Clin. Cardiol. 24, 453–458 (2001)

Does Higher Diastolic Augmentation Predict Clinical Benefit from Enhanced External Counterpulsation?: Data from the International EECP Patient Registry (IEPR)

ANDREW D. MICHAELS, M.D., ELIZABETH D. KENNARD, PH.D.,* SHERYL F. KELSEY, PH.D.,* RICHARD HOLUBKOV, PH.D.,* OZLEM SORAN, M.D.,* SUE SPENCE, R.N., TONY M. CHOU, M.D., FACC

Division of Cardiology, Department of Medicine, University of California at San Francisco Medical Center, San Francisco, California; *Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Summary

Background: Enhanced external counterpulsation (EECP) has been demonstrated to be an effective treatment for stable angina in patients with coronary disease. The hemodynamic effects of EECP are maximized when the ratio of diastolic to systolic pressure area is in the range of 1.5 to 2.0.

Hypothesis: It is hypothesized that patients undergoing EECP who are able to achieve higher diastolic augmentation (DA) ratios may derive greater clinical benefit. This study examines the relationship between the DA ratio and clinical outcomes in patients undergoing EECP.

Methods: We analyzed demographic, noninvasive hemodynamic, and clinical outcome data on 1,004 patients enrolled in the International EECP Patient Registry (IEPR) for treatment of chronic angina between January 1998 and August 1999. Blood pressure waveforms were recorded from finger plethysmography. Six-month clinical outcomes were obtained by telephone interview.

Results: At the end of EECP treatment, 370 (37%) patients had a higher DA ratio (defined as ≥ 1.5) and 634 (63%) had a lower DA ratio (defined as < 1.5). Factors associated with a lower DA ratio included age ≥ 65 years ($p < 0.001$), female gender ($p < 0.001$), left ventricular ejection fraction $< 35\%$ ($p < 0.05$), hypertension ($p < 0.01$), prior coronary bypass surgery ($p < 0.01$), noncardiac vascular disease ($p < 0.001$), multivessel disease ($p < 0.01$), congestive heart failure ($p < 0.01$), current smoking ($p < 0.01$), unsuitability for further revascularization ($p < 0.001$), and higher baseline angina class ($p < 0.001$). There were no significant differences regarding diabetes mellitus, prior coronary angioplasty, prior myocardial infarction, or antianginal medication use between patients with higher or lower DA ratios. Based on a multiple logistic regression model, independent predictors of a DA ratio < 1.5 at the end of EECP included current smoking (odds ratio 3.3; 95% confidence intervals 2.0–5.4); multivessel disease (1.7; 1.3–2.3); female gender (2.2; 1.7–3.0); no prior EECP (1.9; 1.1–3.3); noncardiac vascular disease (2.3; 1.7–2.9); age ≥ 65 years (1.7; 1.4–2.2), and patients not suitable for revascularization (1.6; 1.2–2.0). By the end of therapy, there were no significant differences in myocardial infarction, revascularization rates, or nitroglycerin use with respect to higher DA ratios. At 6-month follow-up, patients with higher DA had a trend toward a greater reduction in angina class compared with those with lower DA ($p = 0.069$). There was a significantly higher rate of unstable angina and congestive heart failure in the group not achieving higher augmentation ($p < 0.05$).

Conclusions: Patients who are younger, male, nonsmoking, and without multivessel coronary or noncardiac vascular disease are most likely to have higher DA with EECP. Patients with higher DA tended to have a greater reduction in angina class at 6-month follow-up compared with those with lower DA ratios. There is evidence that higher DA ratios are associated with improved short- or long-term clinical outcomes, suggesting that clinical benefit from EECP is associated with the magnitude of DA.

Key words: external counterpulsation, diastolic augmentation, noninvasive hemodynamics, coronary artery disease, angina, clinical outcomes

Andrew D. Michaels is supported by the 1999–2000 American Heart Association Postdoctoral Cardiology Fellowship. The IEPR is sponsored by Vasomedical, Inc., Westbury, N.Y.

Address for reprints:

Andrew D. Michaels, M.D.
Division of Cardiology
University of California at San Francisco Medical Center
505 Parnassus Avenue, Box 0124
San Francisco, CA 94143-0124, USA

Received: May 12, 2000
Accepted with revision: October 24, 2000

Introduction

Enhanced external counterpulsation (EECP) is a noninvasive counterpulsation technique that reduces angina and extends time to exercise-induced ischemia in patients with symptomatic coronary disease.[1] In addition to relieving myocardial ischemia, EECP is associated with improved quality of life.[2] It uses sequential inflation of three sets of pneumatic cuffs wrapped around the lower extremities. The cuffs are inflated sequentially at the onset of diastole, producing aortic counterpulsation and diastolic augmentation (DA) and increased venous return. At the onset of systole, the external pressure in the cuffs is released, producing a decrease in systolic pressure (systolic unloading [SU]). These hemodynamic effects may be monitored noninvasively by assessing the finger plethysmographic waveforms.

It has been hypothesized that the sustained benefits of EECP result from effective DA which promotes coronary collateral formation or recruitment.[3,4] Using Doppler echocardiography, a ratio of DA to SU of 1.5–2.0 has been shown to result in improved hemodynamic effects.[3] However, it remains to be demonstrated that higher DA improves the clinical benefit resulting from the application of EECP.

This analysis was undertaken (1) to assess the clinical variables that are associated with higher DA in patients undergoing EECP, and (2) to determine whether patients with higher DA ratios derive greater symptomatic benefit, have fewer adverse cardiac events, and have improved quality of life compared with patients with lower DA ratios.

Methods

The International EECP Patient Registry (IEPR) enrolls consecutive patients undergoing EECP for chronic angina. The IEPR began in January 1998, and to date over 2,000 patients have been enrolled from over 60 centers in the United States and other countries. Since the Registry aims to collect data on as broad a range of patients as possible, the criteria for entry are only that the patient give informed consent and have at least 1 h of EECP treatment for chronic angina.

The registry methodology has been previously described.[5] Briefly, patient demographics, medical history, coronary disease status, and quality-of-life assessments are collected prior to EECP treatment. After the normal course of 35 h of standard EECP treatment[1] (model MC_2, Vasomedical, Westbury, N.Y., USA), data are collected on the degree of augmentation achieved (as measured from the device by the ratio of diastolic to systolic areas and peak pressures using finger plethysmography; Fig. 1), anginal status, antianginal medication use, quality of life, and adverse clinical events. Calculating the DA ratio using either area or peak pressure yields comparable results.[1,3] Patients are interviewed by telephone 6 months after the last EECP treatment session, and yearly thereafter in order to record anginal status, quality of life, and cardiac and other events. For this study, only patients who completed the full course of at least 35 h of treatment and had a 6-month follow-up were included ($n = 1{,}004$). Prior to any data analysis, patients were divided prospectively into those with higher DA ratios (defined as a DA ratio ≥ 1.5), and those with lower DA ratios (defined as < 1.5).

In the statistical analyses, data are presented as percentages for categorical variables or as mean values and standard deviations for continuous variables. Comparisons between groups were done using chi-square tests, *t*-tests, or Cochran-Mantel-Haenszel statistics, as appropriate. A multiple logistic regression model was used to identify independent predictors of whether higher DA was achieved, and to test the effect of higher or lower DA on clinical outcomes. All factors showing a univariate association with the outcome with a p value < 0.2 were entered into the model and a backward selection method was used. Only factors with a p value of < 0.05 remained in the final model.

Results

No significant differences in results were seen using the ratio of augmented peak diastolic to systolic pressure versus the augmented diastolic to systolic area under the curve. The following results present data of the DA ratios calculated from the area under the curve ratios.

Analysis of the finger plethysmographic waveforms on the final day of EECP therapy showed that 370 (37%) of the patients had a DA ratio of ≥ 1.5, and 634 (63%) had a DA ratio of < 1.5. As shown in Table I, statistically significant factors associated with lower DA ratios included age ≥ 65 years, female gender, hypertension, noncardiac vascular disease, and current smoking. Multivessel coronary disease, congestive heart failure, depressed left ventricular systolic function, prior coronary artery bypass graft (CABG) surgery, prior EECP, severe angina class, and coronary anatomy unsuitable for revascularization were also associated with lower DA ratios (Table II). Clinical factors including diabetes mellitus, prior myocardial infarction, and prior percutaneous coronary intervention (PCI) were not associated with lower DA ratios. Equally, the

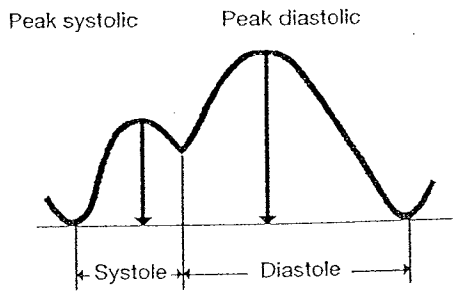

Fig. 1 The arterial pressure waveforms during enhanced external counterpulsation (EECP) are measured by finger plethysmography. The ratio of diastolic augmentation is calculated as the area under the diastolic curve divided by the area under the systolic curve. Note that the reference zero (baseline) used in this calculation is at the point of end diastole.

TABLE I Demographic factors associated with diastolic augmentation

	N	Mean DA ratio	% DA ≥ 1.5
All patients	1,004	1.34 ± 0.69	36.9
Age [b]			
≥ 65 years	577	1.25 ± 0.68	32.1
< 65 years	427	1.45 ± 0.71	43.4
Gender [b]			
Male	770	1.40 ± 0.71	41.0
Female	231	1.12 ± 0.58	22.9
Hypertension [a]			
Yes	690	1.29 ± 0.69	33.9
No	308	1.44 ± 0.70	42.9
Hyperlipidemia			
Yes	755	1.31 ± 0.69	35.4
No	240	1.41 ± 0.72	41.3
Diabetes mellitus			
Yes	398	1.27 ± 0.67	34.4
No	596	1.39 ± 0.71	38.4
Family history			
Yes	745	1.31 ± 0.66	35.4
No	246	1.42 ± 0.78	41.5
Noncardiac vasc [b]			
Yes	293	1.13 ± 0.62	25.9
No	689	1.42 ± 0.71	41.2
Smoking current [a]			
Yes	59	1.02 ± 0.54	17.0
No	936	1.36 ± 0.70	38.4

[a] $p < 0.01$.
[b] $p < 0.001$.
Abbreviation: DA = diastolic augmentation.

TABLE II Disease factors associated with diastolic augmentation

	N	Mean DA ratio	% DA ≥ 1.5
Prior MI			
Yes	644	1.32 ± 0.68	36.2
No	351	1.37 ± 0.73	37.6
Multivessel disease [b]			
Yes	720	1.29 ± 0.68	34.3
No	196	1.48 ± 0.71	45.9
CHF [b]			
Yes	260	1.18 ± 0.62	28.5
No	734	1.39 ± 0.71	39.8
LVEF < 35% [a]			
Yes	127	1.16 ± 0.56	25.2
No	745	1.34 ± 0.69	37.6
Prior PCI			
Yes	600	1.32 ± 0.68	35.2
No	393	1.37 ± 0.68	39.4
Prior CABG [b]			
Yes	609	1.29 ± 0.67	33.5
No	388	1.34 ± 0.73	41.8
Previous EECP [b]			
Yes	45	1.66 ± 0.71	55.6
No	958	1.32 ± 0.69	35.9
Angina class [c]			
I	48	1.74 ± 0.79	58.3
II	229	1.35 ± 0.71	39.3
III	511	1.33 ± 0.68	36.6
IV	216	1.25 ± 0.67	30.0
Candidate for revascularization [c]			
Yes	228	1.47 ± 0.73	45.2
No	741	1.29 ± 0.68	33.7

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: MI = myocardial infarction, CHF = congestive heart failure, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery, EECP = enhanced external counterpulsation, DA = diastolic augmentation.

use of aspirin, beta blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nitrates, or hypolipidemic agents was not associated with lower DA ratios.

Independent predictors of a DA ratio of < 1.5 at the end of EECP therapy were current smoking (odds ratio 3.3; 95% confidence intervals 2.0–5.4), multivessel disease (1.7; 1.3–2.3), female gender (2.2; 1.7–3.0), no prior EECP (1.9; 1.1–3.3), noncardiac vascular disease (2.3; 1.7–2.9), age ≥ 65 years (1.7; 1.4–2.2), and unsuitability of patients for revascularization (1.6; 1.2–2.0). These results are illustrated in Figure 2.

Clinical events and changes in angina class and quality of

($p < 0.05$) and unstable angina ($p < 0.05$), a higher rate of PCI ($p < 0.05$), a lower angina class ($p < 0.01$), and a higher quality-of-life score ($p < 0.001$) than those with lower augmentation. There was no significant difference in death, myocardial

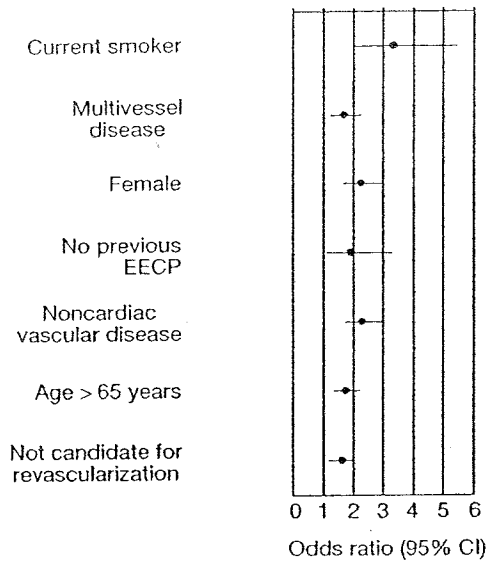

FIG. 2 Odds ratio for augmentation ratio < 1.5. EECP = external enhanced counterpulsation, CI = confidence interval.

A Cochran-Mantel-Haenszel analysis of group differences stratified patients by baseline angina class. Patients with higher DA had a strong trend toward a greater reduction in angina class than did those with lower DA ($p = 0.069$; Fig. 3). An additional logistic regression analysis using the additional covariate of baseline angina class also showed a similar trend toward a greater reduction in angina class in patients with higher DA ($p = 0.097$).

TABLE III Short-term clinical outcomes during 35 h of enhanced external counterpulsation

	DA ratio at end of EECP	
	≥1.5	<1.5
Number of patients	370	634
Events during treatment course (%)		
Unstable angina	0.2	1.1
MI	0.0	0.2
CHF	1.1	0.9
PCI	0.0	0.0
CABG	0.0	0.0
Skin breakdown	1.1	0.6
Angina class (%) [a]		
I	59.2	51.0
II	28.7	33.9
III	9.5	11.8
IV	2.7	3.3
No SL nitroglycerin use (%) [a]	76.6	70.1
QOL score (good or excellent) [b]	55.4	44.1

[a] $p < 0.05$.
[b] $p < 0.01$.
Abbreviations: SL = sublingual, QOL = quality of life. Other abbreviations as in Table II.

Discussion

This IEPR study has identified several independent predictors of achieving higher DA during EECP therapy. Moreover, the incidence of congestive heart failure exacerbation and the improvement in angina class appear to be related to the degree of DA with EECP. Patients with a good or excellent score on quality-of-life assessment following EECP tended to have a higher DA ratio.

It is well recognized that higher DA is not achievable in all patients undergoing EECP treatment. The vast majority of patients undergoing EECP do receive the maximum cuff pressure of 0.04 MPa. Very few patients receive a submaximal cuff pressure because of lower extremity pain during external counterpulsation. The timing of cuff inflation and deflation is initially timed to the electrocardiogram by the EECP device. The timing of the cuff inflation and deflation then may be fine tuned by the EECP operator, and in some cases it is possible that failure to attain higher DA is operator dependent. Enhanced external counterpulsation operators are trained by Vasomedical, Inc. to adjust the inflation and deflation timing to attain maximal DA. Thus, the timing of cuff inflation and deflation is both automated by the EECP device as well as standardized by EECP operator training. Nonetheless, it is unlikely that patient discomfort or operator-related failure to attain higher DA ratios would confound these results.

Prior studies have shown that reaching a DA ratio of ≥ 1.5 maximizes the hemodynamic effects of EECP treatment.[3,4] The DA ratio reported for patients receiving active counterpulsation in the Multicenter Study (MUST)-EECP trial was

TABLE IV Six-month clinical outcomes after enhanced external counterpulsation

	DA ratio at end of EECP	
	≥1.5	<1.5
Number of patients	370	634
Events (%)		
Death	2.2	3.3
Unstable angina [a]	5.1	8.7
MI	2.9	2.8
CHF [a]	2.2	4.9
PCI [a]	4.3	1.7
CABG	1.1	1.3
Cardiac hospitalization	12.2	13.6
Angina class (%) [b]		
I	62.3	55.2
II	26.2	27.0
III	8.9	12.7
IV	2.6	5.1
QOL score good or excellent [c]	50.1	38.9

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations as in Tables II and III.

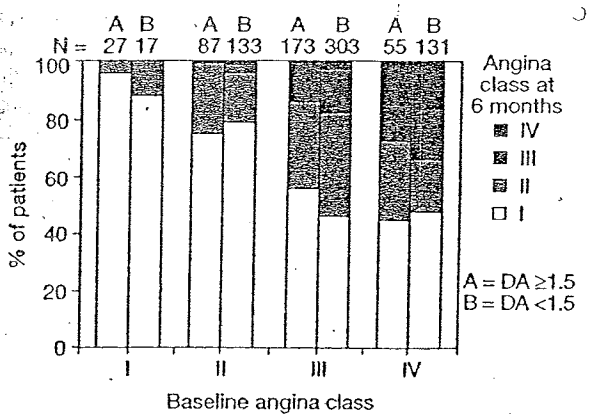

FIG. 3 The change in angina class from baseline to 6 months is shown, stratified by baseline angina class. Data are shown for patients with higher (A) and lower (B) diastolic augmentation. The p value between the groups A and B is 0.069 by Cochran-Mantel-Haenszel statistics.

1.6 ± 0.6, reflecting effective DA in the majority of patients.[1] However, in the present study observing practice patterns, only 37% of patients treated had a DA ratio ≥ 1.5. Female gender was a strong predictor of lower DA. Because the IEPR does not collect weight and body surface area, we could not adjust these results for body habitus. It is possible that the female gender variable may be confounded by body size, where smaller body size may have an important impact on the hemodynamic effects of EECP.

The independent predictors of a DA ratio < 1.5 also included markers of severe vascular disease, such as current smoking, multivessel disease, noncardiac vascular disease, and unsuitability of patients for further revascularization. Patients with these clinical characteristics may have peripheral vascular disease and aortic involvement attenuating the pressure transmission from the pneumatic cuffs around the lower extremities to the upper extremities (where finger plethysmography is performed) and the coronary arteries. Patients with less severe angina class at baseline, immediately after EECP and also at 6-month follow-up, tended to have higher DA ratios. It is possible that patients with more severe angina class also have more significant peripheral vascular disease and lower DA. It is also important to note that the incidence of adverse mechanical complications of EECP, such as skin breakdown, was not related to the degree of DA achieved during therapy (Table III).

Six-month rates of unstable angina and congestive heart failure exacerbation were related to the magnitude of DA during EECP therapy (Table IV). After controlling for gender and heart failure at baseline, patients with a higher DA ratio still had a lower incidence of heart failure exacerbation than did those with lower augmentation. There was no difference in the rates of CABG between the two groups, but there was an increased rate of PCI in patients with higher DA ratios (4.3%) compared with those with lower DA ratios (1.7%; $p < 0.05$). Any interpretation of the association between the magnitude of DA and the 6-month rates of revascularization should be made with caution, given the very small number of patients in both groups undergoing percutaneous or surgical revascularization.

It is important to emphasize that both groups of patients with higher and lower DA ratios did receive active EECP therapy. Because patients with lower DA also had a dramatic and statistically significant reduction in angina class, either the DA ratio cutoff of ≥ 1.5 is too stringent and/or there are other mechanisms of benefit from EECP that are independent of the magnitude of DA. Although the precise mechanism by which EECP improves angina remains undefined, recently presented evidence suggests that EECP may recruit and develop coronary collateral vessels, thereby improving myocardial perfusion.[6] It is unclear whether there is a hemodynamic threshold required to develop coronary collateralization. Others have suggested that EECP may have a beneficial peripheral effect that results in decreased systemic vascular resistance.[7]

A variety of basic science investigations suggest that shear stress in the coronary circulation is a potent activator of angiogenic mechanisms. In developing chick embryos, for example, the vessels with the fastest blood velocity became the main arteries while those with slower velocities atrophied.[8] The fundamental autoregulatory mechanisms are mediated at the level of the endothelium.[9] In response to shear stress, the endothelium upregulates expression of platelet-derived growth factors A and B (PDGF), a mitogen that stimulates vascular remodeling through connective tissue and smooth muscle cell proliferation.[10]

It has been hypothesized that the increased velocity of coronary flow by EECP may provide a shear stress that stimulates changes in the actin cytoskeleton and/or upregulates expression of angiogenic growth factors.[4] It has been reported that mechanical strain mediates fibroblast growth factor-2 (FGF-2) release from vascular smooth muscle and endothelial cells.[11] Other investigators found that patients responding to EECP therapy had a significant increase in circulating levels of the angiogenic vascular endothelial growth factor (VEGF).[12] Other studies have found that EECP therapy has a dose-related, sustained effect in stimulating endothelial cell production of the vasodilator nitric oxide (NO) and in reducing production of the vasoconstrictor endothelin-1.[13,14]

While the hypothesis that shear stress upregulates PDGF, angiogenic growth factors, and NO production seems plausible, it is possible that these changes do not require the shear stress to reach the coronary circulation. If these physiologic changes can occur due to shear stress in the peripheral circulation, the benefit of EECP may be less dependent on the pressure transmitted to the upper extremities and coronary arteries. Further investigation is needed to elucidate the mechanisms by which EECP improves myocardial ischemia.

The limitations of the IEPR have been previously described.[5] We had no data regarding body weight or body surface area. The DA ratios taken only on the final day of EECP may not accurately reflect the level of DA during the entire course of EECP therapy. Comparing differences between these two groups is difficult because all patients included in

the IEPR received active therapy. There may be other confounding variables that were not included in our multivariate analysis. Finally, this sample size still constrains our ability to perform more elaborate multivariate analyses for a fuller assessment of the effects of baseline factors on changes in clinical outcomes.

Conclusions

Among 1,004 patients enrolled in the IEPR who underwent EECP therapy for symptomatic coronary artery disease, only 37% of patients treated were able to generate DA ratios ≥ 1.5. Patients who were younger, male, nonsmokers, without multivessel coronary disease, and without noncardiac vascular disease were more likely to have higher DA ratios with EECP. Overall, patients had a significant symptomatic benefit from EECP therapy, a reduction in angina class, and an improvement in the assessment of quality of life. Patients with higher DA ratios with EECP had a lower incidence of unstable angina and congestive heart failure exacerbation, and also had a strong trend toward a greater reduction in angina class at 6-month follow-up compared with those with lower DA ratios.

It does appear that DA is important in achieving maximal clinical benefit from EECP. This study has demonstrated that several baseline clinical characteristics significantly influence the generation of higher DA during EECP. However, many questions remain unanswered and require further investigation with larger sample sizes. Whether there is a DA ratio threshold below which the clinical benefit derived from EECP is minimal remains an open question. More fully examining the interaction of baseline clinical characteristics and DA ratios on the reduction in angina class and revascularization rates will require further analysis with larger sample sizes.

Acknowledgments

The authors would like to express their thanks to Paul-André de Lame, M.D., Michèle L. Lemaire, M.D., and Dror Rom, Ph.D., for their help with statistical analyses in this manuscript.

References

1. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, Nesto RW: 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;33:1833–1840
2. Arora RR, Chou TM, Jain D, Nesto RW, Fleishman B, Crawford L, McKiernan T: Results of the Multicenter Enhanced External Counterpulsation (MUST-EECP) Outcomes Study: Quality of life benefits sustained twelve months after treatment (abstr). *J Am Coll Cardiol* 1999(suppl);33:339A
3. Suresh K, Simandl S, Lawson WE, Hui JCK, Lillis O, Burger L, Guo T, Cohn PF: Maximizing the hemodynamic benefit of enhanced external counterpulsation. *Clin Cardiol* 1998;21:649–653
4. Soran O, Crawford LE, Schneider VM, Feldman AM: Enhanced external counterpulsation in the management of patients with cardiovascular disease. *Clin Cardiol* 1999;22:173–178
5. Barsness G, Feldman A, Holmes D Jr, Holubkov R, Kelsey S, Soran O, Kennard ED: The International EECP Patient Registry (IEPR): Design, methods, baseline characteristics, and acute results. *Clin Cardiol* 2001;24:435–442
6. Masuda D, Nohara R, Inada H, Hirai T, Li-Guang C, Kanda H, Inubushi M, Tadamura E, Fujita M, Sasayama S: 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;63:407–411
7. Lawson WE, Hui JCK, Zheng ZS, Burger L, Jiang L, Lillis O, Oster Z, Soroff H, Cohn PF: Improved exercise tolerance following enhanced external counterpulsation: Cardiac or peripheral effect? *Cardiology* 1996;87:1–5
8. Zarins CK, Satina MA, Giddens DP, Ku DN, Glagov S: Shear stress regulation of artery lumen diameter in experimental atherogenesis. *J Vasc Surg* 1987;5:413–420
9. Langille BL, O'Donnell F: Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium dependent. *Science* 1986;231:405–407
10. Hsieh HJ, Li NQ, Frangos JA: Shear stress increases endothelial platelet-derived growth factor mRNA levels. *Am J Physiol* 1991; 260:H642–H646
11. Reidy MA: Factors controlling smooth muscle cell proliferation. *Arch Pathol Lab Med* 1992;116:1276–1280
12. Werner D, Friedel J, Kropp J, Weise M, Waltenberger J, Kranz A, Daniel WG: Pneumatic external counterpulsation—a new treatment for selected patients with symptomatic coronary artery disease (abstr). *Eur Heart J* 1998;19(suppl):P506
13. Wu GF, Zheng QS, Zheng ZS, Zhang MQ, Lawson WE, Hui JCK: A neurohormonal mechanism for the effectiveness of enhanced external counterpulsation (abstr). *Circulation* 1999;100(suppl):I-832
14. Qian XX, Wu WK, Zheng ZS, Zhan CY, Yu BY, Lawson WE, Hui JCK: Effect of enhanced external counterpulsation on nitric oxide production in coronary disease (abstr). *J Heart Dis* 1999;1:193