Acute Hemodynamic Effects and Angina Improvement with Enhanced External Counterpulsation

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Enhanced external counterpulsation (EECP) is an effective noninvasive treatment for coronary artery disease. The mechanism of action is felt to be hemodynamic. The complex hemodynamic effects have been simply quantified by calculating a previously described effectiveness ratio (ER).

The EECP Clinical Consortium, a clinical registry of 37 centers, prospectively enrolled 395 chronic stable angina patients (79 women, 316 men, mean age 66 years) to examine the relation of the ER to posttreatment improvement in Canadian Cardiovascular Society angina class (CCS). Women and the elderly underwent planned subgroup analysis. The ER was calculated during the first and last hours of a 35-hour course of EECP treatment.

After EECP, CCS improved by at least 1 class in 88% of patients, 87% of men and 92% of women ($p = NS$), and in 89% of patients ≤ 66 years and 88% of patients > 66 years old ($p = NS$). The initial and final ER were similar in patients with and without improvement in CCS. Significant first-hour ER differences were seen between men and women (0.96 ±0.03 vs 0.76 ±0.04, $p < 0.005$), and between ages ≤ 66 and > 66 years old (1.04 ±0.04 vs 0.81 ±0.03, $p < 0.0001$). However, all subgroups responded equally well to EECP treatment.

EECP is effective in improving CCS in chronic stable angina patients; it has comparable effects in men and women and across a broad range of ages. The hemodynamic effect of EECP (ER) does not predict improvement in CCS and may indicate that other factors, such as neurohormonal changes, may have a significant role in mediating the observed EECP benefits.

Introduction

Enhanced external counterpulsation (EECP) is an effective noninvasive treatment for chronic angina. Treatment with EECP has been shown to decrease subjective angina pectoris and improve exercise treadmill parameters in a multicenter, randomized, controlled clinical trial (MUST-EECP),[1] and in case series reporting on radionuclide stress perfusion.[2,3] Sustained benefits after EECP treatment over 3- and 5-year periods have been reported.[4,5]

During EECP, sequential diastolic inflation of 3 pairs of pneumatic cuffs applied to the lower extremities augments aortic diastolic pressure, increasing the diastolic transmyocardial pressure gradient and increasing coronary blood flow. Cuff inflation also increases venous return and cardiac output, predominately by the Starling mechanism. Simultaneous deflation of the cuffs at the

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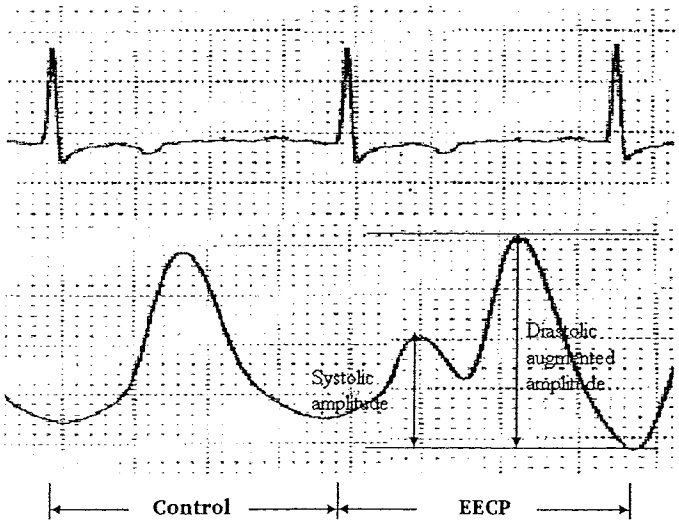
onset of systole decreases left ventricular afterload[6] and contributes to increasing the cardiac output. Patients with a "patent conduit" (either 1 or more native coronaries without proximal disease or with a patent bypass graft[s]) have been demonstrated to have the greatest likelihood of treatment benefit with EECP, possibly mediated by the development or recruitment of collaterals.[7] Transmission of augmented flow volume and pressure to the distal coronary circulation, which requires both changes in acute hemodynamics and a conduit capable of transmitting them, appears, therefore, necessary for sustained EECP benefit. To simply quantitate the acute hemodynamic effects of EECP, an effectiveness ratio (ER) has been validated, using the ratio of the peak amplitudes of diastolic to systolic waveforms detected during counterpulsation by finger plethysmogram,[8] as shown in Figure 1.

The peak diastolic augmented amplitude represents the magnitude of coronary perfusion pressure and therefore should correlate with coronary blood flow. The peak systolic amplitude represents myocardial workload. The value of ER, therefore, is an indicator of myocardial energy supply and demand. It has been shown in our previous paper that the ER value that corresponds to optimal hemodynamic effects of EECP in increasing cardiac output and maximal retrograde flow in the descending aorta is in the range of 1.5 to 2.0.[8] However, the correlation between the ER during EECP and the clinical benefit of EECP has not been investigated.

The current study was designed to prospectively examine whether the ER calculated during EECP treatment predicts improvement in Canadian Cardiovascular Society Functional Class of Angina (CCS). Women and the elderly, subgroups of particular interest, were also analyzed to determine the relationship of their ER to an improvement in anginal class. In addition, the ER was calculated during the first hour and last hour of a 35-hour course of EECP treatment to evaluate whether there are significant ER changes during treatment and, if so, whether the changes are related to improvement in the CCS.

Methods

Patients with chronic angina (Canadian Cardiovascular Society Angina Classes I through IV), despite medical and surgical therapy, were considered for inclusion in the study. Consecutive patients from 37 centers participating in the EECP Clinical Consortium were enrolled from



$$\text{EECP effectiveness ratio (ER)} = \frac{\text{Diastolic augmented amplitude}}{\text{Systolic amplitude}}$$

Figure 1. The effectiveness ratio (ER) is calculated by taking the amplitude of the systolic peak from the point at end diastole (represented by counting the mm) divided by the amplitude of the augmented diastolic peak obtained during EECP treatment.

January 1996 to April 1998. The participating centers included university medical centers, hospitals, clinics, physician's offices, rehabilitation facilities, and freestanding EECP clinics. Exclusion criteria included the following: clinical congestive heart failure, aortic insufficiency, myocardial infarction within the previous 3 months, significant ventricular ectopic activity or atrial fibrillation, nonischemic cardiomyopathy, severe occlusive vascular disease, recurrent deep vein thrombosis, systemic hypertension, and bleeding diathesis.

On entry all patients were having angina despite medical therapy. During the study, medication changes were allowed only after determination by their physicians that adjustment was necessary. No planned interventions were performed during the study. Enrolled patients had a finger plethysmogram recorded with EECP during the initial and last hours of a 35-hour course of EECP treatment. The tracings were analyzed by the Stony Brook University core laboratory in a blinded fashion. The ER was measured as the ratio of peak diastolic to peak systolic amplitudes during EECP as previously described.[8] The Canadian Cardiovascular Society Functional Class of Angina Effort (CCS) was determined before and after treatment.

EECP was performed 1 hour daily for a total of 35 hours. All patients were monitored clinically during EECP treatment. The highest external inflation pressures used during EECP treatment were in the range of 225–275 mm Hg.

Patients were analyzed for improvement in anginal class and for the correlation of angina class improvement with the acute hemodynamic effect of EECP (as assessed by the ER). Subgroups of women and the elderly were separately analyzed and compared. Results were compared by unpaired t test for continuous and chi-squared for discrete variables. Statistical significance was achieved at the 5% level ($p < 0.05$).

Results

The study enrolled 395 patients (79 women, and 316 men) from 37 centers participating in the EECP Clinical Consortium. The mean age was 66.1 ±11.3 years, with a range of 30–97 years.

The CCS anginal class improved in 88% of patients. After EECP, CCS improved by at least 1 class in 87% of men and 92% of women (p = NS). Similar improvements in CCS were demonstrated in 89% of patients less then or equal to 66 years old and in 88% of those patients older then 66 years (p = NS) (Figure 2). There was no significant difference in ER between patients with and without improvement in anginal class, as shown in Figure 3. In addition, the ER during the first hour of treatment for the group of patients with at least 1 CCS class improvement was 0.90 ±0.03 vs 1.05 ±0.09 for those who did not have any class improvement (p = 0.08). Similarly, the

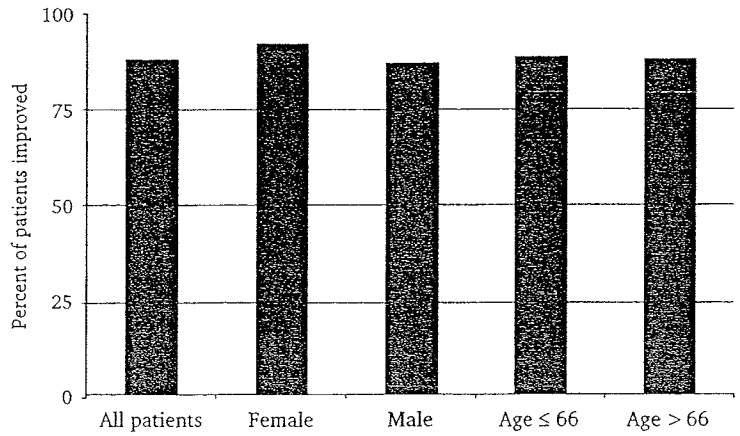


Figure 2. The relation of age and gender to improvement in CCS with EECP treatment.

ER during the last hour of EECP treatment was 1.14 ±0.06 for those who improved their CCS class vs 1.18 ±0.06 for those who did not (p = NS). There was no correlation between the changes in ER between the first and last hour of EECP treatment and their changes in CCS class. However, the mean initial ER was significantly higher in men than in women and also significantly higher in patients with age ≤ 66 compared to those patients > 66 years. All subgroups responded comparably to EECP treatment despite their differences in ER. There was a significant increase in ER in all patient groups observed over the course of EECP (initial ER of 0.92 ±0.03 vs ER of 1.14 ±0.03 upon completion, $p < 0.0001$) (Table I). In summary, the ER obtained during the first hour of treatment and the change in ER over the course of treatment did not predict improvement in anginal class.

Discussion

Medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG), although effective treatments for angina, have significant limitations, especially with advanced coronary artery disease not amenable to revascularization or when medications are ineffective or cause significant side effects.[9,10] EECP, used primarily in patients refractory to medical or revascularization therapy, resulted in significant improvement in angina functional class in most patients in this study.

Of special interest is the observation that EECP was equally effective in both men and women and across a broad range of ages. By contrast, both gender and age appear to be significant determinants of treatment outcomes with both PCI and CABG. Advanced age as well as female gender are associated with increased periprocedural adverse event rates and a higher rate of unsatisfactory outcomes.[11-14] Thus, the observation of comparable clinical efficacy of EECP with regard to age and gender is important when EECP is being considered as an alternative or complementary treatment strategy in CAD patients.

Effective diastolic augmentation, either initially or at the completion of EECP treatment, as measured by the ER, was not a prerequisite for angina class improvement in the present study. Therefore, patients with poor ER should not be discouraged from undergoing EECP treatment. This finding would appear to be at odds with prior studies suggesting the importance of a patent conduit and effective counterpulsation. However, the measures used in prior studies

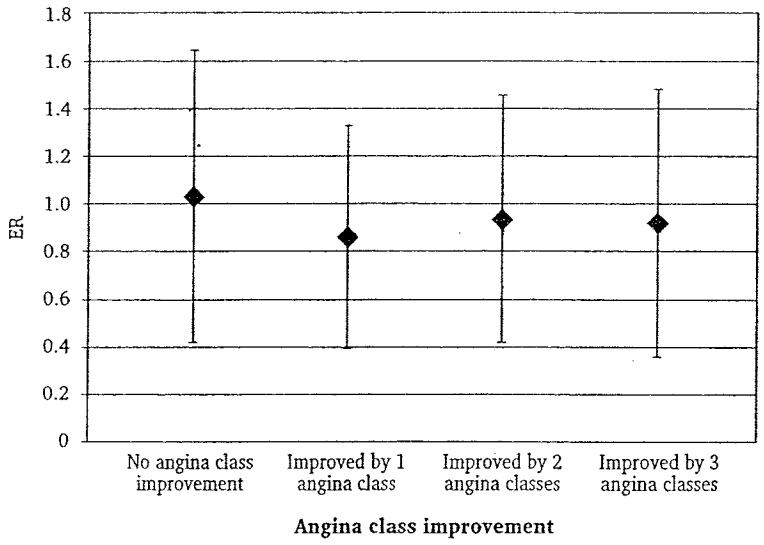


Figure 3. ER and change in CCS angina class.
The effectiveness ratio is not related to the improvement in angina functional class (Canadian Cardiovascular Society) after EECP treatment.

Table I. Improvement in angina CCS class and hemodynamic response according to gender and age.

	Total	Pts # Improved in CCS	Initial ER	Final ER	Change in ER
All groups	395	349 (88%)	0.92 ±0.03	1.14 ±0.03	0.22 ±0.02
Women	79	73 (92%)	0.76 ±0.04 *	0.93 ±0.05	0.16 ±0.04
Men	316	276 (87%)	0.96 ±0.03*	1.19 ±0.03*	0.24 ±0.03
Age ≤ 66 years	186	165 (89%)	1.04 ±0.04	1.28 ±0.05	0.24 ±0.04
Age > 66 years	209	184 (88%)	0.81 ±0.03*	1.02 ±0.04*	0.21 ±0.03

$p < 0.0001$ comparing initial to final ER. *$p < 0.005$ comparing men to women and age ≤ 66 years to > 66 years old.

were different, including treadmill and radionuclide stress testing. Subjective evaluation of treatment efficacy by improvement in angina in prior studies invariably yielded a greater degree in improvement than could be documented by more objective measures. For instance, in the prospective, double-blind, sham-controlled MUST-EECP trial, there was no significant difference (between active and sham groups) in improvement in treadmill time posttreatment.[1] Quality of life measures, however, improved significantly, owing perhaps to a decreased ischemic burden, as demonstrated by an increased time to ST segment depression in the active EECP-treated group.

There were significant differences in the initial ER between men and women, as well as between patients aged ≤ 66 and > 66 years. These differences are probably due to a comparably smaller lower extremity muscle mass and vascular compartment volume in women and in the elderly. However, these differences were not of clinical relevance as assessed by improvement in anginal class.

Improvement in angina is an important aim and outcome of treatment. However, it is important to realize that anginal class improvement is largely a subjective and poorly quantifiable measure. Because EECP response rates approach 90% by this measure, anginal class improvement allows little ability to discriminate differences in effectiveness by pretreatment characteristics or hemodynamic response. While this might be addressed by a dramatic increase in sample size, a placebo effect of unknown magnitude may further mask differences in clinical response. A more objective means of assessing ischemia, instead of angina, may be desirable to clarify the mechanism of action of EECP in future studies.

It is important to realize the pitfalls of finger plethysmography in accurately reflecting central hemodynamics. Besides being a volume versus the more typically used pressure measure, finger plethysmography is affected by peripheral impedance in a not always predictable fashion, such as vasoconstriction due to anxiety. The diastolic augmentation seen on finger plethysmogram does not necessarily reflect coronary flow, which is heavily influenced by the presence of coronary stenoses and distal impedance.

It is also possible that the mechanism of long-term benefit with EECP is not directly related to the magnitude of the acute hemodynamic changes it produces. The increased blood flow may also mediate local and systemic neurohormonal effects, caused by shear stress and increased intravascular pressure and volume. EECP has been demonstrated to affect neurohormonal measures, including: nitric oxide and endothelin levels, lipid peroxidation, atrial natriuretic peptide, and vascular endothelial growth factor.[15-17] These changes may have long-term effects on neurohormonal regulation and vascular remodeling. It is possible that the increase in ER demonstrated over the course of EECP may reflect a more generalized change in endovascular health

and function. While this provides an alternative mechanism whereby clinical benefits may be sustained over a long-term period, the relation of neurohormonal changes to acute hemodynamic measures is also unknown.

Conclusion

EECP appears to be safe and equally effective in both genders and across a wide range of ages as a treatment of chronic stable angina. Even though there were significant differences observed in the efficiency ratio between men and women as well as between patients age ≤ 66 and > 66 years, comparable improvements in angina class following EECP were demonstrated. EECP was well tolerated. Currently available data suggest that EECP is an effective alternative treatment for angina patients.

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