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Enhanced External Counterpulsation Effects on Venous Leg Symptoms

ABSTRACT

Background: Venous diseases encompass a large spectrum of abnormalities in the venous system with complaints, such as aching and swelling. Enhanced external counterpulsation, proven safe and effective in patients with coronary artery disease and chronic heart failure, is a technique that increases venous return and augments diastolic blood pressure. This study assessed the effects of enhanced external counterpulsation on symptoms of venous disease using the Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms questionnaire.

Methods: This study was designed prospectively for evaluating venous symptoms before and after enhanced external counterpulsation treatment. The study population consisted of 30 consecutive patients who were admitted to the cardiology clinic. The Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms questionnaire was applied to assess venous symptoms one day before and after enhanced external counterpulsation treatment.

Results: The mean age of the patients was 64.62 ± 9.67 years. After 35 hours of enhanced external counterpulsation, 28 patients (93%) had at least 1 New York Heart Association functional class reduction compared with baseline and 43% of patients had 2 New York Heart Association functional classes improvement. The New York Heart Association class significantly decreased after enhanced external counterpulsation treatment ($P < .001$). There was a significant improvement in their swelling and night cramps symptoms compared with baseline ($P < .001$ and $P = .05$, respectively). Also, The left ventricular ejection fraction significantly increased after the enhanced external counterpulsation treatment ($P = .02$).

Conclusions: The findings obtained in the present study suggested that patients treated with enhanced external counterpulsation showed a significant reduction in swelling and night cramps symptoms. Although the total VEIN score did not change after the enhanced external counterpulsation procedure, improvement in swelling and night cramps underlines the beneficial effects of enhanced external counterpulsation through the venous vascular territory.

Keywords: Enhanced external counterpulsation, venous diseases, VEINES-sym, coronary artery disease

ORIGINAL INVESTIGATION

INTRODUCTION

Enhanced external counterpulsation (EECP) is an effective and non-invasive Food and Drug Administration (FDA)-approved therapy that increases venous return and augments diastolic blood pressure using inflatable cuffs wrapped around the lower extremities. Enhanced external counterpulsation is one of the most appropriate treatment options for coronary artery disease (CAD) and patients with heart failure (HF) that have failed to efficiently respond to conventional revascularization methods and pharmacotherapy.[1] Several controlled and uncontrolled or randomized studies have shown the benefits of EECP among patients with refractory angina and heart failure.[2-6] The effectiveness of EECP covers improvement in angina severity, angina stability, maximal walking capacity, training-like effects, and generalized improvement in overall health.[6] The anti-ischemic effects are

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sustained up to 5 years in responsive patients.[7] Besides, EECP has a peripheral training effect, which may influence the venous symptoms.

Chronic venous insufficiency (CVI) is one of the major health concerns, affecting approximately 10-30% of the world population, leading to a significant decrease in work productivity and quality of life.[8] CVI is a progressive disease that develops due to ineffective calf muscle pumping and venous reflux. Complaints related to CVI may cover aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching, and restless legs as well.[9] Obesity and the aging population will lead to an increase in the prevalence over time. The diagnosis and treatment modalities are crucial for preventing disease for keeping more destructive results. Because of being supposed to have similar vascular wall pathology, dilating venous disease compromises a large spectrum of functional and histopathological abnormalities in the venous system.[10-12] Thus, a new treatment option for one of those could be beneficial for different territorial vascular pathology. There are many treatment options for CVI to prevent complications and sequelae. Early diagnosis with the non-invasive and simple test may preclude these results. As one of these tests, the Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms (VEINES-QoL/Sym) questionnaire is valid, sensitive and reproducible for measuring venous disease symptoms.

Enhanced external counterpulsation procedure has a training-like effect, which leads to increased venous return. The effects on the venous system and venous return may lead to a reduction in CVI symptoms. Thus, venous leg symptoms can be decreased with this treatment. To our knowledge, the effect of EECP on venous symptoms has never been investigated by a formal questionnaire. The present study aims to investigate the effects of EECP therapy on symptoms of venous disease according to the VEINES-Sym survey.

METHODS

The patients were recruited into the study prospectively in a tertiary university hospital and evaluation of symptoms were performed on the day before starting the EECP treatment and the day after completing of the EECP treatment as a pre and post design method. Thirty-one patients who were referred for EECP therapy or admitted to our clinic were recruited for the study according to inclusion criteria in a prospective and consecutive manner between August 2020 and August 2021. Demographical and clinical features of the patients were obtained on the same day of examination and recorded. Clinical evaluations; physical examination, electrocardiogram, and echocardiography (2D, color, and Doppler) were performed before the EECP treatment. Also, all patients were examined for the presence of varicose veins. The presence of lower extremity venous system disease and subsequent classification has been assessed and categorized according to clinical components of clinical, etiological, anatomical, and pathological (CEAP) classification. Clinical, etiological, anatomical, and pathological classified as follows: grade 0, no visible signs of venous disease; grade 1, telangiectasia or reticular veins; grade 2, varicose veins; grade 3, edema; grade 4, skin changes due to CVD; grade 5, skin changes with healed ulceration; and grade 6, skin changes with active ulceration.[13] The VEINES-Sym questionnaire was used to assess venous leg symptoms before the EECP therapy regardless of whether the patients had varicose veins or not. Thirty-five sessions of EECP, which lasted 1 hour, were conducted under the direct supervision of a physician for 6 weeks (6 times/week). Patients who could not complete at least 30 sessions were excluded. After EECP treatment, physical examination, electrocardiographic, and echocardiographic measurements were performed during the last visit for each patient after 3 days the completion of 35 sessions. Also, all patients who completed the full course of (1 round) EECP were asked to reply VEINES-Sym questionnaire and HF symptoms survey after the 3 days the completion of treatment. All patients were on optimal medical therapy for angina and HF and stable prior to enrollment into the study.

The inclusion criteria were ongoing angina or its equivalent with documented CAD (depend on prior myocardial infarction or coronary artery angiography, which represents stenosis >70% in at least one of the major epicardial arteries), having a diagnosis of HF [reduced left ventricular ejection fraction (LVEF) or mildly reduced LVEF] [New York Heart Association (NYHA) class II or III] despite conventional therapy and over 20 years old. Patients with HF and documented history of ischemic heart disease and/or diagnostic coronary angiography were presumed to have ischemic cardiomyopathy. Heart failure is described as HF guidelines by the European Society of Cardiology.[14] Reduced LVEF is described as LVEF ≤40% and LVEF between 41% and 49% have mildly reduced LV systolic function. Both of these were included in the study because of retrospective analyses from randomized controlled studies in reduced HF that have included patients with ejection fractions in the 40-50% range speculate that they may benefit from similar therapies to those with LVEF ≤40%.[14-20]

Patients who suffered from severe aortic insufficiency, abdominal, or thoracic aortic aneurysm consisted of cardiac

HIGHLIGHTS

- The findings demonstrate that patients treated with enhanced external counterpulsation (EECP) showed a significant reduction in swelling and night cramps symptoms.
- Improvement in swelling and night cramps underlines the beneficial effects of EECP through the venous vascular territory.
- It has been found that 93% of patients had at least 1 New York Heart Association functional class improvement immediately post-treatment.
- This beneficial effect can be attributable to increased venous return through the compression of cuffs and improved functional capacity and ejection fraction mediated by EECP.

arrhythmias, such as uncontrolled atrial fibrillation, decompensate HF, severe peripheral arterial disease, severe hypertension, severe chronic obstructive pulmonary disease, and myocardial infarction within the recent 3 months and refusal to sign an informed consent were excluded from this study. All enrolled participants provided a signed informed consent form before the beginning of the procedure. This observational and prospective study, performed in compliance with the Declaration of Helsinki, was approved by the local Ethics Committee (2/2020.K-053).

VEINES-Sym Questionnaire

Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire consists of 10 items, including 9 venous symptoms (heavy legs, aching legs, swelling, night cramps, heat/burning sensation, restless legs, throbbing, itching, and tingling sensation). Then, it is divided into 5 different frequencies and numbered 1-5 (every day, several times a week, about once a week, less than once a week, and never, respectively). Scores of VEIN-Sym are scaled from 1-5, with 1 being the "every day" and 5 being the "never" for measuring symptom severity. The higher scores indicate better outcomes. The tenth question concerning at what time of the day these symptoms are most intense is not included in the calculation and is only used for descriptive information. Kutlu et al[21] studied the validity and reliability of the VEINES-QoL/Sym questionnaire in the Turkish population. Also, all patients were examined for the presence of varicose veins. The classification was made according to the clinical component of CEAP classification as follows: grade 0, no visible signs of venous disease; grade 1, telangiectasia or reticular veins; grade 2, varicose veins; grade 3, edema; grade 4, skin changes due to CVD; grade 5, skin changes with healed ulceration; and grade 6, skin changes with active ulceration.[14]

Enhanced External Counterpulsation

All enrolled patients were treated with a Luminair (Vasomedical Inc, NY, USA) EECP device with a maximum therapy pressure of 240 mm Hg. Enhanced external counterpulsation was administered in a room located at the hospital, and each 1-hour session was performed by a well-trained nurse. Standard EECP therapy consists of a biomechanical device concluded of 3 basic components: air compressor, treatment table, and a monitoring system; additionally, 3 pairs of integrated air cuffs. Diastolic pressure augmentation during EECP therapy was monitored using finger plethysmography. Initially, these compressive cuffs were wrapped around the patient's lower extremities and buttocks. Then, the cuffs were attached to the air compressor by hoses, which allowed the cuffs to be cyclically inflated and deflated in synchrony with the cardiac cycles guided by electrocardiography. The cuffs were timed to sequentially inflate from distal to proximal (the calves to the buttocks) at the beginning of early diastole; afterward, the pressurized air was quickly relieved at the beginning of systole. This period results in enhancing coronary artery mean pressure by 16% and peak diastolic pressure by 93% due to retrograde aortic flow.[22] This mentioned cycle is repeated during a 1-hour session with every heart beat that is usually performed 35 times within the course of 7 weeks.[22,23]

Statistical Analysis

All statistical analyses were performed using a Statistical Package for Social Science Statistics 22 for Windows (IBM Corp. Chicago, IL, USA). The normality of continuous variables was checked using Kolmogorov–Smirnov test. Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ± standard error. Categorical variables were compared by using the marginal homogeneity test where appropriate. Comparison of normally distributed continuous variables was performed by paired *t*-test, and Wilcoxon *t*-test was used for non-normally distributed variables. $P \leq .05$ was considered to be statistically significant.

RESULTS

Thirty-one consecutive patients who fulfilled the inclusion criteria were included in the statistical analysis. One patient was excluded due to clinical worsening of leg lesion. Baseline demographic and clinical features of the enrolled patients are presented in Table 1. The mean age of the patients was 64.62 ± 9.67 years. Of the study patients, 19 patients (63.3%) had diabetes, while 21 patients (70%) had hypertension. All of the study patients (100%) had CAD, while 4 of them were not eligible for any coronary revascularization procedures. Eleven patients (36.7%) had undergone coronary artery bypass graft surgery. Body mass index decreased from 26.42 ± 4.22 to 25.89 ± 3.62 ($P = .61$) after EECP treatment. Left ventricular ejection fraction (EF) was ≤ 40% in 22 (73.3%) patients included in this study. There was a statistically significant improvement in EF after EECP therapy (before, 33.50 ± 10.59; after 35.57 ± 10.26; $P = .02$). After 35 hours of EECP, 28 patients (93%) had at least 1 NYHA functional class reduction compared with baseline. The mean of the NYHA class significantly decreased from 3.17 ± 0.53 to 1.77 ± 0.57 after EECP treatment ($P < .001$). Of the total cohort, 43% of patients had 2 NYHA functional classes improvement and 50% of patients had 1 NYHA functional class improvement, whereas 7% of patients had no change after EECP treatment. The improvement in the NYHA class was presented in Table 2.

Evaluation of venous disease symptoms and VEINES-Sym scores of the patients are demonstrated in Table 3. There was a significant improvement in patients' swelling and night cramps symptoms ($P < .001$ and $P = .05$, respectively). The other symptoms, such as heavy legs, itching, and burning, decreased, whereas aching, throbbing, and tingling increased with EECP treatment even when both were not statistically significant. However, CEAP clinical score was comparable between pre- and post-treatment.

DISCUSSION

The present study has shown a significant reduction in swelling and night cramps symptoms in patients treated with EECP. Although slight improvement has been observed in other venous leg symptoms, it has not reached the statistically

Table 1. Demographic and Clinical Characteristics of the Patients*

Age (year)		64.62 ± 9.67	
Sex, male		23 (76.7%)	
Diabetes mellitus		19 (63.3%)	
Hypertension		21 (70%)	
Dyslipidemia		17 (56.7%)	
Smoking		6 (20%)	
BMI		26.42 ± 4.22 (before EECP)	$P = .61$
		25.89 ± 3.62 (after EECP)	
Prior CABG		11 (36.7%)	
PCI		25 (83.3%)	
PCI+CABG		10 (33.3%)	
No coronary intervention		4 (13.3%)	
ICD		12 (40%)	
Left ventricular ejection fraction	Reduced (≤40%)	22 (73.3%)	
	Mildly reduced (41-49%)	8 (26.7%)	
Drugs			
Anti-aggregants (ASA and/or clopidogrel)		30 (100%)	
Beta-blockers		28 (93.3%)	
ACE inhibitors/ARB		19 (63.3%)	
Statins		10 (33.3%)	
Diuretics		23 (76.7%)	
Ivabradine		6 (20%)	

*Data are presented as mean ± SD or n (%).
BMI, body mass index; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; ICD, implantable cardioverter-defibrillator; ASA, acetylsalicylic acid; ACE, angiotensin-II converting enzyme; ARB, angiotensin II receptor blockers; SD, standard deviation.

significant level. Our hypothesis was that peripheral training effect and increased venous return could have beneficial effects on the venous leg symptoms.

EECP, which is an FDA-approved non-invasive device, is recommended with class IIb indication for the treatment of patients with chronic stable or refractor angina and heart failure.[5,24,25] An increase in vasculogenesis, proinflammatory cytokines, improved endothelial function, and promotion of angiogenesis has been the main proposed mechanisms of EECP. International Patient Registry results figure out a significant reduction in weekly angina episodes and angina class immediately with EECP treatment.[26] And the prospective evaluations of enhanced external counterpulsation in congestive heart failure study reported a significant increase in exercise duration and improvement at least 1 NYHA class [at least 1 class (86.7%)].[27] Moreover, Loh et al[28] showed that angina episodes decreased at least 1 class of the Canadian Cardiovascular Angina Classification in 78% of the patients in a multicenter study. Similarly, our results demonstrate that 93% of patients had NYHA functional class improvement immediately post-treatment. Of the total cohort, 43% of patients had 2 NYHA functional class improvements and 50% had 1 NYHA functional class improvement, whereas 7% of patients had no change after EECP treatment. Our findings are consistent with previous studies.

The effects of EECP on peripheral arterial function were investigated in several studies. Martin et al[29] showed that measurement of arterial function improved following EECP therapy. These beneficial effects have been validated by a prospective, randomized, sham-controlled study in patients with CAD. It has been found that flow-mediated dilatation of brachial and femoral artery improved, whereas endothelial-derived vasoactive agents reduced.[30] Otherwise, EECP has similar beneficial effects on CAD in patients with the peripheral arterial disease.[31] Even the effects of EECP on the arterial system have been verified; the venous system has not been included so far. To our knowledge, this is the first study evaluating the clinical effectiveness of EECP on venous leg symptoms. According to the results of VEIN score results of our study, some beneficial effects have been found in venous disease symptoms, such as swelling and night cramps.

Study Limitations

The main limitation of our study is that the sample size was small and there was no follow-up period for long-lasting effects. Since the VEIN-Sym questionnaire is a symptom-based assessment of CVI, ultrasonographic evaluation of patients can provide us with further valuable insights regarding the anatomical and functional changes in the peripheral venous system of patients undergoing EECP.

CONCLUSION

The findings demonstrate that patients treated with EECP showed a significant reduction in swelling and night cramps symptoms. Although the total VEIN score did not change after the EECP procedure, improvement in swelling and night cramps underlines the beneficial effects of EECP through the

Table 2. The Improvement in NYHA Classification Pre- and Post-treatment of EECP

		Pre-treatment NYHA Classification					
		Class I	**Class II**	**Class III**	**Class IV**	**Total**	***P***
Post-treatment NYHA Classification	Class I	0	1	8	0	9 (30%)	**<.001**
	Class II	0	1	12	6	19 (63%)	
	Class III	0	0	1	1	2 (7%)	
	Class IV	0	0	0	0	0	
	Total	0	2 (7%)	21 (70%)	7 (23%)	30 (100%)	

EECP, enhanced external counterpulsation; NYHA, New York Heart Association.
Class I, Class II, Class III can be written in bold.

Table 3. Comparison of Venous Leg Symptoms and VEINES-Sym Scores Pre- and Post-treatment of EECP

Symptoms	Pre-treatment (n = 30)	Post-treatment (n= 30)	*P*
Heavy legs	4.27 ± 1.36	4.53 ± 1.00	.23
Aching legs	4.03 ± 1.35	3.67 ± 1.44	.20
Swelling	3.53 ± 1.54	4.57 ± 0.82	**<.001**
Night cramps	3.83 ± 1.42	4.30 ± 1.02	**.05**
Heat/burning	4.47 ± 1.11	4.53 ± 1.00	.69
Restless legs	4.30 ± 1.15	4.30 ± 1.24	1.00
Throbbing	4.63 ± 0.89	4.40±1.16	.15
Itching	4.63 ± 0.96	4.77 ± 0.90	.29
Tingling	4.30 ± 1.26	4.07 ± 1.20	.35
VEINES-Sym score	38.00 ± 7.75	39.17 ± 6.93	.27

Swelling and Night cramps can be written in bold.

venous vascular territory. Indeed, it has been found that 93% of patients had at least 1 NYHA functional class improvement immediately post-treatment. This beneficial effect can be attributable to increased venous return through the compression of cuffs and improved functional capacity and ejection fraction mediated by EECP.

Data Sharing Statement: The data of the current study are available from the corresponding author in reasonable request.

Ethics Committee Approval: This study was conducted according to principles of the Declaration of Helsinki, and approved by Beykent University Ethic Committee (2/2020.K-053).

Informed Consent: All the patients gave their written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.Ç.; Design – B.Ç., E.Y.; Supervision – E.Y.; Fundings – None; Materials – B.Ç.; Data collection &/or processing – B.Ç., H.T., E.Y.; Analysis &/or interpretation – B.Ç., H.T., E.Y.; Literature search – B.Ç., E.Y.; Writing – B.Ç.; Critical review – B.Ç., E.Y.

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Declaration of Interests: The authors declare that they have no competing interest.

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