

STATE-OF-THE-ART PAPER

Enhanced External Counterpulsation and Future Directions

Step Beyond Medical Management for Patients With Angina and Heart Failure

Aarush Manchanda, MD,* Ozlem Soran, MD, MPH, FACC, FESC†

Washington, DC; and Pittsburgh, Pennsylvania

Between 25,000 and 75,000 new cases of angina refractory to maximal medical therapy and standard coronary revascularization procedures are diagnosed each year. In addition, heart failure also places an enormous burden on the U.S. health care system, with an estimated economic impact ranging from \$20 billion to more than \$50 billion per year. The technique of counterpulsation, studied for almost one-half century now, is considered a safe, highly beneficial, low-cost, noninvasive treatment for these angina patients, and now for heart failure patients as well. Recent evidence suggests that enhanced external counterpulsation (EECP) therapy may improve symptoms and decrease long-term morbidity via more than 1 mechanism, including improvement in endothelial function, promotion of collateralization, enhancement of ventricular function, improvement in oxygen consumption (V_{O_2}), regression of atherosclerosis, and peripheral training effects similar to exercise. Numerous clinical trials in the last 2 decades have shown EECP therapy to be safe and effective for patients with refractory angina with a clinical response rate averaging 70% to 80%, which is sustained up to 5 years. It is not only safe in patients with coexisting heart failure, but also is shown to improve quality of life and exercise capacity and to improve left ventricular function long-term. Interestingly, EECP therapy has been studied for various potential uses other than heart disease, such as restless leg syndrome, sudden deafness, hepatorenal syndrome, erectile dysfunction, and so on. This review summarizes the current evidence for its use in stable angina and heart failure and its future directions. (J Am Coll Cardiol 2007;50:1523–31) © 2007 by the American College of Cardiology Foundation

An estimated 6.4 million patients in the U.S. suffer from symptomatic coronary artery disease (CAD), and about 400,000 new cases develop each year (1). Despite optimal medical therapy and invasive procedures, such as angioplasty and cardiac bypass surgery, there are an estimated 300,000 to 900,000 patients in the U.S. who have refractory angina pectoris (RAP). About 25,000 to 75,000 new cases of RAP are diagnosed each year (1).

Daily tasks such as climbing a flight of stairs, walking a dog, or mowing the lawn become impossible without experiencing chest pain for these difficult-to-treat patients. In addition, despite advances in medical therapy for the treatment of heart failure (HF) over the past decade, substantial unmet needs remain, particularly in patients with moderate to severe HF. Heart failure is the number 1 diagnosis in Medicare patients and approximately 5 million Americans experience HF, with 550,000

new cases per year reported (1). It has been estimated that in 2005, the total direct and indirect cost of HF in the U.S. will be equal to \$27.9 billion, and approximately \$2.9 billion annually is spent on drugs for the treatment of HF (1). Only a few consensus therapies exist to treat HF beyond medical management, and many patients now are left to suffer their symptoms and restrict their activities chronically, and anticipate a reduced life expectancy.

Current nonpharmacological options available for these patients with RAP with or without underlying HF include neurostimulation (transcutaneous electrical nerve stimulation and spinal cord stimulation), enhanced external counterpulsation (EECP) therapy, laser revascularization techniques, gene therapy, and newer interventional procedures such as percutaneous in situ coronary venous arterialization or percutaneous in situ coronary artery bypass (2). Of these modalities, EECP therapy represents the only truly noninvasive technique for which both a reduction of angina symptoms, improvement in objective measures of myocardial ischemia, and improvement in left ventricular function (both systolic and diastolic) have been shown (3–5). This review summa-

From the *Department of Internal Medicine, The George Washington University, Washington, DC; and the †Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. Dr. Soran serves on the Speakers' Bureau of Vasomedical, Inc.

Manuscript received April 2, 2007; revised manuscript received May 25, 2007, accepted July 17, 2007.

Abbreviations and Acronyms

- CAD** = coronary artery disease
- cGMP** = cyclic guanosine monophosphate
- EECP** = enhanced external counterpulsation
- EF** = ejection fraction
- HF** = heart failure
- LVD** = left ventricular dysfunction
- NYHA** = New York Heart Association
- RAP** = refractory angina pectoris

izes the current evidence for the use of EECP therapy in stable angina and HF and its future directions.

Historical Perspective

Almost one-half century ago, researchers at Harvard University conducted experiments with counterpulsation showing that this technique markedly reduces the workload, and thus oxygen consumption, of the left ventricle. In 1953, Kantrowitz and Kantrowitz (6) described diastolic augmentation as a means of improving coronary blood

flow. Birtwell et al. (7) did pioneering work toward the development of this technique and were first to apply this concept by developing the initial arterial counterpulsator in the U.S. Zheng et al. (8) were the first to report the benefits of external counterpulsation in the 1980s by using the first pneumatic counterpulsation device. Lawson et al. (9–13) at the State University of New York, Stony Brook, undertook a number of open-label studies with the enhanced system, EECP, between 1989 and 1998 using both objective and subjective end points. These studies, although open and nonrandomized, showed statistical improvement in exercise tolerance by patients as evidenced by thallium-stress testing and partial or complete resolution of coronary perfusion defects as evidenced by radionuclide imaging studies. In 1999, Arora et al. (14) reported results of the first double-

blind randomized placebo-controlled multicenter trial (MUST-EECP [Multicenter Study of Enhanced External Counterpulsation]) (14). Since then, EECP therapy has emerged as an effective, noninvasive, and durable therapeutic option for patients not only with angina but also with HF.

Technique

The technique of EECP therapy consists of electrocardiogram-gated rapid, sequential compression of the lower extremities taking place during diastole, followed by simultaneous decompression during systole. These actions produce hemodynamic effects similar to those of an intraaortic balloon pump, but unlike an intra-aortic balloon pump, EECP therapy also increases venous return (Fig. 1).

Cuffs resembling oversized blood pressure cuffs—on the calves, the lower thighs, and the upper thighs, including the buttocks, inflate rapidly and sequentially—via computer-interpreted electrocardiogram signals—starting from the calves and proceeding upward to the buttocks (Fig. 1) during the resting phase of each heartbeat (diastole). This has the effect of creating a strong retrograde counterpulse in the arterial system, forcing freshly oxygenated blood toward the heart and coronary arteries, while simultaneously increasing the volume of venous blood return to the heart under increased pressure.

Just before the next heartbeat, before the systole, all 3 cuffs simultaneously deflate, significantly reducing the workload of the heart. 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, reducing the amount of work the heart must do to pump oxygenated blood to the rest of

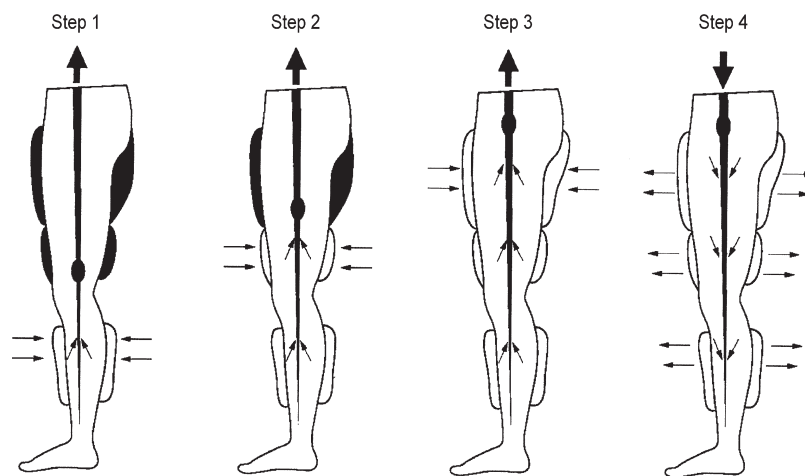


Figure 1 Technique of EECP

Three pairs of pneumatic cuffs are applied to the calves, lower thighs, and upper thighs. The cuffs are inflated sequentially during diastole, distal to proximal. The compression of the lower-extremity vascular bed increases diastolic pressure and flow and increases venous return. The pressure is then released at the onset of systole. Inflation and deflation are timed according to the R-wave on the patient's cardiac monitor. The pressures applied and the inflation–deflation timing can be altered by using the pressure waveforms and electrocardiogram on the enhanced external counterpulsation (EECP) therapy monitor.

the body. The inflation-deflation activity is monitored with the help of a finger plethysmogram and coordinated by a microprocessor that interprets electrocardiogram signals from the patient's heart and actuates the inflation and deflation cycles. The end result of this sequential squeezing of the legs is to create a pressure wave that significantly increases peak diastolic pressure, benefiting circulation to the heart muscle and other organs, while also reducing systolic pressure and systemic vascular resistance to the general benefit of the vascular system. A typical treatment course consists of 35 outpatient treatments administered as 1 h per day over 7 weeks.

Mechanism of Action of EECP

Recent advances in the understanding of coronary arterial physiology and response to EECP therapy have provided some insight into possible modes of effect and an explanation for the benefits seen with EECP therapy (Fig. 2.) However, most of the experience is from small animal or human uncontrolled studies, and the mechanism of the sustained antianginal benefit with EECP remains unclear.

Development of new functional collateral vessels by increasing nitric oxide and decreasing endothelin-1 levels to the ischemic myocardium was postulated as the mechanism of action for EECP therapy by many early studies conducted. Masuda et al. (15) reported that the development of functional collateral vessels is one of the mechanisms of EECP therapy using ammonia positron emission tomogra-

phy. Endothelial shear stress from increased diastolic augmentation after EECP therapy was shown to augment endothelium-derived relaxing factor/nitric oxide production (16) and to cause down-regulation of endothelin-1 levels, thereby recruiting more collateral vessels (17). Akhtar et al. (18) recently showed that EECP therapy has a sustained, dose-related effect in stimulating endothelial cell production of the vasodilator nitric oxide and in decreasing production of endothelin-1. However, an increase in myocardial perfusion on nuclear stress tests was inconsistent with improvement in symptoms (Table 1), making it unlikely as a sole mechanism of benefit.

In recent studies by Tao et al. (19,20), EECP therapy demonstrated stabilization of coronary endothelium, an effect very similar to that of athletic training. These recent studies confirm the earlier results by Bonetti et al. (21); they had seen improvement in the peripheral endothelial function (RH-PAT) in their patients after 35 h of EECP treatment. Zhang et al. (22) also showed retardation of the atherosclerosis process by the metabolic effects of external counterpulsation therapy on the NF-kappa signaling pathways. Recently Levenson et al. (23) postulated that an increase in cyclic guanosine monophosphate (cGMP) acutely after EECP therapy might in part be responsible for the improved peripheral arterial function. Cyclic guanosine monophosphate regulates vascular smooth muscle tone, which may improve arterial function. Fifty-five subjects were randomized into 2 groups to receive either sham (control) or active EECP therapy during 1 h. Plasma and platelet cGMP were measured immediately before and after EECP therapy by radioimmunoassay. One hour of EECP therapy increased cGMP plasma concentration by 52% and platelet content by 19%. This theory of endothelial stabilization has attracted the most attention in the recent past as one of the primary mechanisms of action, with more clinical trials needed to further understand it completely.

Arora et al. (24) showed a trend toward increased vascular endothelial growth factor levels after EECP therapy in human subjects, thereby confirming the findings of Chen et al. (25) in the canine model. Vascular endothelial growth factor, along with other growth factors such as fibroblast growth factor, is the most widely studied in gene therapy for RAP. It is considered important in promoting angiogenesis or neorevascularization of the ischemic myocardium. However, failure to show consistent improvement in myocardial perfusion as discussed above makes neorevascularization unlikely, an argument similar to the one against collateralization.

Ochoa et al. (26) recently reported the acute effects of EECP therapy on oxygen uptake: VO_2 at rest in adults with symptomatic CAD compared with healthy volunteers using sham control group. They measured VO_2 continuously in 20 adults during a single treatment session of EECP therapy, including 10 subjects with previous coronary revascularization who were referred for EECP therapy for refractory angina and 10 healthy, sedentary volunteers. Both groups showed a small, sustained increase in VO_2 during EECP

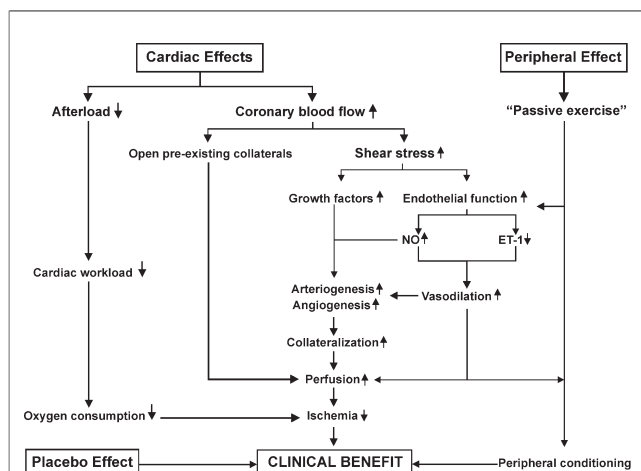


Figure 2 Possible Mechanisms Responsible for the Clinical Benefit Associated With EECP Therapy

Acute afterload reduction decreases myocardial demand. By increasing coronary blood flow, enhanced external counterpulsation (EECP) therapy is thought to promote myocardial collateralization via opening of preformed collateral vessels, arteriogenesis, and angiogenesis. Increased blood flow and shear stress also may improve coronary endothelial function, favoring vasodilation and myocardial perfusion. In addition, improvement in endothelial function may further promote collateral formation by arteriogenesis and angiogenesis. In addition to a peripheral training effect, a minor placebo effect is considered to contribute to the symptomatic benefit of EECP therapy. ET = endothelin; NO = nitric oxide.

Table 1 Published Trials of EECP in Patients With Stable Angina

Study (Ref. #)	Year	N	Treatment Duration (h)	Angina Relief (% \geq 1 CCS Class \uparrow)	Nitroglycerine Use Versus Frequency	Exercise Capacity (%)	Time to ST-Segment Depression on Stress Test	Cardiac Perfusion (% of Patients)	Other Findings
Zheng et al. (8)	1983	200	12	\downarrow (97%)	NA	NA	NA	NA	—
Lawson et al. (10)	1992	18	36	\downarrow (100%)	\downarrow	\uparrow 67	NA	\uparrow (78%)	—
Lawson et al. (11,12)	1996	27	35	NA	NA	\uparrow 81	NA	\uparrow (78%)	In addition, EECP therapy seemed to decrease PVR and HR response to exercise, the so-called training effect
Lawson et al. (13)	1998	60	35	\downarrow	NA	\uparrow	NA	\uparrow (75%)	Benefit sustained at 2-yr follow-up
Arora et al. (14)	1999	139	35	\downarrow	\downarrow	\uparrow	\uparrow	NA	Only double-blind trial to date using sham controls
Lawson et al. (27)	2000	33	35	\downarrow (100%)	\downarrow	NA	NA	\uparrow (79%)	Benefit sustained at 5-yr follow-up
Lawson et al. (28)	2000	2,289	35	\downarrow (74%)	NA	NA	NA	NA	EECP consortium. Efficacy was independent of provider setting or experience
Masuda et al. (29)	2001	11	35	NA	NA	\uparrow	\uparrow	\uparrow	Coronary perfusion increased both at baseline and during dipyridamole provocation
Stys et al. (30)	2001	395	35	\downarrow (88%)	NA	NA	NA	NA	EECP was equally effective in men and women and young and elderly (>65 yrs)
Barsness et al. (31)	2001	978	35	\downarrow (81%)	\downarrow	NA	NA	NA	EECP therapy can be used for those who prefer noninvasive treatment to avoid revascularization
Stys et al. (32)	2002	175	35	\downarrow (85%)	NA	\uparrow	NA	\uparrow (83%)	—
Fitzgerald et al. (33)	2003	4,454	35	\downarrow *	\downarrow *	NA	NA	\uparrow	*Comparable benefit seen for both previously revascularized and PUMPERS
Tartaglia et al. (34)	2003	25	35	\downarrow (93%)	NA	\uparrow	\uparrow (80%)	NA	—
Lawson et al. (35)	2006	363	35	\downarrow (72%)*	\downarrow 52*	NA	NA	NA	*Benefit sustained at 2 yrs
Lawson et al. (36)	2005	746	32	\downarrow (72%)	\downarrow	NA	NA	NA	Equal benefit in both systolic and diastolic heart failure
Novo et al. (37)	2006	25	35	\downarrow (84%)	NA	NA	NA	\uparrow (36%) dobutamine stress if possible echocardiography	Maximal benefit seen in patients with worst systolic failure
Lawson et al. (38)	2006	1,458	35	\downarrow	\downarrow	\uparrow	NA	NA	EECP therapy was found to be equally beneficial in mild vs. severe anginal symptoms
Loh et al. (39)	2006	58	35	\downarrow (86%)*	\downarrow	\uparrow	NA	NA	*Sustained improvement in 78% at 1-yr follow-up

*Comment related to the particular variable in the referenced study.

CCS = Canadian Cardiovascular Society; EECP = enhanced external counterpulsation; HR = heart rate; NA = not applicable; PUMPERS = candidates for percutaneous coronary intervention and/or coronary artery bypass graft and chose enhanced external counterpulsation therapy as their initial revascularization treatment; PVR = peripheral vascular resistance.

treatment. Because VO_2 is an independent predictor of increased exercise capacity, it led them to conclude that increase in VO_2 may also in part be one of the mechanisms by which EECP therapy increases exercise tolerance in stable angina patients (26).

In summary, further studies are needed to elucidate both the mechanism of action and the overall effects of EECP therapy, or a combination of the above mechanisms may explain the sustained benefit from EECP therapy in the clinical trials (27).

EECP and Angina

Several nonrandomized and randomized trials have shown a consistently positive clinical response among patients of RAP treated with EECP therapy (Table 1) (8–14,28–39). Benefits associated with EECP therapy include reduction of 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 (Table 1). Patients with severely disabling angina at baseline and those without a history of smoking are more likely to improve their angina class after EECP therapy (40).

Most of the studies on EECP therapy cannot be double-blind and lack good control groups because of technical limitations, which have frequently raised questions of operator bias in the past. But the MUST-EECP study, a randomized, double-blind, sham-controlled trial, also showed the clinical benefit of EECP therapy in patients with chronic stable angina and positive exercise stress tests (14). In this study, 139 patients (mean age 63 years, range 35 years to 81 years) with angina pectoris (typical Canadian Cardiovascular Society classes I, II, and III angina) and documented coronary ischemia were equally randomized to hemodynamically inactive counterpulsation with EECP versus active counterpulsation. 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. Moreover, a MUST-EECP substudy showed a significant improvement in quality-of-life parameters in patients assigned to active treatment, which was sustained during a 12-month follow-up period (41).

Results from the International EECP Patient Registry (31,33,35) and the EECP Clinical Consortium (28) have shown that the symptomatic benefit observed in controlled studies also translates to the heterogeneous patient population seen in clinical practice. Moreover, follow-up data indicate that the clinical benefit may be maintained for up to 5 years in patients with a favorable initial clinical response

(27,35). One of the ongoing debates with most of the published trials discussed earlier (Table 1) is that the increased exercise tolerance reported after EECP therapy may, at least in part, be attributed to a training effect.

EECP in Angina With Left Ventricular Dysfunction

When providing EECP therapy to the HF population, the primary concern of the initial researchers was that the increased venous return resulting from EECP therapy could precipitate pulmonary edema in angina patients with severe left ventricular dysfunction (LVD). Soran et al. (42,43) evaluated the safety and efficacy of EECP therapy in patients with angina and severe LVD (ejection fraction [EF] <35%). The outcomes of EECP treatment were followed up in 363 patients enrolled in the International EECP Patient Registry, an international multicenter study of EECP therapy for the treatment of patients with chronic angina. The EECP therapy was observed to be a safe and effective treatment of angina in patients with severe LVD who were not considered good candidates for revascularization by coronary artery bypass graft or percutaneous coronary intervention (43). After completion of treatment, there was a significant reduction in severity of angina: 72% improved from severe angina to no angina or mild angina. Fifty-two percent of patients discontinued nitroglycerin use. Quality of life showed a significant increase. At 2-year follow-up, this angina reduction was maintained in 55%, 83% survived, and event-free (death/myocardial infarction/percutaneous coronary intervention/coronary artery bypass graft) survival rate was 70%. Forty-three percent had no cardiac hospitalization; 81% had no congestive HF event (43).

Lawson et al. (44) also evaluated RAP patients with preserved left ventricular function (EF >35%) and with severe left ventricular dysfunction (EF ≤35%) who were treated with a 35-h course of EECP therapy. Bioimpedance measurements of cardiovascular function were obtained before the first and again after the 35th hour of EECP therapy. Twenty-five patients were enrolled, 20 with preserved left ventricular function and 5 with severe left ventricular dysfunction. Angina class improved similarly in both groups. The severe left ventricular dysfunction group, in contrast to the preserved left ventricular function group, increased cardiac power, stroke volume, and cardiac index and decreased systemic vascular resistance with treatment. This study suggests that EECP could benefit patients experiencing CAD with severe left ventricular dysfunction directly by improving cardiac power and indirectly by decreasing systemic vascular resistance (44).

EECP Therapy in HF

Most of the data to date on the efficacy and safety of EECP therapy in HF are from small studies (45,46). In a pilot study of clinically stable patients diagnosed with mild to moderate HF (New York Heart Association [NYHA]

functional class II or III) and a left ventricular EF <35%, Soran et al. (45) found EECP treatment to be safe with no unexpected adverse events during the application of EECP treatment. Soran et al. (45) also conducted a multicenter feasibility study in which stable HF (New York Heart Association functional class II to III, ischemic and nonischemic etiology) patients with left ventricular EF <35% were treated with 35 1-h sessions of EECP therapy over a 7-week period and followed up over a 6-month period. The mean EF for the ischemic and nonischemic groups was $25.6 \pm 7.1\%$ and $18.7 \pm 7.4\%$, respectively. Mild to moderate valvular heart disease was the most common etiology for the group with nonischemic etiology. Study results showed that EECP therapy was safe and well-tolerated in this group of patients (46). In addition, EECP therapy was associated with significant improvements in exercise capacity as measured by peak oxygen uptake and exercise duration and in quality of life at 1 week and 6 months after EECP treatment. Although safety was the primary end point of this feasibility study, the efficacy results suggest that EECP therapy can increase peak oxygen uptake, improve exercise capacity and functional status, as well as improve the patient's quality of life, for both the short term and long term (6 months) after the completion of EECP therapy. Although study subjects benefited from EECP therapy to a similar degree regardless of ischemic or nonischemic etiology of their HF, because of a small number of patients in the nonischemic group, further studies need to be conducted to evaluate the effectiveness of EECP in patients with a nonischemic etiology (46).

Based on these results, a larger, controlled study of EECP therapy in patients with stable HF (NYHA functional classes II and III) and LVD was undertaken called the PEECH (Prospective Evaluation of EECP in Heart Failure) trial (47), results of which were recently

published. It was a controlled, randomized, single-blind, parallel-group, multicenter study of 187 patients with symptomatic but stable HF (NYHA functional classes II and III, ischemic and nonischemic etiology) and a left ventricular EF $\leq 35\%$ was designed to assess the efficacy of EECP therapy in patients with stable HF. Medical therapy is optimized in all patients based on the recommendations of the Heart Failure Society of America (usual care), and then randomized between 2 treatment groups, usual care or EECP therapy (35 h over 7 weeks). The EECP therapy improved exercise tolerance, quality of life, and NYHA functional class without an accompanying increase in peak VO_2 . Investigators also assessed whether differences existed in response to EECP therapy in patients with HF secondary to either ischemic or nonischemic dilated cardiomyopathy. Albeit in a relatively small sample size, subgroup analysis based on etiology of disease showed benefit in patients with ischemic cardiomyopathy, whereas this difference was not seen in the small number of patients with nonischemic disease. Because patients were not blinded to therapy, these benefits of EECP therapy may be attributable to a placebo effect. However, the usefulness of EECP therapy by physicians must be individualized based on their assessment of the totality of EECP therapy data. Further studies may help elucidate both the mechanism of action and the overall effects of EECP therapy.

Limitations of the Technique

It is important to point out that EECP therapy is not for everyone. This noninvasive outpatient procedure can be somewhat uncomfortable for patients because of the high-pressure sequential compression of the cuffs. It is not recommended for certain types of valvular heart disease

Table 2 Side Effects and Contraindications of Enhanced External Counterpulsation

Side effects

- Leg or waist pain
- Skin abrasion or ecchymoses
- Bruises in patients using Coumadin when INR dosage is not adjusted
- Paresthesias
- Worsening of heart failure in patients with severe arrhythmias

Contraindications

- Coagulopathy with an INR of prothrombin time >2.5
- Arrhythmias that may interfere with triggering of EECP system (uncontrolled atrial fibrillation, flutter, and very frequent premature ventricular contractions)
- Within 2 weeks after cardiac catheterization or arterial puncture (risk of bleeding at femoral puncture site)
- Decompensated heart failure
- Moderate to severe aortic insufficiency (regurgitation would prevent diastolic augmentation)
- Severe peripheral arterial disease (reduced vascular volume and muscle mass may prevent effective counterpulsation, increased risk of thromboembolism)
- Severe hypertension >180/110 mm Hg (the augmented diastolic pressure may exceed safe limits)
- Aortic aneurysm (≥ 5 mm) or dissection (diastolic pressure augmentation may be deleterious)
- Pregnancy or women of childbearing age (effects of EECP therapy on fetus have not been studied)
- Venous disease (phlebitis, varicose veins, stasis ulcers, prior or current deep vein thrombosis or pulmonary embolism)
- Severe chronic obstructive pulmonary disease (no safety data in pulmonary hypertension)

EECP = enhanced external counterpulsation; INR = international normalized ratio.

Table 3 Future Directions and Potential Uses of EECP

Study (Ref. #)	Year/Country	Number of Patients	Treatment Duration (h)	Potential Uses of EECP Therapy in Conditions Other Than RAP and HF	Remarks
Werner et al. (48)	2005/Germany	19	2	Hepatorenal syndrome Safety: EECP therapy was tolerated by healthy and cirrhotic patients alike Efficacy: EECP therapy increased MAP and increased urinary production (urinary flow rate) in patients with end-stage cirrhosis and hepatorenal syndrome	Potential role of EECP therapy in diuresis and increased urinary flow in patients with end-stage liver disease who are awaiting transplant
Rajaram et al. (49)	2005/U.S.	6	35	Restless leg syndrome Relief of symptoms and change in the IRLS score from 28.8 to 6.0 after EECP therapy Benefit sustained for 6 months; IRLS score was 3.3 at the end of 6 months	It was a small, uncontrolled case series
Hilz et al. (50)	2004/Germany	38	1	Peripheral vasodilatation and skin effects similar to those during exercise	Potential role of EECP therapy in improving vascular flow in mild nonulcerative peripheral vascular disease
Nike Sports Research Lab (51)	2004/U.S.	19 vigorously active men in training	35	Improvement in postural instability and ataxia in EECP treatment group as compared with control	EECP therapy had no significant effect on the physiological parameters considered to be the best for predicting performance in endurance-type sportsmen: V_{O_2} , lactate levels, work tolerance time
Froschermaier et al. (52)	1998/Germany	13	35	Increase in the penile artery flow by 200%, and 11 of 13 reported improved erectile function	Case series looking at EECP therapy and erectile dysfunction
Offergeld et al. (53)	1998/Germany	30	5-10	Treatment of sudden deafness and tinnitus (vascular in origin) Tinnitus decreased in 47% of the patients by an average of 16 dB	Hearing threshold increased in 28%, on average by 19 dB Improvement persisted at 1-year follow-up

EECP = enhanced external counterpulsation; HF = heart failure; MAP = mean arterial pressure; RAP = refractory angina pectoris; IRLS = International Restless Leg Severity Scale.

(especially aortic insufficiency), or for those with recent cardiac catheterization, an irregular heart rhythm, severe hypertension, significant blockages in the leg arteries, or a history of deep venous thrombosis (Table 2). For anyone else, however, the procedure seems to be quite safe.

Future Directions and Conclusions

Throughout the world, EECP therapy has been studied for various potential uses other than heart disease (48–53) (Table 3). Its role in improving endothelial function might be beneficial in the treatment of patients with Cardiac Syndrome X, which is marked by severe chest pain caused by myocardial dysfunction, often without detectable atherosclerosis. Mayo Clinic investigators have reported successful treatment of Cardiac Syndrome X with severely symptomatic coronary endothelial dysfunction in the absence of obstructive CAD with standard 35-h course of EECP therapy (54). However, it is important to realize that EECP therapy is an option for patients with angina refractory to medical treatment who are not candidates for interventional or surgical revascularization. The American Heart Association recommends it as a Class IIb (Level of Evidence: B) intervention for treatment of RAP, among other nonpharmacological approaches such as neurostimulation (Class IIb, Level of Evidence: B) and transmyocardial laser revascularization (Class IIa, Level of Evidence: A) (55). The European Society of Cardiology views EECP therapy as an interesting modality available for treatment of RAP with more clinical trials needed to define its role in treating RAP (56). Enhanced external counterpulsation therapy is a valuable outpatient procedure providing acute and long-term relief of anginal symptoms and improved quality of life among a group of patients with symptomatic ischemic heart disease with or without congestive HF.

Reprint requests and correspondence: Dr. Ozlem Soran, University of Pittsburgh Cardiovascular Institute, 200 Lothrop Street, UPMC, Presbyterian Hospital, F-748, Pittsburgh, Pennsylvania 15213. E-mail: soranzo@upmc.edu.

REFERENCES

- American Heart Association. Heart Disease and Stroke Statistics. Dallas, TX: American Heart Association, 2005.
- Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. *J Am Coll Cardiol* 2002;39:923–34.
- Urano H, Ikeda H. Enhanced external counter pulsation 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.
- Cohen J, Grossman W, Michaels AD. Portable enhanced external counterpulsation for acute coronary syndrome and cardiogenic shock: a pilot study. *Clin Cardiol* 2007;30:223–8.
- Lawson WE, Silver MA, Hui JC, Kennard ED, Kelsey SF. Angina patients with diastolic versus systolic heart failure demonstrate comparable immediate and one-year benefit from enhanced external counterpulsation. *J Card Fail* 2005;11:61–6.
- Kantrowitz A, Kantrowitz A. Experimental augmentation of coronary flow by retardation of coronary artery pressure pulse. *Surgery* 1953;34:678–87.
- Birtwell WC, Ruiz U, Soroff HS, DesMarais D, Deterling RA Jr. Technical consideration in the design of a clinical system for external left ventricular assist. *Trans Am Soc Artif Intern Organs* 1968;14:304–10.
- Zheng ZS, Li TM, Kambic H, et al. Sequential external counterpulsation (SECP) in China. *Trans Am Soc Artif Intern Organs* 1983;29:599–603.
- Lawson WE, Hui JC, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? *Cardiology* 1996;87:271–5.
- Lawson WE, Hui JCK, Soroff HS, et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *Am J Cardiol* 1992;70:859–62.
- Lawson WE, Hui JCK, Zheng ZS, et al. Can angiographic findings predict which coronary patients will benefit from enhanced external counterpulsation? *Am J Cardiol* 1996;77:1107–9.
- Lawson WE, Hui JCK, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? *Cardiology* 1996;87:271–5.
- Lawson WE, Hui JCK, Guo T, Burger L, Cohn PF. Prior revascularization increases the effectiveness of enhanced external counterpulsation. *Clin Cardiol* 1998;21:841–4.
- 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.
- 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.
- Tseng H, Peterson TE, Berk BC. Fluid shear stress stimulates mitogen-activated protein kinase in endothelial cells. *Circ Res* 1995;77:869–78.
- Garlichs CD, Zhang H, Werner D, John A, Trägner P, Daniel WG. Reduction of serum endothelin-1 levels by pneumatic external counterpulsation (abstr). *Can J Cardiol* 1998;14 Suppl:87F.
- 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.
- Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. *Circ Res* 1994;74:349–53.
- Tao J, Tu C, Yang Z, Zhang Y, Chung XL. Enhanced external counterpulsation improves endothelium-dependent vasorelaxation in the carotid arteries of hypercholesterolemic pigs. *Int J Cardiol* 2006;112:269–74.
- 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.
- Zhang Y, Chen XL, He XH, et al. Effects of enhanced external counterpulsation in atherosclerosis and NF-kappaB expression: a pig model with hypercholesterolemia. *Zhonghua Bing Li Xue Za Zhi* 2006;35:159–64.
- 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.
- Arora R, Chen HJ, Rabbani L. Effects of enhanced counterpulsation on vascular cell release of coagulation factors. *Heart Lung* 2005;34:252–6.
- Chen XL, He XH, Zhang Y, et al. (Effect of chronic enhanced external counterpulsation on arterial endothelial cells of porcine with hypercholesterolemia). *Di Yi Jun Yi Da Xue Xue Bao* 2005;25:1491–3.
- 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.
- Lawson WE, Hui JCK, 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.
- Lawson WE, Hui JCK, Lang G. Treatment benefit in the enhanced external counterpulsation consortium. *Cardiology* 2000;94:31–5.

29. 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.
30. Stys T, Lawson WE, Hui JCK, Lang G, Liuzzo J, Cohn PF. Acute hemodynamic effects and angina improvement with enhanced external counterpulsation. *Angiology* 2001;52:653-8.
31. Barsness G, Feldman AM, Holmes DR, Holubkov R Jr., Kelsey SF, Kennard ED. The International EECP Patient Registry (IEPR): design, methods, baseline characteristics, and acute results. *Clin Cardiol* 2001;24:435-42.
32. Stys TP, Lawson WE, Hui JCK, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. *Am J Cardiol* 2002;89:822-82.
33. Fitzgerald CP, Lawson WE, Hui JC, Kennard ED, IEPR Investigators. Enhanced external counterpulsation as initial revascularization treatment for angina refractory to medical therapy. *Cardiology* 2003;100:129-35.
34. Tartaglia J, Stenerson J Jr., Charney R, Ramasamy S, Fleishman BL, Gerardi P. Exercise capability and myocardial perfusion in chronic angina patients treated with enhanced external counterpulsation. *Clin Cardiol* 2003;26:287-90.
35. Lawson WE, Hui JC, Kennard ED, Kelsey SF, Michaels AD, Soran O. Two-year outcomes in patients with mild refractory angina treated with enhanced external counterpulsation. *Clin Cardiol* 2006;29:69-73.
36. Lawson WE, Silver MA, Hui JC, Kennard ED, Kelsey SF. Angina patients with diastolic versus systolic heart failure demonstrate comparable immediate and one-year benefit from enhanced external counterpulsation. *J Card Fail* 2005;11:61-6.
37. Novo G, Bagger JP, Carta R, Koutroulis G, Hall R, Nihoyannopoulos P. Enhanced external counterpulsation for treatment of refractory angina pectoris. *J Cardiovasc Med* 2006;7:335-9.
38. Lawson WE, Hui JC, Kennard ED, Kelsey SF, Michaels AD, Soran O, IEPR Investigators. Two-year outcomes in patients with mild refractory angina treated with enhanced external counterpulsation. *Clin Cardiol* 2006;29:69-73.
39. Loh PH, Louis AA, Windram J, et al. The immediate and long-term outcome of enhanced external counterpulsation in treatment of chronic stable refractory angina. *J Intern Med* 2006;259:276-84.
40. Lawson WE, Kennard ED, Hui JC, Holubkov R, Kelsey SF, IEPR Investigators. Analysis of baseline factors associated with reduction in chest pain in patients with angina pectoris treated by enhanced external counterpulsation. *Am J Cardiol* 2003;92:439-43.
41. Arora RR, Chou TM, 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 Investig Med* 2002;50:25-32.
42. Soran OZ, 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.
43. 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.
44. Lawson WE, Kennard ED, Holubkov R, et al., IEPR investigators. Benefit and safety of enhanced external counterpulsation in treating coronary artery disease patients with a history of congestive heart failure. *Cardiology* 2001;96:78-84.
45. Soran OZ. Efficacy and safety of enhanced external counterpulsation in mild to moderate heart failure: a preliminary report (abstr). *J Card Fail* 1999;3 Suppl 1:195.
46. Soran OZ. Enhanced external counterpulsation in patients with heart failure: a multicenter feasibility study. *Congest Heart Fail* 2002;8:204-8.
47. Feldman AM, Silver MA, Francis GS, et al., for the PEECH Investigators. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 2006;48:1198-205.
48. Werner D, Tragner P, Wawer A, Porst H, Daniel WG, Gross P. Enhanced external counterpulsation: a new technique to augment renal function in liver cirrhosis. *Nephrol Dial Transplant* 2005;20:920-6.
49. Rajaram SS, Shanahan J, Ash C, Walters AS, Weisfogel G. Enhanced external counter pulsation (EECP) for restless legs syndrome (RLS): preliminary negative results in a parallel double-blind study. *Sleep Med* 2006;7:390-1.
50. Hilz MJ, Werner D, Marthol H, Flachskampf FA, Daniel WG. Enhanced external counterpulsation improves skin oxygenation and perfusion. *Eur J Clin Invest* 2004;34:385-91.
51. Myhre LG, Muir I, Schutz RW, Rantala B, Thigpen T. Enhanced external counterpulsation for improving athletic performance. Paper presented at: Experimental Biology 2004; April 17-21, 2004; Washington, DC.
52. Froschermaier SE, Werner D, Leike S, Schneider M, Waltenberger J, Daniel WG, Wirth MP. Enhanced external counterpulsation as a new treatment modality for patients with erectile dysfunction. *Urol Int* 1998;61:168-71.
53. Offergeld C, Werner D, Schneider M, Daniel WG, Hüttenbrink KB. Pneumatic external counterpulsation (PECP): a new treatment option in therapy refractory inner ear disorders? *Laryngorhinootologie* 2000;79:503-9.
54. Bonetti PO, Gadasalli SN, Lerman A, Barsness GW. Successful treatment of symptomatic coronary endothelial dysfunction with enhanced external counterpulsation. *Mayo Clin Proc* 2004;79:690-2.
55. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 2003;107:149-58.
56. Fox K, Garcia MAA, Ardissino D, et al. Guidelines on management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006;27:1341-81.