Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 41, No. 11, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00428-5

STATE-OF-THE-ART PAPER

Enhanced External Counterpulsation for Ischemic Heart Disease

What's Behind the Curtain?

Piero O. Bonetti, MD, David R. Holmes, Jr, MD, FACC, Amir Lerman, MD, FACC, Gregory W. Barsness, MD, FACC

Rochester, Minnesota

Enhanced external counterpulsation (EECP) has been shown to reduce angina and to improve objective measures of myocardial ischemia in patients with refractory angina. Prospective clinical studies and large treatment registries suggest that a course of EECP is associated with prolongation of the time to exercise-induced ST-segment depression and resolution of myocardial perfusion defects, as well as with enhanced exercise tolerance and quality of life. With a growing knowledge base supporting the safety and beneficial clinical effects associated with EECP, this therapy can be considered a valuable treatment option, particularly in patients who have exhausted traditional revascularization methods and yet remain symptomatic despite optimal medical care. However, although the concept of external counterpulsation was introduced almost four decades ago, and despite growing evidence supporting the clinical benefit and safety of this therapeutic modality, little is firmly established regarding the mechanisms responsible for the beneficial effects associated with this technique. Suggested mechanisms contributing to the clinical benefit of EECP include improvement in endothelial function, promotion of coronary collateralization, enhancement of ventricular function, peripheral effects similar to those observed with regular physical exercise, and nonspecific placebo effects. This review summarizes the current evidence for a contribution of these mechanisms to the clinical benefit associated with EECP. (J Am Coll Cardiol 2003;41:1918–25) © 2003 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). As more patients survive a primary coronary event, this number will likely continue to grow, as will the cohort of patients who remain symptomatic despite optimal medical therapy. Unfortunately, a considerable segment of this population is not amenable to standard revascularization procedures, such as percutaneous coronary intervention and coronary artery bypass graft surgery, because of unsuitable coronary anatomy, multiple previous revascularization attempts, or additional comorbid conditions. Currently, several alternative therapeutic options are available for patients with refractory angina, including neurostimulation (transcutaneous electrical nerve stimulation and spinal cord stimulation), laser revascularization techniques, and enhanced external counterpulsation (EECP) (2). Of these modalities, EECP represents the only truly noninvasive technique for which both a reduction of anginal symptoms and an improvement in objective measures of myocardial ischemia have been shown.

Several small trials demonstrated a consistently positive clinical response among patients treated with EECP (Table 1). Benefits associated with EECP include reduction of angina (3–9) and nitrate use (5,6,8), increased exercise tolerance (5,7,9–12), favorable psychosocial effects and enhanced quality of life (13,14), as well as prolongation of the time to exercise-induced ST-segment depression (10,12) and an accompanying resolution of myocardial perfusion defects (5–12). The randomized, double-blinded, sham-controlled Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) documented the clinical benefit of EECP in patients with chronic stable angina and positive exercise stress tests (Table 2) (15). Moreover, a MUST-EECP substudy demonstrated a significant improvement in quality of life parameters in patients assigned to active treatment, which was sustained during a 12-month follow-up period (16). Results from the International EECP Patient Registry (IEPR) (17) and the EECP Clinical Consortium (18) have demonstrated 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 five years in patients with a favorable initial clinical response (8,17,19).

Despite the growing body of evidence supporting the clinical benefit of EECP therapy in patients with chronic angina, the mechanisms by which this technique improves

From the Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota. This work was supported by the Mayo Foundation; the Margarete und Walther Lichtenstein Stiftung Basel, Switzerland; the Freiwillige Akademische Gesellschaft Basel, Switzerland; and an unrestricted grant from Vasomedical Inc. Jonathan Abrams, MD, acted as Guest Editor for this manuscript.

Manuscript received August 1, 2002; revised manuscript received February 21, 2003, accepted February 27, 2003.

Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CAD = coronary artery disease
EECP = enhanced external counterpulsation
HGF = hepatocyte growth factor
IEPR = International Enhanced External Counterpulsation Patient Registry
LV = left ventricular
LVEF = left ventricular ejection fraction
MUST-EECP = Multicenter Study of Enhanced External Counterpulsation
NO = nitric oxide
VEGF = vascular endothelial growth factor

symptoms are poorly understood. By reviewing the currently available literature, this article summarizes the mechanisms potentially responsible for the clinical benefit observed with EECP.

Principles and hemodynamic effects of 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 from distal to proximal in early diastole and rapidly deflated at the onset of systole (Fig. 1). Analogous to intraaortic balloon counterpulsation, the rapid inflation raises diastolic pressure (diastolic augmentation) while the rapid cuff deflation promotes lower extremity arterial "runoff" and leads to a decrease in systolic pressure (systolic unloading) in both the aorta and the coronary arteries (20). Unlike intraaortic balloon counterpulsation, EECP also enhances venous return, further promoting an increase in cardiac output (21). These hemodynamic effects lead to increased blood flow in multiple vascular beds, including the coronary arterial circulation (Table 3) (20,22).

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) (Fig. 2). Doppler echocardiographic studies during application of EECP indicate that an effectiveness ratio of 1.5 to 2 is associated with an optimal increase in both systolic antegrade and diastolic retrograde aortic flow (23). 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 (3,24,25).

Table 2. Effect of EECP on Subjective and Objective Parameters of Myocardial Ischemia in the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) (15)

	Active EECP	Sham-EECP	p Value
Change from baseline in angina count per day	−0.033 ± 0.27	0.15 ± 0.27	< 0.05
Change in time to exercise-induced 1-mm ST-segment depression (s)	37 ± 11	−4 ± 12	0.01

EECP = enhanced external counterpulsation.

Effect on endothelial function. The endothelium plays a crucial role in vascular homeostasis (26). Whereas normal endothelial function is characterized by atheroprotective properties, endothelial dysfunction is now considered an early step in atherogenesis (27,28). Endothelial dysfunction is characterized by impaired bioavailability of endothelium-derived nitric oxide (NO), which has vasodilatory, antiplatelet, antithrombotic, antiproliferative, and anti-inflammatory properties. However, endothelial production of the major opponent of NO, endothelin-1, a potent vasoconstrictor that also exerts prothrombotic, mitogenic, and proinflammatory effects, is increased in the setting of endothelial dysfunction (29). This imbalance between vasodilators and vasoconstrictors leads to an impairment of endothelium-dependent vasodilation, which represents the functional characteristic of endothelial dysfunction. Importantly, the presence of coronary endothelial dysfunction is associated

Table 1. Published Controlled and Uncontrolled Trials of Enhanced External Counterpulsation in Patients With Stable Angina

Study (Ref.)	Year	n	Treatment Duration (h)	Angina (% ≥1 CCS Class)*	Nitrate Use	Exercise Tolerance (%)*	Time to ST Depression	Cardiac Perfusion (%)*
Zheng et al. (4)	1983	200	12	↓ (97)	N/A	N/A	N/A	N/A
Lawson et al. (5)	1992	18	36	↓ (100)	↓	↑ (67)	N/A	↑ (78)
Lawson et al. (11)	1996	27	35	N/A	N/A	↑ (81)	N/A	↑ (78)
Lawson et al. (6)	1996	50	35	↓ (100)	↓	N/A	N/A	↑ (80)
Lawson et al. (7)	1998	60	35	↓	N/A	↑	N/A	↑ (75)
Arora et al. (15)	1999	139	35	↓	↓	↑	↑	N/A
Lawson et al. (8)	2000	33	35–36	↓ (100)	↓	N/A	N/A	↑ (79)
Lawson et al. (18)	2000	2,289	35	↓ (74)	N/A	N/A	N/A	N/A
Urano et al. (12)	2001	12	35	N/A	N/A	↑	↑	↑
Masuda et al. (10)	2001	11	35	N/A	N/A	↑	↑	↑
Stys et al. (3)	2001	395	35	↓ (88)	N/A	N/A	N/A	N/A
Barsness et al. (17)	2001	978	35	↓ (81)	↓	N/A	N/A	N/A
Stys et al. (9)	2002	175	35	↓ (85)	N/A	↑	N/A	↑ (83)

*When reported in the original article, the percentage of patients for whom the criterion applies are listed in parentheses.
CCS = Canadian Cardiovascular Society; N/A = not assessed.

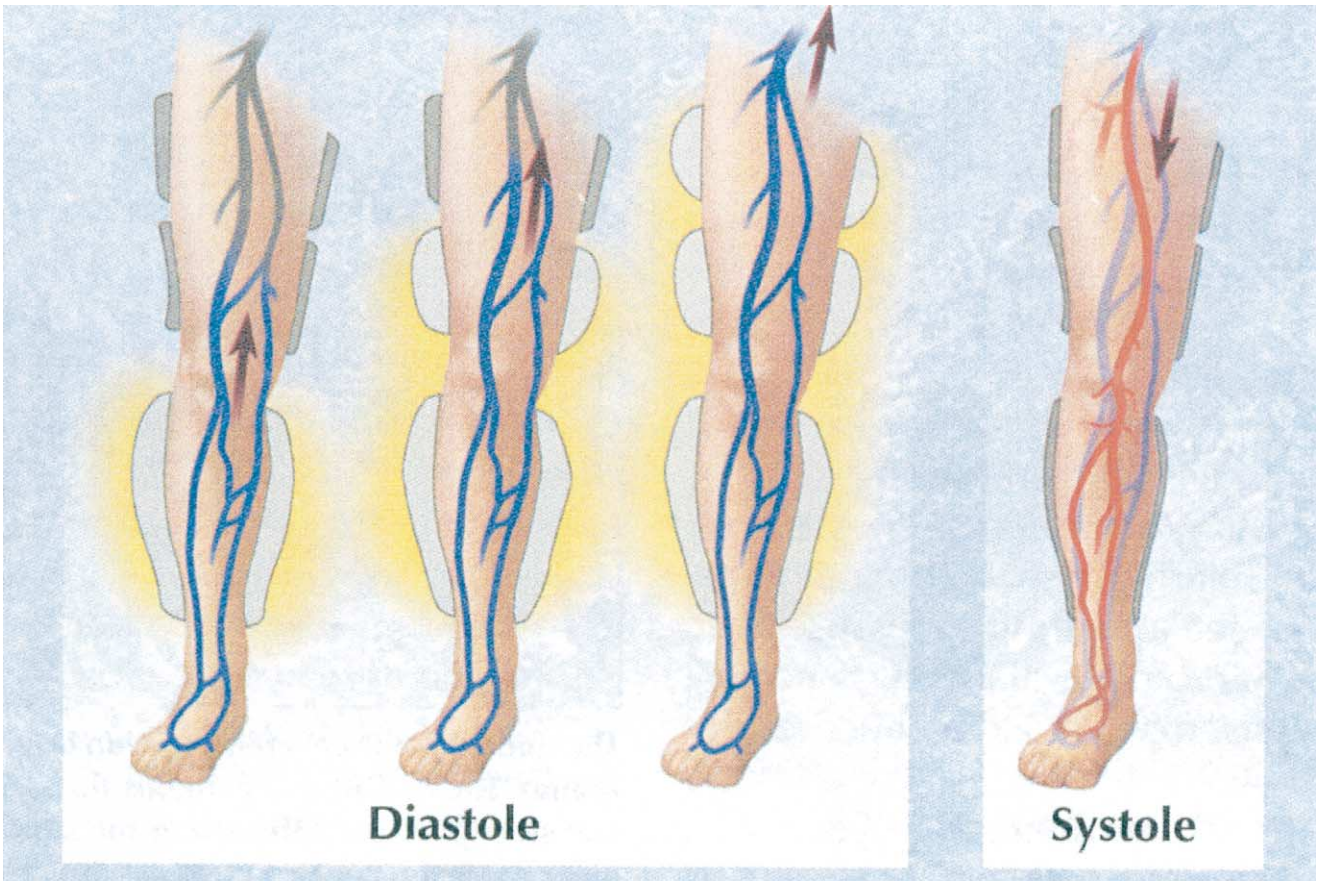

Figure 1. Principle of enhanced external counterpulsation. Three pairs of pneumatic cuffs are wrapped around the calves, lower thighs, and upper thighs. During early diastole, these cuffs are inflated sequentially from distal to proximal, resulting in a "milking effect" of blood from the lower extremities. At the onset of systole, all cuffs are deflated, resulting in acute afterload reduction. Modified from the October 2001 *Mayo Clinic Health Letter*. Copyright Mayo Foundation for Medical Education and Research. All rights reserved. Used with permission.

with myocardial ischemia and an adverse prognosis irrespective of the presence of obstructive coronary lesions (28).

Growing evidence suggests that improvement in endothelial function represents an important mechanism for the clinical benefit observed with EECP. Central to this concept is the increase in organ blood flow observed during treatment (20,22). In the absence of significant vascular obstruction, EECP-induced increases in blood flow translate into enhanced endothelial shear stress (30,31). Increased shear stress represents a major stimulus for endothelial NO release

Table 3. Effect of Enhanced External Counterpulsation on Blood Flow in Different Vascular Beds

Study (Ref.)	Cuff Location	Applied Pressure	Vessel	Method	Flow Change
Werner et al. (22)	Calves, lower thighs	200 mm Hg	Carotid artery	Duplex	+19%
	Calves, lower thighs	200 mm Hg	Vertebral artery	Duplex	+12%
	Calves, lower thighs	200 mm Hg	Hepatic artery	Duplex	+25%
	Calves, lower thighs	200 mm Hg	Renal artery	Duplex	+21%
	Calves, lower thighs	200 mm Hg	Abdominal aorta	Duplex	+88%
	Calves, lower thighs	200 mm Hg	Internal iliac artery	Duplex	+144%
	Calves, lower thighs	200 mm Hg	Left coronary main stem	Transesophageal Doppler echocardiography	+18%
	Calves, lower + upper thighs	300 mm Hg	Carotid artery	Duplex	+26%
	Calves, lower + upper thighs	300 mm Hg	Left coronary main stem	Transesophageal Doppler echocardiography	+42%
Michaels et al. (20)	Calves, lower + upper thighs	100–300 mm Hg	Left or right coronary artery	Intracoronary Doppler	+109%
	Calves, lower + upper thighs	100–300 mm Hg	Left or right coronary artery	Corrected TIMI frame count	+28%

TIMI = Thrombolysis In Myocardial Infarction.

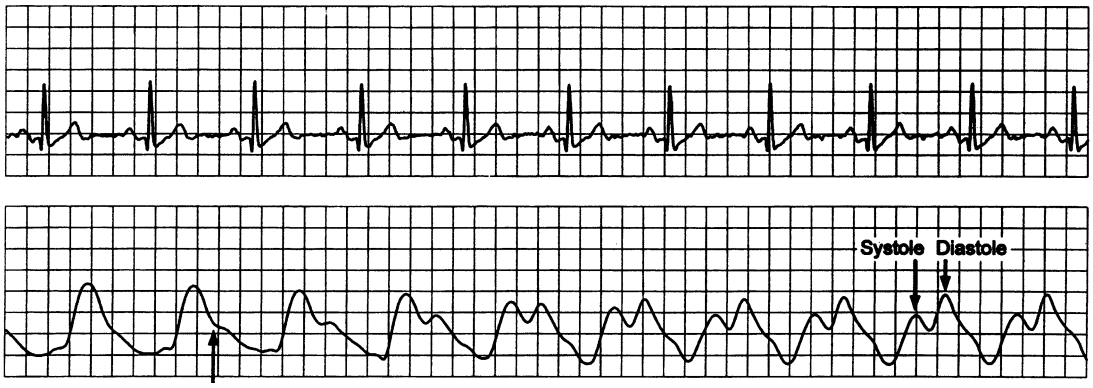

Figure 2. Electrocardiogram **(upper panel)** and finger plethysmographic recording **(lower panel)** after initiation of enhanced external counterpulsation (EECP). Enhanced external counterpulsation leads to an increase in diastolic pressure (diastolic augmentation) and a decrease in systolic pressure (systolic unloading). The magnitude of EECP-induced hemodynamic changes is commonly assessed by measuring the diastolic-to-systolic effectiveness ratio, which is calculated by dividing the peak diastolic amplitude by the peak systolic amplitude of the finger plethysmographic signal.

and vasodilation (32–34). Shear stress also modulates endothelial endothelin-1 release, as sustained exposure of the endothelium to low levels of shear stress stimulates endothelin-1 release, whereas longer exposure to higher shear stress levels is associated with a reduction of endothelial endothelin-1 release (34,35). Therefore, an appropriate level of shear stress is considered a key factor for the maintenance of a functional endothelium (36,37).

Given this important role of shear stress for endothelial homeostasis, it seems plausible that EECP, by enhancing vascular shear stress, may favorably affect endothelial function. Supporting this presumption, a significant increase in plasma NO levels was found one month following completion of a course of EECP in patients with CAD (38). In another study, EECP was associated with a significant and dose-related increase in plasma NO levels in patients with CAD whose baseline NO levels were significantly lower than those of healthy controls. Most strikingly, by the end of treatment, average NO levels in treated patients had risen to levels comparable to those measured in the control group (21). Similarly, it was demonstrated that a course of EECP was associated with a significant increase in plasma NO levels and a significant decrease in plasma endothelin-1 levels in patients with CAD. These changes of plasma NO and endothelin-1 levels were in proportion to treatment duration, and these changes from baseline persisted one month after completion of EECP (21).

Enhanced external counterpulsation may also affect oxidative stress, which is associated with various cardiovascular risk factors and is considered a key factor in the development of endothelial dysfunction and atherosclerosis (39). In patients with CAD, EECP was shown to be associated with a linear decrease in plasma markers of oxidative stress in proportion to the number of hours of treatment (21). Although the exact mechanism for the reduction of oxidative stress observed in this study is not clear, it has been shown that reactive oxygen species and NO interact chemically to neutralize each other. It can therefore be speculated that improved endothelial function and increased NO bioavailability with EECP may reduce oxidative stress. Preliminary data also indicate that EECP may decrease plasma angiotensin II levels in patients with CAD (40). Thus, given the promoting effect of angiotensin II on vascular superoxide production (41), EECP-induced lowering of angiotensin II levels might also contribute to a decrease in oxidative stress.

Indirect evidence for the existence of a beneficial effect of EECP on endothelial function stems from the observation that the level of diastolic augmentation, or the effectiveness ratio, tends to increase over the course of treatment (3,25). The magnitude of the effectiveness ratio achieved during EECP depends not only on device-related factors, such as cuff inflation pressure and timing of inflation/deflation sequence, but also on individual patient-dependent parameters, including arterial stiffness. An increase in arterial stiffness leads to systolic pressure elevation and, therefore, decreases the effectiveness ratio. Arterial stiffness is influenced by the functional status of the arterial wall including the bioavailability of endothelium-derived NO. Indeed, endothelial dysfunction is associated with increased arterial stiffness (42). Thus, it can be speculated that an improvement in the effectiveness ratio during EECP mirrors improvement in endothelial function. In line with this hypothesis, recent data of 2,486 patients from the IEPR indicate that patients whose effectiveness ratio improves over the course of treatment also tend to experience the greatest reduction in angina class up to six months after treatment (25), supporting the notion that improvement in endothelial function may, indeed, contribute to the clinical benefit observed with EECP.

Taken together, these indirect findings suggest a desirable effect of EECP on endothelial function. However, further studies to address the effect of EECP on well-established parameters of endothelial function, such as endothelium-dependent vasodilation, are required to more specifically define the impact of EECP on endothelial function.

Effect on coronary collateral supply. Enhancement of collateral perfusion involves opening or expansion of pre-

formed collaterals as well as formation of new collateral vessels. Aside from ischemia, an increase in endothelial shear stress is considered a major stimulus for collateral development and recruitment (43), underlying the hypothesis that EECP may exert its beneficial effects at least in part by enhancement of coronary collateralization through development of these shear forces.

The simplest mechanism by which EECP might increase collateral perfusion is by opening preformed collateral channels, either directly via increasing diastolic blood pressure and flow or indirectly via release of vasodilatory mediators such as NO, as discussed earlier. Canine studies have shown an acute, significant increase in the patency of hind limb collateral and anastomotic branches in response to 1 h of external counterpulsation (44) and acute enhancement of capillary density in experimental myocardial infarction treated with external counterpulsation (21). The translation of these findings to the situation in humans, however, is limited by the fact that collaterals develop much faster in dogs than in humans.

Similarly, the shear forces induced by EECP may influence arteriogenesis and angiogenesis. Arteriogenesis, the formation of larger collateral arteries via the addition of endothelial cells, smooth muscle cells, fibroblasts, and connective tissue to preexisting collateral arterioles, represents another mechanism involved in the enhancement of coronary collaterals (45). The primary initiating stimulus for this vascular remodeling process is felt to be an increase in shear stress (44), making arteriogenesis an attractive mechanism by which EECP might improve myocardial perfusion. Angiogenesis, the de novo formation of capillary blood vessels via sprouting of endothelial cells from existing blood vessels, may also be promoted by EECP. Angiogenesis is a complex process that depends on a well-coordinated interplay of a myriad of vascular-specific and -nonspecific factors (46). Notably, vascular shear stress may upregulate endothelial production of growth factors (such as vascular endothelial growth factor [VEGF] and platelet-derived growth factor) that are crucial for the proper sequence of angiogenesis (47,48). In this way, shear stress may also be an important player in the angiogenic process.

Indirect evidence for the existence of a pro-arteriogenic and pro-angiogenic effect of EECP stems from studies showing an increase in various vascular growth factors in response to treatment. A significant increase in plasma VEGF levels was reported in five patients with refractory angina who experienced a 50% reduction in anginal episodes after a course of EECP, whereas no change in plasma VEGF concentration was found in four patients whose symptoms did not respond to EECP (21). Furthermore, in 11 patients with stable angina, an increase in plasma levels of basic fibroblast growth factor, VEGF, and hepatocyte growth factor (HGF) was demonstrated after a course of EECP (49). Interestingly, HGF is a very potent angiogenic factor that shows a greater angiogenic potential than VEGF (50).

A link between vasodilation and angiogenesis is suggested by the observation that in vivo angiogenesis is accompanied by vasodilation and that several angiogenic factors have vasodilating properties (51). For example, VEGF was shown to enhance endothelial nitric oxide synthase expression and activity (52–54), stimulating NO-dependent vasodilation (55). On the other hand, endothelial NO production is crucial for the stimulatory effect of VEGF on the growth of endothelial cells and their organization in network-like structures (53). The strongest evidence for a pivotal role of NO in the angiogenic process stems from a study investigating the angiogenic response in a murine model of hindlimb ischemia (56). In this study, angiogenesis in the ischemic hindlimb was significantly impaired in mice with targeted disruption of the gene encoding endothelial nitric oxide synthase as compared with wild-type controls. These results indicate that NO represents a crucial cofactor for angiogenesis. Thus, it can be speculated that disease states associated with a decrease in NO bioavailability, such as endothelial dysfunction, may limit angiogenesis, whereas interventions that improve endothelial function may promote angiogenesis.

Vasculogenesis, the in situ formation of blood vessels involving bone marrow-derived endothelial progenitor cells, was recently described as an additional mechanism that may contribute to collateral development (57). Aside from certain cytokines or tissue ischemia (58), VEGF may promote endothelial progenitor cell mobilization and differentiation in vivo (59,60). Given the increase in plasma VEGF levels observed in some EECP-treated patients, it can be hypothesized that vasculogenesis might also be a mechanism by which EECP promotes collateral development in certain patients with CAD.

In summary, these findings suggest a potential for EECP to enhance coronary collateralization. Moreover, it appears that the presumed effect of EECP on endothelial function might further increase the pro-angiogenic potential of this technique. However, an increase in plasma levels of various angiogenic growth factors does not necessarily translate into enhanced coronary collateralization, and there is still little direct evidence for a stimulating effect of EECP on cardiac collateral formation. Thus, further studies are necessary to define the exact role of neovascularization for the beneficial effect of EECP.

Peripheral effect. The question whether EECP is associated with a nonspecific peripheral "training effect" was studied in 27 patients with chronic stable angina who underwent a maximal stress test before and after a course of EECP (11). After treatment a significant increase in exercise duration was noted in these patients, while peak double product remained unchanged, which was due mainly to a distinct, although not statistically significant, reduction in maximal blood pressure. Similar findings were reported in 175 patients with chronic stable angina who underwent a baseline exercise stress test before EECP treatment and either a maximal exercise stress test or an exercise stress test

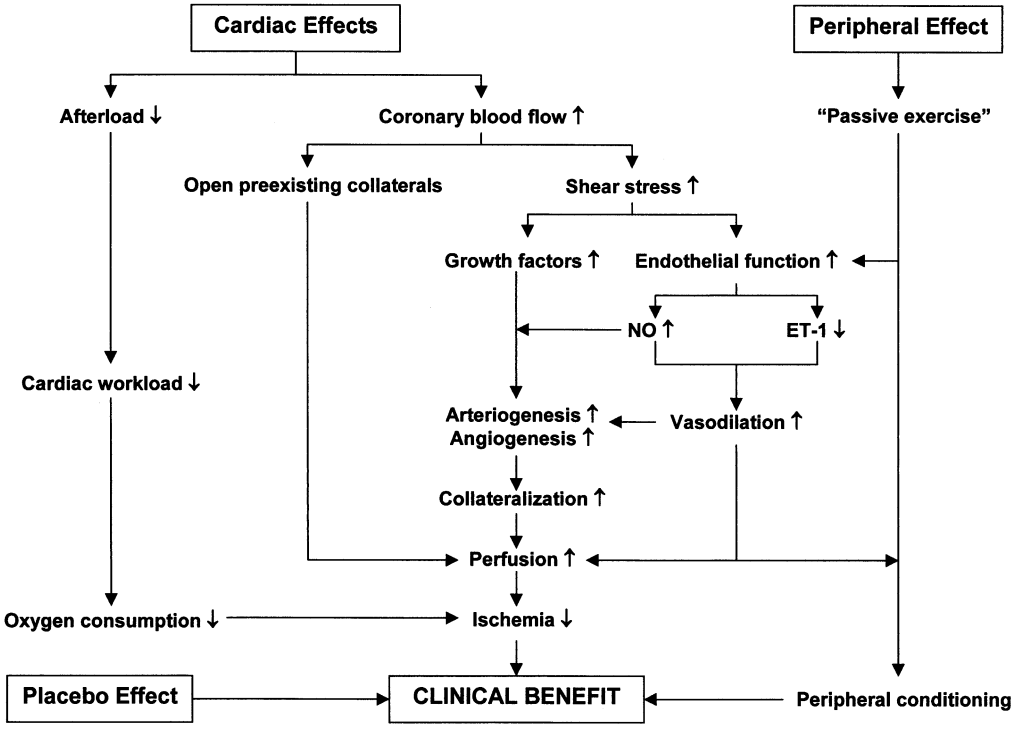

Figure 3. Possible mechanisms responsible for the clinical benefit associated with enhanced external counterpulsation (EECP). Acute afterload reduction decreases myocardial demand. By increasing coronary blood flow, EECP is thought to promote myocardial collateralization via opening of preformed collaterals, arteriogenesis, and angiogenesis. Increased blood flow and shear stress may also improve coronary endothelial function favoring vasodilation and myocardial perfusion. In addition, improvement in endothelial function may further promote collateral formation by arteriogenesis and angiogenesis. Besides a peripheral training effect, a minor placebo effect is considered to contribute to the symptomatic benefit of EECP. ET = endothelin; NO = nitric oxide.

to the same level as before treatment within six months after completion of EECP therapy (9). In this study, patients who underwent maximal post-EECP exercise stress testing showed a significant improvement in exercise duration with no change in peak double product, whereas the same exercise level as before EECP was achieved with a significantly lower double product, supporting the notion that EECP, similar to physical training, may promote a decrease in peripheral vascular resistance.

Using positron emission tomography, it was found that a course of EECP improved myocardial perfusion, both at rest and in response to dipyridamole, in 11 patients with CAD (38). However, maximal exercise stress tests before and after EECP showed a similar peak double product, despite a significant increase in time to 1-mm ST-segment depression and a trend towards longer total exercise time, suggesting that the increase in exercise tolerance found in these patients was partly due to a peripheral effect of EECP.

These data suggest the importance of both an improvement in myocardial perfusion and a decrease in peripheral resistance in achieving the clinical benefit associated with EECP. Peripheral effects might be particularly important for the symptomatic improvement observed in patients without evidence for enhanced myocardial perfusion after EECP.

Effect on ventricular function. By reducing afterload and promoting venous return, EECP acutely enhances cardiac output up to 25% (61,62). However, the venous return augmentation by EECP has also raised concerns about the possibility of inducing pulmonary edema in patients with impaired left ventricular (LV) function and heart failure. To date, little is known about the effect of EECP in patients with impaired LV function or heart failure, although this procedure was recently granted FDA approval for the treatment of patients with angina and accompanying heart failure. Evidence supporting a beneficial effect of EECP on ventricular function includes an uncontrolled study demonstrating a significant reduction of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) plasma levels in response to a course of EECP in 11 patients with stable angina (10). A similar reduction in plasma levels of BNP but not ANP was found in 12 patients with refractory stable angina and normal LV ejection fraction (LVEF) after 35 h of EECP (12). Treatment did not alter systolic LV function but significantly improved parameters of diastolic ventricular function, indicating a role for EECP in the treatment of patients with predominant or isolated diastolic ventricular dysfunction. The effect of EECP on LV systolic function was investigated in eight patients with severely impaired LVEF (mean 25%) (63). After EECP therapy, these patients showed a significant increase in LVEF (to 29%), which was accompanied by a significant decrease in resting heart rate.

The presence of LV dysfunction does not appear to

substantially impair clinical response to EECP in patients with angina. In a pilot study assessing the effect and safety of EECP in heart failure (64), 26 patients with either idiopathic or ischemic heart failure (New York Heart Association class II to III) and an average LVEF of 23% experienced significantly improved exercise tolerance and quality of life after a course of EECP, with no serious adverse events. A retrospective IEPR analysis demonstrated that 129 patients with a LVEF <35% before treatment achieved similar reductions in angina compared with patients with preserved LV function (65).

In summary, current evidence suggests a positive effect of EECP on both diastolic and systolic ventricular function. Moreover, preliminary data indicate that EECP represents an effective and safe treatment for stable patients with impaired ventricular function. However, we still have to await the results of larger ongoing trials investigating the efficacy and safety of EECP in patients with heart failure before this treatment can be definitively recommended for treatment of this patient population.

Nonspecific placebo effects. The prolonged duration of EECP treatment (seven weeks), and the fact that this therapy is limited to specific centers where close medical attention is provided, opens the possibility that nonspecific factors may have a significant effect in reducing the symptoms of treated patients. Such factors include increased patient compliance with drug treatment regimens and close adherence to treatment guidelines among treating physicians and interested practitioners. In addition, several lines of evidence indicate that the use of medical devices may be associated with an enhanced placebo effect (66).

The fact that many patients experience significant symptomatic improvement, even in the absence of optimal diastolic augmentation during treatment, indicates that a placebo effect may indeed contribute to the symptomatic benefit observed with EECP (3,23). Data from the randomized, sham-controlled MUST-EECP trial, however, suggest that nonspecific factors, although possibly contributing to the observed effects, are not the only determinants of the clinical benefit observed with EECP (Table 2) (15).

Conclusions. Enhanced external counterpulsation is a valuable outpatient procedure, providing acute and long-term relief of anginal symptoms and improved quality of life among a heterogeneous group of patients with symptomatic ischemic heart disease. Recent evidence suggests that EECP may improve symptoms via various mechanisms, including improvement in endothelial function, promotion of collateralization, enhancement of ventricular function, and peripheral effects similar to those observed in response to regular physical exercise. In addition, nonspecific placebo effects might contribute to the observed symptomatic benefit (Fig. 3). However, most of this evidence is based on the results of small, uncontrolled trials or on preliminary reports. Therefore, controlled trials, including sham-EECP control groups, are needed to further define the role of the presumed mechanisms of action of EECP. Also, more has to be learned about which patients benefit the most from EECP treatment. Finally, the results of ongoing trials in patients with impaired LV function will help define the role of EECP as a therapeutic tool in this rapidly growing patient population. At present, with a symptomatic benefit documented in thousands of patients along with a favorable safety profile, EECP can be considered a valuable treatment option in patients with refractory angina.

Reprint requests and correspondence: Dr. Gregory W. Barsness, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: barsness.gregory@mayo.edu.

REFERENCES

1. American Heart Association. 2002 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association, 2001.
2. Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. J Am Coll Cardiol 2002;39:923–34.
3. 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.
4. Zheng ZS, Li TM, Kambic H, et al. Sequential external counterpulsation (SECP) in China. Trans Am Soc Artif Intern Organs 1983; 29:599–603.
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.
6. 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.
7. 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.
8. 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.
9. 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;89:822–4.
10. 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.
11. Lawson WE, Hui JCK, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology 1996;87:271–5.
12. 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.
13. Fricchione GL, Jaghab K, Lawson W, et al. Psychosocial effects of enhanced external counterpulsation in the angina patient. Psychosomatics 1995;36:494–7.
14. Springer S, Fife A, Lawson W, et al. Psychosocial effects of enhanced external counterpulsation in the angina patient: a second study. Psychosomatics 2001;42:124–32.
15. 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.
16. 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.
17. Barsness G, Feldman AM, Holmes DR Jr., Holubkov R, Kelsey SF, Kennard ED, and the International EECP Patient Registry Investigators. The International EECP Patient Registry (IEPR): design,

methods, baseline characteristics, and acute results. Clin Cardiol 2001;24:435–42.
18. Lawson WE, Hui JCK, Lang G. Treatment benefit in the enhanced external counterpulsation consortium. Cardiology 2000;94:31–5.
19. Lawson WE, Hui JCK, Zheng ZS, et al. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am J Cardiol 1995;75:840–1.
20. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. Circulation 2002;106:1237–42.
21. Barsness GW. Enhanced external counterpulsation in unrevascularizable patients. Curr Interv Cardiol Rep 2001;3:37–43.
22. Werner D, Schneider M, Weise M, Nonnast-Daniel B, Daniel WG. Pneumatic external counterpulsation: a new noninvasive method to improve organ perfusion. Am J Cardiol 1999;84:950–2.
23. Suresh K, Simandl S, Lawson WE, et al. Maximizing the hemodynamic benefit of enhanced external counterpulsation. Clin Cardiol 1998;21:649–53.
24. Michaels AD, Kennard ED, Kelsey SF, et al. Does higher diastolic augmentation predict clinical benefit from enhanced external counterpulsation? Data from the International EECP Patient Registry (IEPR). Clin Cardiol 2001;24:453–8.
25. Lakshmi MV, Kennard ED, Kelsey SF, Holubkov R, Michaels AD. Relation of the pattern of diastolic augmentation during a course of enhanced external counterpulsation (EECP) to clinical benefit (from the International EECP Patient Registry [IEPR]). Am J Cardiol 2002;89:1303–5.
26. Celermajer DS. Endothelial dysfunction: does it matter? Is it reversible? J Am Coll Cardiol 1997;30:325–33.
27. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801–9.
28. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003; 23:168–75.
29. Lerman A, Burnett JC Jr. Intact and altered endothelium in regulation of vasomotion. Circulation 1992;86 Suppl III:12–9.
30. Kern MJ, Aguirre FV, Tatineni S, et al. Enhanced coronary blood flow velocity during intraaortic balloon counterpulsation in critically ill patients. J Am Coll Cardiol 1993;21:359–68.
31. Kern MJ, Aguirre F, Bach R, Donohue T, Siegel R, Segal J. Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. Circulation 1993;87:500–11.
32. Corson MA, James NL, Latta SE, Nerem RM, Berk BC, Harrison DG. Phosphorylation of endothelial nitric oxide synthase in response to fluid shear stress. Circ Res 1996;79:984–91.
33. Dimmeler S, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. Nature 1999;399:601–5.
34. Davies PF. Flow-mediated endothelial mechanotransduction. Physiol Rev 1995;75:519–60.
35. Kuchan MJ, Frangos JA. Shear stress regulates endothelin-1 release via protein kinase C and cGMP in cultured endothelial cells. Am J Physiol 1993;264:H150–6.
36. Niebauer J, Cooke JP. Cardiovascular effects of exercise: role of endothelial shear stress. J Am Coll Cardiol 1996;28:1652–60.
37. Traub O, Berk BC. Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force. Arterioscler Thromb Vasc Biol 1998;18:677–85.
38. 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.
39. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840–4.
40. Lawson WE, Hui JCK, Lu L, Zheng ZS, Zhang MQ. Beneficial effects of EECP on the renin-angiotension system in patients with coronary artery disease (abstr). Eur Heart J 2001;22 Suppl:538.
41. Mollnau H, Wendt M, Szöcs K, et al. Effects of angiotensin II infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/cGMP signaling. Circ Res 2002;90:e58–65.
42. Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolino AP, Cockcroft JR. Nitric oxide regulates local arterial distensibility in vivo. Circulation 2002;105:213–7.
43. Kersten JR, Pagel PS, Chilian WM, Warltier DC. Multifactorial basis for coronary collateralization: a complex adaptive response to ischemia. Cardiovasc Res 1999;43:44–57.
44. Cai D, Wu R, Shao Y. Experimental study of the effect of external counterpulsation on blood circulation in the lower extremities. Clin Invest Med 2000;23:239–47.
45. Van Royen N, Piek JJ, Buschmann I, et al. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. Cardiovasc Res 2001;49:543–53.
46. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. Nature 2000;407:242–8.
47. Gan L, Miocic M, Doroudi R, Selin-Sjögren L, Jern S. Distinct regulation of vascular endothelial growth factor in intact human conduit vessels exposed to laminar fluid shear stress and pressure. Biochem Biophys Res Commun 2000;272:490–6.
48. Resnick N, Collins T, Atkinson W, Bonthron DT Dewey CF Jr., Gimbrone MA. Platelet-derived growth factor B chain promoter contains a cis-acting shear-stress-responsive element. Proc Natl Acad Sci USA 1993;90:4591–5.
49. Masuda D, Nohara K, Kataoka K, Hosokawa R, Kanbara N, Fujita M. Enhanced external counterpulsation promotes angiogenesis factors in patients with chronic stable angina (abstr). Circulation 2001;104: II445.
50. Van Belle E, Witzenbichler B, Chen D, et al. Potentiated angiogenic effect of scatter factor/hepatocyte growth factor via induction of vascular endothelial growth factor. Circulation 1998;97:381–90.
51. Ziche M, Morbidelli L. Nitric oxide and angiogenesis. J Neurooncol 2000;50:139–48.
52. Hood JD, Meininger CJ, Ziche M, Granger HJ. VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. Am J Physiol 1998;274:H1054–8.
53. Papapetropoulos A, García-Cardeña G, Madri JA, Sessa WC. Nitric oxide production contributes to the angiogenic properties of vascular endothelial growth factor in human endothelial cells. J Clin Invest 1997;100:3131–9.
54. Fulton D, Gratton JP, McCabe TJ, et al. Regulation of endothelium-derived nitric oxide production by the protein kinase. Akt Nature 1999;399:597–601.
55. Ku DD, Zaleski JK, Liu S, Brock TA. Vascular endothelial growth factor induces EDRF-dependent relaxation in coronary arteries. Am J Physiol 1993;265:H586–92.
56. Murohara T, Asahara T, Silver M, et al. Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. J Clin Invest 1998;101:2567–78.
57. Freedman SB, Isner JM. Therapeutic angiogenesis for coronary artery disease. Ann Intern Med 2002;136:54–71.
58. Takahashi T, Kalka C, Masuda H, et al. Ischemia- and cytokine-induced mobilization of bonemarrow-derived endothelial progenitor cells for neovascularization. Nat Med 1999;5:434–8.
59. Asahara T, Takahashi T, Masuda H, et al. VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. EMBO J 1999;18:3964–72.
60. Kalka C, Masuda H, Takahashi T, et al. Vascular endothelial growth $factor_{165}$ gene transfer augments circulating endothelial progenitor cells in human subjects. Circ Res 2000;86:1198–202.
61. Cohen LS, Mullins CB, Mitchell JH, Alsobrook HD. Sequenced external counterpulsation and intraaortic balloon pumping in cardiogenic shock. Am J Cardiol 1973;32:656–61.
62. Singh M Holmes DR Jr., Tajik AJ, Barsness GW. Noninvasive revascularization by enhanced external counterpulsation: a case study and literature review. Mayo Clin Proc 2000;75:961–5.
63. Gorcsan J III, Crawford L, Soran O, et al. Improvement in left ventricular performance by enhanced external counterpulsation in patients with heart failure. J Am Coll Cardiol 2000;35 Suppl:230A.
64. Soran OZ, Fleishman B, DeMarco T, et al. Enhanced external counterpulsation in patients with heart failure: a multicenter feasibility study. Congest Heart Fail 2002;8:204–8.
65. Soran O, Kennard ED, Holubkov R, Strobeck J, Feldman AM. Six month outcome of patients with left ventricular dysfunction treated with enhanced external counterpulsation for chronic angina. Eur Heart J 2000;21 Suppl:598.
66. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? J Clin Epidemiol 2000;53:786–92.