Enhanced External Counterpulsation (EECP): Historical Background in the Treatment of Coronary Artery Disease and Its Emerging Role in Chronic Heart Failure

Özlem SORAN, MD, FACC, FESC

Associate Professor of Medicine, Cardiovascular Institute, Director of EECP Research Lab, University of Pittsburgh, Pennsylvania, USA

Summary

An epidemic of heart failure worldwide continues unabated. Recent developments in diagnostic and therapeutic techniques offer initial promise, but additional advances are needed to significantly alter this trend. Enhanced External Counterpulsation (EECP), which increases perfusion in the myocardium and other vascular beds, is known to decrease symptoms, increase functional capacity, and improve quality of life in patients with angina. Currently it is being investigated for the treatment of heart failure and, among potential new therapies, is unique in its noninvasive nature. This paper describes the current status of EECP for the treatment of heart failure and reviews its background in the treatment of coronary artery disease. ***(Türk Kardiyol Dern Arş 2004; 32: 309-317)***

Key words: *Coronary artery disease, enhanced external counterpulsation (EECP), heart failure*

Özet

Güçlendirilmiş Eksternal Kontrpulsasyon (EECP): Koroner Arter Hastalığının Tedavisinde Tarihçesi ve Kronik Kalp Yetersizliğinde Gelişen Rolü

Kalp yetersizliği dünyada epidemik boyutlara ulaşmıştır. Son yıllarda geliştirilen tedavi yöntemleri ve diagnostik tekniklere rağmen bu artış yavaşlatılamadığından halen yeni tedavi yöntemlerine ihtiyac duyulmaktadır. Miyokardium ve diğer vasküler yataklarda perfüzyonu artıran güçlendirilmiş eksternal kontrpulsasyon (EECP), koroner arter hastalığı teshiş edilmiş, angina şikayeti mevcut hastalarda semptomları iyileştirmekte, fonksiyonel kapasiteyi ve yaşam kalitesini artırmaktadır. Son yıllarda ise EECP kalp yetersizliği tedavisinde kullanılmaya başlanmış ve girişimsel olmayan özelliği ile kalp yetersizliğinde potansiyel tedavi yöntemleri arasına girmiştir. Bu derlemede EECP nin koroner arter hastalığı ve kalp yetersizliği tedavisinde ki yeri gözden geçirilmiştir. ***(Türk Kardiyol Dern Arş 2004; 32: 309-317)***

Anahtar kelimeler: *Güçlendirilmiş eksternal kontrpulsasyon (EECP), kalp yetersizliği, koroner arter hastalığı*

The dramatic rise in rates of congestive heart failure (CHF) is a major contributor to epidemic levels of cardiovascular disease worldwide. An estimated 4.9 million Americans suffer from CHF with 550,000 new cases reported each year, while estimates for the U.K. include a prevalence of 760,000 cases and incidence of 63,000 new cases annually [1]. Aging of the population in developed countries is a major factor contributing to the rise. Beyond the age

Address for Correspondence: University of Pittsburgh Cardiovascular Institute, 200 Lothrop Street, Scaife Hall S-571, Pittsburgh, PA 15213, USA Tel: 412 647 4411 Fax: 412 647 3913 e-mail: soranzo@msx.upmc.edu
Received: 21 April, accepted 15 June 2004

of 65, CHF incidence approaches 10 per 1,000 in the U.S. population and an estimated 1 in 5 people free of heart failure at age 40, regardless of gender, will develop CHF sometime in their life. Nearly 22% of male and 46% of female heart attack victims will be disabled with CHF within 6 years. Heart failure is the most frequent cause of hospitalization in the elderly and currently accounts for somewhere between five and ten percent of all hospital admissions. There were approximately 1 million hospital discharges for heart failure in 2000 compared with only 377,000 in 1979. Besides the morbidity associated with heart failure, it is also associated with significant mortality, contributing to about 262,300 deaths each year in the U.S. Eight in ten men and seven in ten women under age 65 who have CHF will die within 8 years [1].

Onat et al, conducted a survey study to determine the prevalence of heart disease in Turkish adults in a random sample of 3689 subjects 20 years of age or older in 59 communities representing the Turkish adult population. Their results showed that the prevalence of heart failure alone was 3% among the participants diagnosed with coronary heart disease [2]. Based on Onat`s findings we estimate the prevalence of heart failure in Turkish adults in 2004 will be approximately 80-90 thousand.

Major therapeutic goals in treating a patient with heart failure include prolonging life, preventing hospitalizations, and improving overall quality of life. Outpatient medical therapy for heart failure most often includes diuretics, angiotensin converting enzyme (ACE) inhibitors, digoxin, and, more recently, beta blockers [3]. ACTION HF (Action of Heart Failure) Consensus Recommendations and the Heart Failure Society of America (HFSA) Practice Guidelines now strongly advocate the use of β-blockers in mild to moderate heart failure, though they were once contraindicated [3]. However, there are limited therapeutic options beyond medical therapy, and virtually none that are noninvasive.

Evidence from a randomized clinical trial, from multiple analyses of a large patient registry, and from various open label investigations has shown that enhanced external counterpulsation (EECP) decreases symptoms in patients with angina. However, its role in the treatment of patients with heart failure is not yet defined and has only recently been the subject of investigations. Our aim in this paper is to describe the current role of EECP for the treatment of CHF and review it's historical background in the treatment of CAD.

Enhanced External Counterpulsation (EECP)

A standard EECP treatment course comprises 35 one-hour sessions over a seven-week period. Three pairs of pneumatic cuffs, wrapped around the calves, lower thighs, and upper thighs are sequentially inflated with compressed air in early diastole, beginning distally and progressing proximally, and then rapidly deflated at the onset of systole. Analogous to intraaortic balloon counterpulsation, the rapid inflation raises diastolic pressure (diastolic augmentation) and coronary blood flow while the rapid cuff deflation promotes lower extremity arterial "runoff" and leads to a decrease in systolic pressure (systolic unloading). Unlike intraaortic balloon counterpulsation, EECP also enhances venous return, further promoting an increase in cardiac output. These hemodynamic effects lead to increased blood flow in multiple vascular beds, including the coronary arterial circulation.

The magnitude of EECP-associated hemodynamic changes can be estimated noninvasively by measuring the diastolic to systolic effectiveness ratio using finger plethysmography (peak diastolic amplitude divided by the peak systolic amplitude). Doppler echocardiographic studies during application of EECP indicate that an ef-

fectiveness ratio of 1.5 to 2 is associated with an optimal increase in both systolic antegrade and diastolic retrograde aortic flow. However, given that a considerable proportion of patients who derive symptomatic benefit do not achieve an effectiveness ratio of 1.5 to 2, the clinical significance of this finding is unclear.

Historical Background: EECP in the treatment of Coronary Artery Disease (CAD)

We have reviewed the historical background of EECP in detail previously [4]. In the early 1990s, EECP was being investigated for the treatment of symptomatic patients with chronic angina. Most of the early data was from anecdotal case reports and case series. In a small study of 18 patients with angina refractory to medical therapy, Lawson et al. demonstrated that EECP resulted in a significant improvement in anginal symptoms in all 18 patients [5]. In addition, EECP was observed to be effective in improving exertional thallium perfusion defects and exercise duration in 14 of the 18 patients, suggesting improved perfusion to ischemic regions of the myocardium [5]. These benefits were sustained for up to five years after treatment [6]. Lawson et al. also reported the first case of EECP used as an adjunct to angioplasty for a patient with unstable angina, in which complete resolution of persistent fixed perfusion defects occurred without PTCA or surgical intervention [7].

Another case report describes an increase in both coronary perfusion and coronary blood flow reserve following ECCP in a patient who had undergone PTCA but experienced restenosis at the PTCA site and progressive coronary stenosis [8]. EECP was also shown to improve both coronary perfusion and coronary flow reserve in a patient undergoing two-stage repair for aortic regurgitation complicated by severe coarctation of the thoracoabdominal aorta due to Takayasu's Arteritis [9].

The multicenter study of enhanced external counterpulsation (MUST-EECP) was the first randomized placebo controlled trial of EECP for chronic angina [10]. In the MUST-EECP trial, 139 outpatients with angina, a documented history of CAD, and a positive exercise treadmill test, received 35 hours of active counterpulsation (CP) or inactive counterpulsation over a period of four to seven weeks. Although exercise duration increased in both groups, this difference was not statistically significant. Time to >1-mm ST-segment depression, however, increased significantly in the active CP group compared to the inactive group ($p=0.01$). More active CP patients experienced a decrease in angina symptoms as well. Thus, this was the first randomized, placebo-controlled trial demonstrating EECP reduces angina episodes and increases both exercise time and onset time of ischemic ST depression in patients with symptomatic CAD [10]. A substudy of the MUST-ECCP trial further showed that EECP resulted in significant improvements in quality of life which were sustained for up to 12 months after treatment [11].

In a prospective trial of 395 patients with chronic stable angina from centers participating in the EECP Clinical Consortium, Stys et al. demonstrated that ECCP improved anginal class in both men and women across a broad range of ages [12]. Specifically, after EECP, the Canadian Cardiovascular Society angina class (CCS) improved by at least one class in 88% of patients (87% of men and 92% of women), and in 89% of patients <66 years and 88% of patients >66 years old. Additionally, the hemodynamic effect of EECP was not a predictor of anginal class improvement, suggesting that other factors such as neurohormonal changes may play a role in ECCP's observed benefits [12].

A recent comparison of 1-year outcomes between 323 patients enrolled in the IEPR and 448 patients in the National Heart Lung and Blood Institute (NHLBI) Dynamic Registry

who were deemed suitable candidates for percutaneous coronary intervention (PCI) revealed that both survival and rates of coronary artery bypass grafting during follow-up were comparable between patient groups. One year following treatment with either EECP (IEPR) or PCI (Dynamic Registry), somewhat fewer of the IEPR patients reported no anginal symptoms compared to the Dynamic Registry patients ($p<0.001$). PCI candidates treated with EECP had 1-year event rates comparable to patients in the Dynamic Registry who received elective PCI. Thus, EECP appears to be a safe treatment option in patients with symptomatic CAD who are suitable for revascularization with PCI [13].

The international EECP patient registry (IEPR) was designed to document the safety and efficacy of EECP in a variety of clinical settings. Uniquely, this study enrolls consecutive angina patients from academic and non-academic, hospital-basedand free-standing treatment centers with no exclusions due to demographics, clinical status or outcome. To date, more than 7,000 patients have been enrolled from U.S. sites and (this doesn't sound right!) countries. We reported, in a comparison of refractory angina patients from Turkey and the U.S. treated with EECP, that Turkish patients presenting for EECP treatment show very different baseline profiles with respect to risk factors, medical history (more likely to have a history of CHF), comorbidities, and anginal symptoms. However, both cohorts achieved substantial reduction in angina and improvement in quality of life with EECP, despite an unfavorable baseline profile [14].

Urano et al. also demonstrated that EECP improves exercise tolerance and reduces myocardial ischemia in patients with CAD by improving LV diastolic filling [15]. Stys et al. further reported an improvement in stress myocardial perfusion in a study of 175 patients with chronic stable angina undergoing ECCP at maximal exercise levels [16]. A baseline pre-EECP radionuclide perfusion treadmill stress testing (RPST) was performed within one month prior to EECP treatment and results were compared to a follow-up RPST performed within 6 months of completion of EECP treatment. Four centers performed post EECP RPST to the same level of exercise as pre-EECP while 3 centers performed maximal RPST post-EECP. In the centers performing the same level of exercise, 83% had significant improvement in RPST perfusion images. Fifty-four percent (54%) of patients who underwent maximal RPST revealed significant improvement in perfusion images.

Linnemeier et al. studied whether EECP is a safe and effective treatment for angina in octogenarians. These authors reported a 76% reduction in angina and a significantly improved quality of life, emphasizing an 81% maintenance of angina improvement at 6-month follow-up [17].

In summary, clinical studies of EECP have shown consistent reduction in anginal episodes, sustained improvement in CCS Angina Class, increased time to ST-segment depression, greater exercise work-load (METS), fewer stress-induced reversible perfusion defects and better health-related quality of life.

Of historical significance is the fact that heart failure was considered a contraindication for studies examining the effects of ECCP on CAD. Recently, a multicenter feasibility trial was the first to show the safety and efficacy of EECP in heart failure [18]. As with β-blockers in the treatment of heart failure, the role of ECCP has evolved over time such that it was cleared by FDA in 2002 for the treatment of heart failure.

EECP for Angina in Severe Left Ventricular Dysfunction

We have evaluated outcomes of EECP treatment in 1999 in 466 patients enrolled in the IEPR and reported that EECP was a safe and ef-

fective treatment for angina in patients with severe LVD (≤35%) not considered good candidates for revascularization by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) [19]. Patients who completed treatment experienced a significant reduction in CCS angina class accompanied by significant improvement in quality of life, with the degree of improvement independent of the severity of LVD before treatment. A follow-up report in 2002 demonstrated that these benefits were maintained for at least two years following EECP treatment [20].

Another study of 1,957 patients from the international EECP patient registry for angina compared outcomes six months following completion of therapy in 548 patients who reported a history of heart failure to those without a similar history [21]. Patients in the heart failure cohort were older, had CAD of longer duration, and had experienced prior infarcts and revascularizations more often. No difference was seen during treatment in the rate of major adverse cardiac events (MACE, i.e. death, myocardial infarction, revascularization) between groups, though exacerbation of heart failure occurred somewhat more frequently in patients with a history of heart failure. Despite a notably more adverse baseline profile, 68% of patients with a history of heart failure achieved improvement in angina class with a comparable benefit observed in quality of life measures. Moreover, for the six months following EECP, patients in the heart failure cohort maintained their reduction in anginal symptoms and rates of unstable angina, MI, CABG and PCI were similar. However, they were more likely to experience a major adverse cardiac event because of higher rates of CHF exacerbation, cardiac hospitalion and death.

Vilkas et al also found EECP to be safe and well-tolerated in patients with severe left ventricular dysfunction(LVD) [22]. Angina class according to the Canadian Cardiovascular Society (CCS) classification improved in 60% of patients with LVD (LVEF < 35%) compared with 79% of patients without (LVEF>35%). Significantly, patients with ischemic cardiomyopathy demonstrated improvement in cardiac function while those with preserved ventricular function did not. This study suggests, therefore, that EECP therapy is safe and may also improve angina and cardiac function in patients with ischemic cardiomyopathy.

Efficacy and Safety of EECP in CHF

A small, multicenter feasibility study, conducted under an investigational device exemption granted by the FDA, evaluated patients with chronic, stable, mild-to-moderate heart failure (NYHA class II-III) and an LVEF < 35% who received a standard course EECP therapy (35 1-hour sessions over 7 weeks) [23]. Patients achieved significant improvement in oxygen uptake at maximal exercise (VO_2max) and exercise duration one week and six months following EECP treatment, along with significant improvement in measures of quality of life. The authors concluded that EECP was safe and well tolerated in these patients and that the improvements obtained in peak oxygen consumption, exercise capacity, functional status and quality of life, for both the short- and long-term, indicated that further study was warranted. Results also suggested that study subjects benefited from EECP to a similar degree, regardless of whether their heart failure stemmed from ischemic or non-ischemic etiology.

Gorcsan et al performed ultrasound examinations in a subset of patients enrolled in the feasibility study to test the hypothesis that EECP may have beneficial effects on left ventricular (LV) function in patients with heart failure [24]. These authors used a relatively load independent measure of LV performance, a measure known as preload-adjusted maximal power (PAMP), to assess changes in LV function fol-

lowing a 35-hour course of EECP. Pressure-volume relationships derived from surrogate LV volumes estimated from echocardiographic images with automated border detection and LV ejection pressures estimated from photoplythesmograpy were used to calculate PAMP non-invasively from the following equation: (Pressure x Flow) / (End-diastolic Area) [25]. Significant increases in PAMP and LVEF, as well as a significant reduction in heart rate were seen one-week and six-months after completing EECP therapy, indicating that EECP can improve LV function in heart failure patients and may be a useful adjunct to medical therapy in these patients [24].

Mechanism of EECP:

It is not yet clear by what mechanism EECP achieves its effects. Current theories include mechanical changes in hemodynamics (increased coronary blood pressure, flow, and ventricular contractility, and reduced cardiac workload), neurohorme-mediated changes in vascular (increased nitric oxide and decreased endothelin) and cardiac tissue (reduced BNP) homeostasis, and endothelial-mediated changes in microcirculatory anatomy and perfusion (angiogenesis stemming from increased shear stress resulting in release of VEGF, HGF, and FGF). EECP accomplishes mechanical changes in hemodynamic parameters by inflating oversized cuffs applied to the lower extremities sequentially from distally to proximally, thereby raising diastolic aortic pressure and increasing coronary perfusion pressure (diastolic augmentation) and flow. Venous return is also increased due to compression of the vascular beds of the legs. A significant reduction in vascular impedance and ventricular workload is achieved by an instantaneous decompression of all cuffs just prior to the onset of systole (ventricular unloading). Together, these effects coupled with the increase in venous return act to raise cardiac output [26-28].

Alternatively, patients may accrue benefit from effects induced by changes in circulating levels of certain vasoactive neurohormones, similar to changes seen with athletic training. Wu et al showed a dose-related, sustained increase in endothelial cell production of the vasodilator nitric oxide (NO) and decrease in production of the vasoconstrictor endothelin (ET-1) [29]. Qian et al showed even more clearly that the level of NO increased linearly in proportion to the EECP dose (hours of treatment) [30]. Other studies have shown that EECP improves endothelial function and enhances vascular reactivity. Significant improvement ($p<0.05$) in peripheral arterial tone after each EECP treatment was reported by Bonetti et al using peripheral arterial tonometry (RH-PAT index) assessed during reactive hyperemia [31]. Of note, the average RH-PAT index continued to be significantly higher than before EECP therapy ($p<0.05$) one month after completion of therapy.

A study by Masuda et al contributed evidence in support of multiple mechanisms of action [32]. They demonstrated an increase in pharmacologically-induced coronary vasodilation and myocardial perfusion after EECP treatment. Levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were reduced after a course of EECP treatments, and the level of circulating NO level was increased at rest. Time to 1 mm ST-segment depression on exercise was increased significantly; similarly, exercise duration trended in the same direction.

Urano et al surmised that EECP reduces exercise induced myocardial ischemia and improves LV diastolic filling in patients with CAD [15]. Assessing similar as well as different factors, their work demonstrated that plasma BNP levels decreased after EECP, positive correlated with left ventricular end diastolic pressure and negatively correlated with peak filling rate.

Earlier work by Masuda demonstrated that EECP promotes the release of angiogenesis factors such as hepatocyte growth factor, basic fi-

broblast growth factor and vascular endothelial growth factor. This theory holds angiogenesis is stimulated by vascular growth factors that are released as a result of increased shear stress, such as that associated with augmented diastolic flow during EECP [28].

Lastly, EECP's mode of action could derive from changes in ventricular function that occur independent of changes in cardiac load. Gorscan et al showed an improvement in PAMP (a relatively load independent measure of LV performance) and EF, along with a decrease in heart rate, in patients with Class II-III heart failure and LVEF ≤ 40%.

Heart Failure Patients may benefit from EECP if they: [33]

1. Are diagnosed with moderate to severe levels of CHF, e.g. NYHA Class II, III (decompensated acute heart failure patients are not candidates for EECP treatment)
2. Have heart failure of ischemic or idiopathic cardiomyopathy
3. Are in stable condition with manageable peripheral edema
4. Have left ventricular dysfunction (LVD, EF ≤ 35%)
5. Have other co-morbid states that increase their surgical risks such as diabetes or pulmonary disease.

Suggestions to follow during the treatment of heart failure patients; [33]

1. Verify that the subject is in stable condition
2. Obtain Vital Signs
3. Initiate pulse oximetry measurements and record oxygen saturation
4. Inititiate EECP treatment
5. Record a during-session plethsmography tracing
6. Record oxygen saturation every 20 minutes, reevaluate the patient condition if oxygen saturation decreases by 4% or more from the initial measurement.
7. Terminate the session 60 minutes after initiating the application of the device.

Conclusion

EECP is a noninvasive, out-patient based treatment shown to improve myocardial perfusion, angina symptoms, exercise tolerance, and quality of life in patients with CAD. The U.S. Food and Drug Administration (FDA) cleared EECP in 2002 for the indication of treatment of congestive heart failure, adding to the previously established indications of stable or unstable angina pectoris, acute myocardial infarction, or cardiogenic shock. A positive decision for reimbursement of EECP for angina was reached in 1999 by the Centers for Medicare and Medicaid Services (CMS) and all private insurance companies and managed care providers also provide reimbursement for EECP therapy in USA.

Recent studies demonstrate that EECP also has positive effects in patients with heart failure. Large registry studies conducted in diverse practice settings have proven EECP to be safe and effective in patients with angina and severe left ventricular dysfunction. Moreover, feasibility studies now indicate that EECP increases peak oxygen uptake and exercise duration while improving functional status and quality of life in patients with heart failure. The PEECH Trial (Prospective Evaluation of EECP in Congestive Heart Failure), a multicenter, prospective randomized, controlled clinical trial, is currently on-going to verify the efficacy of EECP as an adjunctive therapy in the management of patients with chronic stable heart failure.

REFERENCES

1. American Heart Association. 2003 Heart and Stroke Statistical Update. Dallas, Tex.: American Hear Association; 2002

2. Onat A, Senocak MS, Surdum- Avci G, Ornek E. Prevalence of coronary heart disease in Turkish adults. Int J Cardiol 1993; 39: 23-31

3. Packer M, Cohn JN: Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999; 83(suppl 2A): 1A-38A

4. Soran O, Crawford LE, Schneider VM et al: EECP in the management of patients with cardiovascular disease. Clin Cardiol 1999; 22:173-8

5. Lawson WE, Hui JC, Soroff HS, et al: Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am J Cardiol 1992; 70: 859-62

6. 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

7. Lawson WE, Hui JC, Oster ZH, et al: Enhanced external counterpulsation as an adjunct to revascularization in unstable angina. Clin Cardiol 1997; 20: 178-80

8. Masuda D, Nohara R, Inada H et al: Improvement of regional myocardial and coronary blood flow reserve in a patient treated with enhanced external counterpulsation. Evaluation by Nitrogen-13 Ammonia PET. Jpn Circ J 1999; 63: 407-11

9. Minakata K, Konishi Y, Matsumoto M, Nonaka M, Yamada N: Two-stage repair for aortic regurgitation complicated by severe coarctation of the thoracoabdominal aorta due to Takayasu's arteritis. Jpn Circ J 1999; 63: 412-3

10. Arora RR, Chou TM, Jain D, 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

11. Arora, RR, ChouTM, Jain D, 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 Invest Med 2002; 50: 25-32

12. Stys T, Lawson WE, Hui JCK, Lang G, et al: Acute hemodynamic effects and angina improvement with enhanced external counterpulsation. Angiology 2001; 52: 653-8

13. Holubkov R, Kennard ED, Foris JM, et al: Comparison of patients under going enhanced external counterpulsation and percutaneous coronary intervention for stable angina pectoris. Am J Cardiol 2002; 89:1182-6

14. Soran O, Sengul A, Ikizler C, Yener T, Kennard ED: A comparision of refractory angina patients treated with enhanced external counterpulsation (EECP) from Turkey and the United States: a report from the international EECP patient registry. South Med J 2002; 95:S7

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

16. Stys TP, Lawson WE, Hui JC et al: Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol 2002; 89: 822-4

17. Linnemeier G, Michales AD, Soran O, Kennard ED: Enhanced external counterpulsation in the management of angina in the elderly. Am Geriatr Cardiol 2003; 12: 90-4

18. Soran OZ, Fleishman B, Demarco T, et al: Enhanced external counterpulsation in patients with heart failure: a multicenter feasibility study. CHF. 2002; 8: 204-8

19. Strobeck JE, Reade R, Kennard ED, et al: Enhanced external counterpulsation is a safe and effective treatment for angina in patients with severe left ventricular dysfunction. J Cardiac Fail 1999; 72: 268

20. Soran O, Kennard ED, Feldman AM: Does enhanced external counterpulsation reduce the refractory angina burden in patients with left ventricular dysfunction? - A 2 years follow-up study. J Heart Failure 2002; 7: 259

21. Lawson WE, Kennard ED, Holubkov et al, for the IEPR Investigators: Benefit and safety of enhanced external counterpusation in treating coronary artery disease patients with a history of congestive heart failure. Cardiology 2001; 96:78-84

22. Vilkas D, Suresh K, Lawson W, et al: Does EECP improve cardiac function in ischemic cardiomyopathy? Abstract: Presented in the CR2002 (Clinical Research 2002) of the American Federation for Medical Research on April 12, 2002 at Baltimore, Maryland.

23. Soran OZ, DeMarco T, Crawford LE, et al: Safety of enhanced external counterpulsation in heart failure patients. Circulation 1999; 100:I-300 (#1567).

24. Gorcsan III J, Crawford L, Soran OZ, et al: Improvement in left ventricular performance by enhanced external counterpulsation in patients with heart failure. JACC 2000; 35: 230A: 901-5

25. Mandarino et al: [Author Query: Title of publication?] J Am Coll Cardiol 1998; 31: 861-8

26. Taguchi I, Ogawa K, Oida A, Abe S, Kaneko N, Sakio H: Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. Am J Cardiol 2000; 86:1139-41

27. Michales MD, Accad M, Ports TA, Grossmann W: Left ventricular systolic unloading and augmentation of in-

tracoronary pressure and Doppler flow during enhanced external counterpulsation. Circ 2002; 106:1237-42

28. Masuda D, Nohara R, Kataoka K: Enhanced external counterpulsation promotes angiogenesis factors in patients with chronic stable angina. Circ 2001;104 II 445:2109

29. Wu GF, Qiang SZ, Zheng ZS: A neurohormaonal mechanism for the effectiveness of the enhanced external counterpulsation. Circ 1999; 100: I-832: 4390

30. Qian X, Wu W, Zheng ZS: Effect on enhanced counterpulsation on nitric oxide production in coronary disease. J Heart Disease 1999; 1: 193:769

31. 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

32. Masuda D, Nohara R, Hirai T, et al: Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina. Eur Heart J 2001; 22: 1451-8

33. Soran O: A new treatment modality in heart failure: Enhanced external Counterpulsation (EECP). Cardiology in review 2004; 12: 15-20