Soroff HS, Zheng ZS, Kaydan DS, Sasvary D, Aktins H, Cohn PF. Efficacy of enhanced external counter-pulsation in the treatment of angina pectoris. Am J Cardiol 1992;70:859–862.

4.   Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, MacKiernan T, Nesto RW. 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.

5.   Sinvhal RM, Gowda RM, Khan IA. Enhanced external counterpulsation for refractory angina pectoris. Heart 2003;89:830-833.

6.   Barsness G, Feldman AM, Holmes DR, Jr., Holubkov R, Kelsey SF, Kennard ED. The International EECP Patient Registry (IEPR): design, methods, baseline characteristics, and acute results. Clin Cardiol 2001;24:435- 442.

7.   Bonetti PO, Holmes DR, Jr., Lerman A, Barsness GW. Enhanced external counterpulsation for ischemic heart disease: what's behind the curtain? J Am Coll Cardiol 2003;41:1918-1925.

8.   Michaels AD, Linnemeier G, Soran O, Kelsey SF, Kennard

ED. 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.

9. Lawson WE, Hui JC, Kennard ED, Kelsey SF, Michaels AD, Soran O, International Enhanced External Counterpulsation Patient Registry Investigators. Two-year outcomes in patients with mild refractory angina treated with enhanced external counterpulsation. Clin Cardiol 2006;29:69-73.

10. Pettersson T, Bondesson S, Cojocaru D, Ohlsson O, Wackenfors A, Edvinsson L. One year follow-up of patients with efractory angina pectoris treated with enhanced external counterpulsation. BMC Cardiovascular Disorders 2006;6:28-31.

11. Soran O, De Lame PA, Fleishman B, Grossman W, Feldman AM. The Safety and Efficacy Enhanced External Counterpulsation (EECP) In-Patients with Heart Failure: A Multi-center Feasibility Study. Congest Heart Fail 2002;8:204-208.

12. Soran O, Kennard ED, Kelsey SF, Holubkov R, Strobeck J, Feldman AM. Enhanced External Counterpulsation as treatment for Chronic Angina in patients with Left Ventricular Dysfunction: A Report from the International EECP Patient Registry (IEPR). Congest Heart Fail 2002;8:297-302.

13. Soran O, Kennard ED, Kfoury AG, Kelsey SF, for the 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.

14. Feldman AM, Silver MA, Francis GS, Abbottsmith CW, Fleishman B, Soran O, Lame PA, Varrricchione T. Enhanced external countrepulsation Improves Exercise tolerance in Patients with Chronic Heart Failure. Am Coll Cardiol 2006;48:1198-1120.

15. Taguchi I, Ogawa K, Kanaya T, Matsuda R, Kuga H, Nakatsugawa M. Effects of Enhanced External Counterpulsation on Hemodynamics and Its Mechanism Relation to Neurohumoral Factors. Circ J 2004;68:1030–1034.

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. Taguchi I, Ogawa K, Kanaya T, Matsuda R, Kuga H, Nakatsugawa M. Effects of enhanced external counterpulsation on hemodynamics and its mechanism. Circ J 2004;68:1030-1034.

18. 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 hronic stable angina; evaluation by(13)N-ammonia positron emission tomography. Eur Heart J 2001;22:1451-1458.

19. Kuchan MJ, Frangos JA. Shear stress regulates endothelin-1 release via protein kinase C and cGMP in cultured endothelial cells. Am J Physiol 1993;264:150-156.

20. Barsness GW. Enhanced external counterpulsation in unrevascularizable patients. Curr Interv Cardiol Rep 2001;3:37-43.

21. Kersten JR, Pagel PS, Chilian WM, Warltier DC. Multifactorial basis for coronary collateralization: a complex adaptive response to ischemia. Cardiovasc Res 1999;43:44-57.

22. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohata T, Imaizumi T. 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;37:93–99.

23. 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.

24. 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.

25. Novo G, Bagger JP, Carta R, Koutroulis G, Hall R, Nihoyannopoulos P. Enhanced external counterpulsation for treatment of refractory angina pectoris. J Cardiovasc Med (Hagerstown) 2006;7:335-339.