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

Amerika Birleşik Devletleri ve Türkiye'de koroner arter hastalığı nedeni ile güçlendirilmiş eksternal kontrpulsasyon tedavisi gören hastalarda olaysız sağkalım oranları ve uzun dönem klinik sonuçlarının karşılaştırılması

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ABSTRACT

Objectives: This study assessed the long-term efficacy of EECP (Enhanced External Counterpulsation) in Turkish (TR) patients initially and compared these results with the United States (US) in a real world setting.

Study design: In this study, 2072 patients were treated and followed in the US and 82 patients were treated and followed in TR. The International EECP Patient Registry Phase I and II was initiated and coordinated at the University of Pittsburgh. The aim of the "registry" was to assess the outcomes of clinical trials in a real world setting. Another unique feature of this study was to enroll patients not only from university hospitals but also from private hospitals, educational hospitals, and treatment centers.

Results: TR patients had less diabetes, hypertension, and hyperlipidemia than US patients ($p<0.01$). TR patients also had a higher proportion of diastolic augmentation ($p<0.001$). Both groups showed a significant reduction in the severity of angina after a 35h EECP course ($p<0.001$). Major Adverse Cardiac Events (MACE) rate (death, coronary artery bypass graft, percutaneous coronary intervention, myocardial infarction) was low in both groups during treatment (2.5% vs. 2.7%). At 1 year follow up, 84% of TR and 76% of US patients had maintained the improvement of angina.

Conclusion: Patients presenting for EECP treatment from TR had different baseline profiles from US patients. However, despite the high risk baseline characteristics, both cohorts achieved similar reduction in angina. In the long term follow-up, the MACE rate was low and the improvement after EECP was sustained in most of the patients.

ÖZET

Amaç: Güçlendirilmiş eksternal kontrpulsasyon (EECP) tedavisi gören ilk Türk (TR) hasta grubunun klinik sonuçları, Amerika Birleşik Devletleri'ndeki (ABD) sonuçlarla karşılaştırıldı ve EECP'nin uzun dönem etkinliği değerlendirildi.

Çalışma planı: Bu çalışmada, ABD'den 2072 hasta, TR'den 82 hasta tedavi edilerek izlendi. "The International EECP Patient Registry Phase I and II" Pittsburgh Üniversitesi'nde başlatılıp ve koordine edildi. Kayıtların amacı, klinik çalışma sonuçlarını gerçek yaşam şartlarında değerlendirmekti. Bu çalışmanın bir diğer önemli özelliği ise sadece üniversite hastaneleri değil, aynı zamanda özel hastaneler, eğitim hastaneleri ve tedavi merkezlerinden de hasta alınmasıydı.

Bulgular: TR hastalarda diyabet, hipertansiyon, hiperlipidemi daha azdı ($p<0.01$), diyastolik augmentasyon oranı daha yüksekti ($p<0.001$). Her iki grupta da, 35 saat EECP tedavisi sonrası anjina pektoris şiddeti önemli ölçüde azalma gösterdi ($p<0.001$). Majör istenmeyen kardiyak olay (MACE) oranı (ölüm, koroner arter baypas greft, perkütan koroner girişim, miyokart enfarktüsü) EECP tedavisi sırasında her iki grupta da düşüktü (%2.5 ve %2.7). Bir yıl takip sonucunda TR hastalarında %84, ABD hastalarında %76 oranında anjina sınıfındaki iyileşme devam ediyordu.

Sonuç: EECP tedavisi alan TR hasta grubunun temel karakteristik özellikleri ABD grubundan farklıydı. Bununla birlikte, yüksek risk profiline rağmen, her iki hasta grubunda anjina şiddetinde benzer azalma sağlandi. Uzun dönem takiplerinde, MACE oranı düşüktü ve hastaların çoğunda EECP tedavisi sonrası iyileşme devam ediyordu.

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An estimated 17.6 million patients in the United States (US) suffer from symptomatic coronary artery disease (CAD) and despite optimal medical therapy and invasive procedures, such as percutaneous coronary intervention (PCI) and cardiac bypass surgery (CABG), there are an estimated 300,000 to 900,000 patients in the US who suffer from disabling angina.[1,2] In Turkey, the prevalence of atherosclerotic heart disease is 3.8% in adults (4.1% in men, 3.5% in women).[3] Age-adjusted (45-74 years) overall cardiac mortality rate in Turkey is 7.4 and 4.1 per 1000 person-years in men and women, respectively.[4,5]

Abbreviations:

CABG	*Cardiac bypass surgery*
CAD	*Coronary artery disease*
ECG	*Electrocardiography*
EECP	*Enhanced external counterpulsation*
IEPR	*The International EECP Patient Registry*
MACE	*Major adverse cardiac events*
MUST-EECP	*Multicenter Study of Enhanced Counter Pulsation*
PCI	*Percutaneous coronary intervention*
TR	*Turkish*

Daily tasks such as climbing a flight of stairs, walking a dog, or mowing the lawn become infeasible without experiencing chest pain for these difficult-to-treat patients.[6] Current non-pharmacologic options for patients with disabling angina are limited. Enhanced external counterpulsation (EECP) therapy offers a safe and effective treatment option for such patients. Several placebo controlled randomized[6-9] and non-randomized clinical studies[8,10-15] have shown beneficial effects of EECP in CAD patients including significant reduction in angina symptoms, improvement in objective measures of myocardial ischemia, functional capacity, and improvement in left ventricular function (both systolic and diastolic).[6]

EECP therapy is a noninvasive, outpatient treatment consisting of electrocardiography (ECG)-gated sequential leg compression, which produces hemodynamic effects similar to those of an intra-aortic balloon pump. However, EECP therapy also increases venous return different from an intra-aortic balloon pump.[16] Since 1999, it has gained wide acceptance in the management of severe angina in the US.

It has been approved by the Food and Drug Administration for the treatment of stable angina, unstable angina, cardiogenic shock, acute myocardial infarction and heart failure. Although primarily used in the United States the treatment is now also being used in Turkey. The purpose of this study is to compare the efficacy, repeat EECP and one year major adverse cardiovascular rates in patients treated with EECP for angina management in the Turkish (TR) population and within the US in a real world setting.

PATIENTS AND METHODS

Patient population and study design

The International EECP Patient Registry (IEPR) Phase I and II has been initiated and coordinated at the University of Pittsburgh and has enrolled consecutive patients who underwent EECP therapy for chronic angina from 90 centers between 1998 and 2004. Since all clinical outcome results on EECP have been coming from clinical trials, the aim of the registry was to assess the outcomes of the clinical trials in the real world setting without using inclusion and exclusion criteria. Another unique feature of this study was to enroll patients not only from university hospitals but also from private hospitals, educational hospitals, and treatment centers.

In this study, 2072 patients were treated and followed in the US and 82 were treated and followed in TR. In Turkey, one center from Ankara was invited to join the study since there was only one site in Turkey at the time of IEPR study initiation. The IEPR methods have been described previously.[2] Patients in the IEPR were required to give informed consent. The IEPR tracks the demographics, baseline characteristics, clinical events, and outcomes of consecutive patients who underwent EECP treatment for angina, with no exclusion due to demographics, clinical status, or outcome. At 1 year, patients were interviewed by telephone or at a clinic visit, and data concerning interim clinical events, hospitalizations, and current symptomatology were recorded. Major adverse cardiac events (MACE) were specified as the composite of death, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. Patient data were included only from sites with 85% complete follow-up.

EECP therapy is composed of an air compressor unit, a computer module, 3 sets of pneumatic cuffs, and a treatment table (Vasomedical, Inc, Westbury, NY, US). Cuffs are wrapped around the patient's calves, thighs, and upper thighs (including buttocks) and a computer-controlled pneumatic system acts to inflate and deflate the cuffs. Inflation and deflation are triggered by events in the cardiac cycle through micro-

Table 1. Baseline characteristics

	Turkey (n=82)		United States (n=2072)		*p*
	%	Mean±SD	%	Mean±SD	
Age (years)		61.3±11.9		67±10.9	**p<0.001**
Age ≥65 (years)	42		59.7		**p<0.01**
Male	75.6		73.5		
Prior PCI or CABG	57		88.6		**p<0.001**
Prior MI	69.5		71.9		
CHF	46.3		34.2		**p<0.05**
Family history of CAD	67.9		80.8		**p<0.01**
Hypertension	42.7		76.4		**p<0.001**
Hyperlipidemia	59.3		87.4		**p<0.001**
Diabetes	31.7		44.0		**p<0.05**
LVEF		40.6±18.9		46.6±14.6	**p<0.001**
Angina class					
I	35.1		0.9		**p<0.001**
II	26.0		7.1		
III	22.1		64.7		
IV	16.9		27.3		
Episodes of angina (week)		11.9±14.4		11.2±13.9	
Medications					
Beta blocker	51.2		76.3		**p<0.001**
CACB	19.8		41.9		**p<0.001**
ACEI	52.4		45.1		
ARB	6.1		11.3		
Lipid lowering	43.9		79.0		**p<0.001**
Nitrates	76.8		77.0		
Nitro use (week)		14.2±15.8		9.1±11.3	**p<0.01**
Not candidate for PCI or CABG	67.9		88		**p<0.001**
Multivessel disease (>%70)	43.8		74.7		**p<0.001**

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; MI: Myocardial infarction; CHF: Congestive heart failure; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction; CACB: Calcium channel blocker; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

processor-interpreted electrocardio graphic signals. Cuffs resembling oversized blood pressure cuffs–on the calves and lower and upper thighs, including the buttocks–inflate rapidly and sequentially via computer interpreted ECG signals, starting from the calves and proceeding upward to the buttocks during diastole. This creates a strong retrograde counterpulsation in the arterial system. This sequential compression results in augmented diastolic pressure which increases coronary perfusion and provides enhanced afterload reduction and increased venous return with a following increase in cardiac output. Rapid deflation of the cuffs at the onset of systole enhances systolic unloading and reduces the workload of the heart by decreasing peripheral vascular resistance. This is achieved because the vascular beds in the lower extremities are relatively empty when the cuffs are deflated, significantly lowering the resistance to blood ejected by the heart and reducing the amount of work the heart must do to pump oxygenated blood to the rest of the body. Systolic and diastolic pressure waves are monitored throughout treatment by noninvasive finger plethys-

mography. A typical treatment course consists of 35 one hour sessions over a 5-7 week period and is usually well tolerated with a low risk of adverse events.

Statistical analysis

Baseline characteristics are presented for categorical variables as the proportion of patients who reported and as mean ± standard deviation (SD) for continuous variables. Statistical significance was tested using Chi-squared or Fisher tests for categorical analyses and Wilcoxon tests for continuous variables. Kaplan-Meier survival analysis was used to estimate rates of adverse events at 1 year following start of EECP. Statistical differences were determined using the log rank test. Two-tailed *p* values less than 0.05 were considered statistically significant.

RESULTS

In this study, 2072 were treated and followed in the US and 82 in TR. TR patients were younger (p<0.001) with a similar proportion of men (75.6% vs. 73.5%) and were less obese than US patients (p<0.001). Duration of coronary artery disease was less in TR patients (p<0.01) and previous revascularization was 57% for TR patients vs. 89% for US patients (p<0.001). Heart failure was reported in 46% of TR patients and 34% of US patients. TR patients were less likely to have had PCI (p<0.001). CABG rates were 49% for TR patients vs. 71% for US patients (p<0.001). Sixty eight percent of patients from TR and 88% from US were no longer candidates for further revascularization (p<0.001). TR patients had less hypertension and hyperlipidemia than US patients (p<0.001). TR patients had less chronic renal insufficiency (p<0.01) and peripheral vascular disease as well (p<0.001). Patients from TR had less Class III and IV stable angina (p<0.001) with a similar rate of unstable angina but higher rates of heart failure. Forty four percent patients from TR and 75% from the US had multivessel disease (p<0.001). Medication use (beta blockers, CA Channel blockers and lipid lowering drugs) was higher in the US patients (Table 1).

After a mean treatment course of 33 hours for the US group and 36 hours for the TR group (p<0.01), 91% of TR patients vs. 77% of US patients had at least one Canadian Cardiovascular Society (CCS) class angina reduction (p<0.01). MACE during the treatment course (2.5% vs. 2.7%) and discontinuation of nitroglycerin usage after the treatment was similar in both groups (Table 2). At 1 year follow up, 83% of TR patients and 76% of US patients had maintained the improvement in angina class (p=NS); (Table 2). Survival rate was 100% in TR and 96% in US. MACE free survival rate was 95% in patients from TR vs. 83% in the US (p=0.011). Repeat EECP rates at 1 year follow up were lower in TR patients (2.3% vs. 8.9%, p<0.075).

DISCUSSION

Several randomized placebo control[7-9,17-20] and non-randomized trials[11-13,16,21-23] have demonstrated a firm, positive clinical response among patients with CAD treated with EECP. Benefits associated with EECP therapy include reduction in angina and nitrate use, increased exercise tolerance, favorable psychosocial effects, and enhanced quality of life as well as prolongation of the time to exercise-induced ST-segment depression and an accompanying resolution of myocardial perfusion defects. Numerous clinical trials have shown EECP therapy to be safe and effective for patients with CAD, with a clinical response rate averaging 70% to 80%, which is maintained up to 5 years.[1,16,21,22,24,25]

Although placebo-controlled randomized and non-randomized studies have shown beneficial effects of EECP therapy, investigators saw the need to assess the effectiveness of EECP in real-world settings, leading them to develop the IEPR under the management of the University of Pittsburgh. The main aim of the registry was to assess the outcomes of the clinical trials in a real world setting without applying any inclusion and exclusion criteria while maintaining indications and contraindications only.[26]

The present results show and reflect the utilization patterns and cardiovascular outcomes in the real world setting in two distinct patient populations who have undergone EECP therapy. Patients treated with EECP in TR and the US showed very different baseline (demographic and clinical) profiles. However, there was only one center in Turkey at the time of IEPR study initiation; therefore, this one center was invited to take part in this study. Hence, the results from Turkey cannot be generalized to the entire Turkish population.

Patients in our study had chronic multivessel coronary artery disease. EECP therapy is often used for

Table 2. Post-EECP outcome

	Turkey (n=82)		United States (n=2072)		*p*
	%	Mean±SD	%	Mean±SD	
Hours of treatment		36.3±5.4		33.3±9.1	**p<0.01**
Completed treatment	95.1		84.5		**p<0.01**
Diastolic augmentation					
First peak		1.1±0.4		0.7±0.5	**p<0.001**
First area		1.1±0.4		0.9±0.6	**p<0.01**
Last peak		1.3±0.5		1.0±0.6	**p<0.001**
Last area		1.4±0.7		1.2±0.7	**p<0.05**
Angina					**p<0.001**
No angina	69.6		17.4		
Class I	16.5		19.4		
Class II	7.6		36.6		
Class III	5.1		20.0		
Class IV	1.3		6.6		
Angina down by ≤1 class	90.7		77.4		**p<0.01**
Episodes of angina (week)		1.2±3.2		2.8±6.4	**p<0.05**
PRN nitro use	23.8		38.9		**p<0.01**
Nitro frequency (week)		3.7±4.3		5.0±7.6	
Events during treatment					
Skin problems	0.0		3.2		
Musculoskeletal	0.0		1.5		
Unstable angina	0.0		3.7		
CHF	0.0		2.0		
Death	1.2		0.8		
MI	1.2		1.1		
CABG	0.0		0.3		
PCI	0.0		0.9		
Death/MI/CABG/PCI	2.5		2.7		
Angina status at 1 year					
Angina					**p<0.001**
No angina	67.4		27.0		
Class I	27.9		17.2		
Class II	4.7		31.2		
Class III	0.0		19.0		
Class IV	0.0		5.7		

PRN: As needed; EECP: Enhanced external counterpulsation; CHF: Congestive heart failure; MI: Myocardial infarction; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention.

patients with refractory angina pectoris; however, patients who deny undergoing invasive revascularization may undergo EECP therapy. In the US, the majority of patients who were suffering from angina refractory to medical therapy or conventional revascularization techniques underwent EECP therapy. In TR only 57% of patients had prior PCI or CABG and 32% were candidates for invasive revascularization at

the time of EECP therapy. However, these patients denied undergoing further invasive procedures.

Medication use (beta blockers, CA Channel blockers and lipid lowering drugs) were also significantly higher in US patients. The major reasons for this difference were higher side effect profiles seen in polydrug therapy and low compliance rates seen in TR patients.

Another interesting finding was that the diastolic augmentation ratio was significantly higher in TR when compared to the US at baseline. The finger plethysmogram tracing is used to set, monitor and adjust the timing of EECP therapy and to quantify the hemodynamic effects of counterpulsation. During EECP, cuff inflation and deflation change the arterial waveform so that the diastolic peak is elevated, indicating diastolic augmentation, while the end diastolic pressure and the systolic peak are lowered, demonstrating systolic unloading. The measurement of augmentation is based upon the ratio of the diastolic (D) to systolic (S) wave, or the D/S ratio. The D/S ratio may be measured in terms of area or peak. The peak measurement (P) is more common as it is easily done by estimation. The goal of EECP is P $\geq$1.0, which is called optimal therapeutic diastolic augmentation. One reason to explain this difference was that US patients had a more extensive disease with higher rates of risk factors. At the end of the EECP course, however, both groups achieved optimal therapeutic diastolic augmentation which can explain why both cohorts achieved similar substantial reduction in angina with high event free survival rates at 1 year follow up. Similar results have been demonstrated in other studies.[1,21,27,28]

The effects of EECP therapy on exercise-induced myocardial ischemia and angina were evaluated in MUST-EECP (Multicenter Study of Enhanced Counter Pulsation), the first multicenter, prospective, randomized, double blinded, sham controlled trial in patients with refractory angina. This trial was conducted at seven centers with 55 patients in the active EECP group and 65 in the sham group completing the study.[7] Average pre-treatment and post-treatment exercise duration, time to 1-mm ST-segment depression, daily number of angina attacks and glyceryl trinitrate were collected. Patients in the active EECP therapy group showed a statistically significant increase in time to exercise-induced ST-segment depression when compared with sham and baseline, and reported a statistically significant decrease in the frequency of angina episodes when compared with sham and baseline. Exercise duration increased significantly in both groups; however, the increase was greater in the active EECP group. Follow-up was done at 1 year to assess the quality of life. There was a significant difference between the groups favoring the active EECP arm in regards to quality of life.[7] Our study results in regards to angina reduction and low event rates confirmed the results of randomized clinical trial outcomes in the real world settings.

Mechanism of action studies suggests that EECP shows its effectiveness through collateral development, endothelial function and neurohormonal improvement.[8,15,22,29-31]

The best treatment options for patients with disabling angina have not been fully described. EECP therapy is a valuable, safe, outpatient procedure providing acute and long-term benefits in angina relief in patients with symptomatic CAD with or without congestive heart failure.

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REFERENCES

1. Soran O, Kennard ED, Kfoury AG, Kelsey SF; 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. [CrossRef]
2. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics-2010 update: a report from the American Heart Association. Circulation 2010;121:e46-e215. [CrossRef]
3. Onat A, Keleş İ, Çetinkaya A, Başar Ö, Yıldırım B, Erer B, et al. Prevalence of coronary mortality and morbidity in the Turkish Adult Risk Factor Study: 10-year follow-up suggests coronary "Epidemic". Arch Turk Soc Cardiol 2001;29:8-19.
4. Unuvar N. Türkiye hastalık yükü çalışması. http://tusak.saglık.gov.tr, 2004.
5. Onat A, Murat SN, Çiçek G, Ayhan E, Örnek E, Kaya H, et al. Regional distribution of all-cause mortality and coronary disease incidence in Turkey: findings of Turkish Adult Risk Factor survey 2010. Arch Turk Soc Cardiol 2011;39:263-8.
6. Manchanda A, Soran O. Enhanced external counterpulsa-

tion and future directions: step beyond medical management for patients with angina and heart failure. J Am Coll Cardiol 2007;50:1523-31. [CrossRef]

7. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;33:1833-40. [CrossRef]
8. Braith RW, Conti CR, Nichols WW, Choi CY, Khuddus MA, Beck DT, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham-controlled study. Circulation 2010;122:1612-20. [CrossRef]
9. Wu G, Du Z, Hu C, Zheng Z, Zhan C, Ma H, et al. Angiogenic effects of long-term enhanced external counterpulsation in a dog model of myocardial infarction. Am J Physiol Heart Circ Physiol 2006;290:H248-54. [CrossRef]
10. Zheng ZS, Li TM, Kambic H, Chen GH, Yu LQ, Cai SR, et al. Sequential external counterpulsation (SECP) in China. Trans Am Soc Artif Intern Organs 1983;29:599-603.
11. Lawson WE, Hui JC, Soroff HS, Zheng ZS, Kayden DS, Sasvary D, et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am J Cardiol 1992;70:859-62. [CrossRef]
12. Lawson WE, Hui JC, Zheng ZS, Burger L, Jiang L, Lillis O, et al. Can angiographic findings predict which coronary patients will benefit from enhanced external counterpulsation? Am J Cardiol 1996;77:1107-9. [CrossRef]
13. Lawson WE, Hui JC, Zheng ZS, Burgen L, Jiang L, Lillis O, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology 1996;87:271-5. [CrossRef]
14. Lawson WE, Hui JC, Guo T, Burger L, Cohn PF. Prior revascularization increases the effectiveness of enhanced external counterpulsation. Clin Cardiol 1998;21:841-4. [CrossRef]
15. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohara 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;37:93-9. [CrossRef]
16. Stys T, Lawson WE, Hui JC, Lang G, Liuzzo J, Cohn PF. Acute hemodynamic effects and angina improvement with enhanced external counterpulsation. Angiology 2001;52:653-8. [CrossRef]
17. Feldman AM, Silver MA, Francis GS, Abbottsmith CW, Fleishman BL, Soran O, et al. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1198-205. [CrossRef]
18. Ochoa AB, deJong A, Grayson D, Franklin B, McCullough P. Effect of enhanced external counterpulsation on resting oxygen uptake in patients having previous coronary revascularization and in healthy volunteers. Am J Cardiol 2006;98:613-5. [CrossRef]
19. Buschmann EE, Utz W, Pagonas N, Schulz-Menger J, Busjahn A, Monti J, et al. Improvement of fractional flow reserve and collateral flow by treatment with external counterpulsation (Art.Net.-2 Trial). Eur J Clin Invest 2009;39:866-75.
20. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, et al. 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. J Investig Med 2002;50:25-32. [CrossRef]
21. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study. Clin Cardiol 2000;23:254-8. [CrossRef]
22. Masuda D, Nohara R, Hirai T, Kataoka K, Chen LG, Hosokawa R, et al. 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;22:1451-8.
23. Lawson WE, Hui JC, Lang G. Treatment benefit in the enhanced external counterpulsation consortium. Cardiology 2000;94:31-5. [CrossRef]
24. Pettersson T, Bondesson S, Cojocaru D, Ohlsson O, Wackenfors A, Edvinsson L. One year follow-up of patients with refractory angina pectoris treated with enhanced external counterpulsation. BMC Cardiovasc Disord 2006;6:28. [CrossRef]
25. Manchanda A, Aggarwal A, Aggarwal N, Soran O. Management of refractory angina pectoris. Cardiol J 2011;18:343-51.
26. 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;93:461-4. [CrossRef]
27. 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. [CrossRef]
28. Soran O, Kennard ED, Bart BA, Kelsey SF; IEPR Investigators. Impact of external counterpulsation treatment on emergency department visits and hospitalizations in refractory angina patients with left ventricular dysfunction. Congest Heart Fail 2007;13:36-40. [CrossRef]
29. Levenson J, Pernollet MG, Iliou MC, Devynck MA, Simon A. Cyclic GMP release by acute enhanced external counterpulsation. Am J Hypertens 2006;19:867-72. [CrossRef]
30. Casey DP, Conti CR, Nichols WW, Choi CY, Khuddus MA, Braith RW. Effect of enhanced external counterpulsation on inflammatory cytokines and adhesion molecules in patients

with angina pectoris and angiographic coronary artery disease. Am J Cardiol 2008;101:300-2. [CrossRef]

31. Soran O. The role of enhanced external counterpulsation therapy in the management of coronary artery disease. In: Piscione F, editor. Angina pectoris. InTech 2011. p. 137-58. Available from: http://www.intechopen.com/books/angina-pectoris/the-role-of-enhanced-external-counterpulsation-therapy-in-the-management-of-coronary-artery-disease.

Key words: Aged; angina pectoris/mortality/therapy; coronary artery disease/epidemiology; counterpulsation/methods; enhanced external counterpulsation; follow-up studies; heart failure/epidemiology; registries; treatment outcome; Turkey/epidemiology.

Anahtar sözcükler: Yaşlı; anjina pektoris/mortalite/tedavi; koroner arter hastalığı/epidemiyoloji; kontrpulsasyon/yöntemler; geliştirilmiş dış kontrapulsasyon; izlem çalışması; kalp hastalığı/epidemiyoloji; kayıtlar; tedavi sonucu; Türkiye/epidemiyoloji.