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])

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Enhanced external counterpulsation (EECP) is a noninvasive counterpulsation technique that reduces angina and extends time to exercise-induced ischemia in patients with symptomatic stable angina.[1] In addition to relieving myocardial ischemia, EECP is associated with improved quality of life. It uses a sequential inflation of 3 sets of pneumatic cuffs wrapped around the lower extremities. The cuffs are inflated sequentially at the onset of diastole, producing aortic counterpulsation, diastolic augmentation (DA), and increased venous return. At the onset of systole, external pressure in the cuffs is released, producing a decrease in systolic pressure (systolic unloading). These hemodynamic effects are monitored noninvasively by assessing the finger plethysmographic waveforms. A typical course of EECP involves 1 to 2 hours/day for a total of 35 hours of therapy. It has been hypothesized that the sustained benefits of EECP result from effective DA, which promotes coronary collateral formation or recruitment.[2] A previous study has demonstrated that patients who are younger, male, nonsmoking, and without multivessel coronary or noncardiac vascular disease are most likely to have higher DA at the end of an EECP treatment course.[3] Patients with higher DA ratios at the end of EECP tended to have a greater reduction in angina class than those with lower DA ratios, suggesting that clinical benefit from EECP is associated with the magnitude of DA. That initial study was limited by assessing the DA ratios on the final day of EECP therapy. This present analysis further investigates the role of DA in EECP by assessing the impact of DA levels both at the first and last treatment session with EECP.

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The International EECP Patient Registry (IEPR) enrolls consecutive patients undergoing EECP for chronic angina. The IEPR began in January 1998, and to date >5,000 patients have been enrolled from >100 centers in the United States and other countries. Because 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 hour of EECP treatment for chronic angina.

The Registry methods have been previously described.[4] Briefly, data are collected on patient demographics, medical history, coronary disease status, and quality-of-life assessments before EECP treatment. After EECP treatment, data are collected on the degree of augmentation achieved (as measured from the device by a ratio of diastolic-to-systolic areas and peak pressures using finger plethysmography), anginal status, quality of life, and adverse clinical events. All treatment was performed using the EECP system (model MC_2, Vasomedical, Westbury, New York). Patients are interviewed by telephone 6 months after their last EECP treatment session, and yearly thereafter to record anginal status, quality of life, and cardiac and other events. For this study, only patients who completed at least 35 hours of EECP treatment and who had recorded values for DA peak ratio at both the first and last hours were included (n = 2,486). Data from 9 patients with DA ratios >4 were excluded.

For this analysis, the patients were divided according to whether their DA was above or below the median value at the first and last day of EECP therapy. The median value for initial DA was 0.7 and for the final DA, 1.0. Patients with an initial DA ratio ≤0.7 were categorized as having a low initial DA, whereas those with a ratio >0.7 were in the high initial group. Patients with a final DA ratio ≤1.0 were categorized as having a low final DA, whereas those with a ratio >1.0 were in the high final group.

In the statistical analyses, data are presented as percentages for categorical variables or as mean values and SDs for continuous variables. Comparisons among the 4 groups were done using chi-square, Wilcoxon, 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 DA levels 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 used. Only factors with a p value <0.05 remained in the final model.

Finger plethysmographic waveforms were analyzed on the first and final day of EECP therapy to determine the peak diastolic-to-systolic ratio during

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TABLE 1 Demographic Factors and Pattern of DA

Variable	Pattern of DA			
	Low-Low (n = 1,009)	Low-High (n = 281)	High-Low (n = 250)	High-High (n = 946)
Age (yrs) (mean ± SD)*	68.2 ± 10.2	66.2 ± 11.0	66.7 ± 10.5	64.5 ± 10.3
Men*	70.8%	73.7%	75.6%	86.0%
Years since CAD diagnosis (mean ± SD)*	11.4 ± 8.0	10.1 ± 8.1	10.2 ± 8.1	9.8 ± 7.8
Hypertension*	74.0%	62.8%	66.1%	63.7%
Diabetes mellitus*	45.5%	49.6%	42.2%	32.6%
Family history of CAD	76.9%	74.9%	74.5%	76.3%
Noncardiac vascular disease*	35.5%	29.3%	24.8%	17.8%
Current smoking*	8.0%	5.0%	9.9%	4.0%

*p <0.001.
CAD = coronary artery disease.

TABLE 2 Coronary Disease Factors and Pattern of DA

Variable	Pattern of DA			
	Low-Low (n = 1,009)	Low-High (n = 281)	High-Low (n = 250)	High-High (n = 946)
Prior myocardial infarction	67.1%	64.9%	65.6%	64.0%
Multivessel disease*	81.7%	74.3%	82.8%	73.0%
Congestive heart failure*	33.7%	27.2%	26.9%	22.1%
Prior PCI or CABG†	87.1%	81.3%	85.4%	81.6%
Candidate for revascularization*	15.6%	19.2%	15.6%	27.6%
Anginal episodes/wk (mean ± SD)	9.6 ± 12.8	8.8 ± 11.9	9.4 ± 12.1	9.0 ± 12.7
Angina class (mean)*	3.05	3.06	3.03	2.91
I	1.8%	1.4%	2.0%	5.6%
II	15.2%	17.8%	12.0%	18.1%
III	55.5%	58.4%	62.0%	57.9%
IV	31.5%	24.9%	27.2%	20.7%

*p <0.001; †p <0.01.
CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

EECP in 2,486 patients. During the first hour of treatment, the median DA ratio was 0.7 (mean 0.83 ± 0.51). During the last hour of treatment, the median DA ratio increased to 1.0 (mean 1.15 ± 0.61). Of the total study cohort of 2,486 patients, 1,009 (40.6%) had a DA ratio below or equal to the median level both at the beginning and end of EECP (termed low-low group), 281 (11.3%) had a DA ratio below or equal to the median at the beginning and a ratio above the median at the end of treatment (low-high group), 250 (10.1%) had a DA ratio above the median at the beginning and a ratio below or equal to the median at the end of EECP (high-low group), and 946 patients (38.1%) had a DA ratio above the median at the beginning and end of treatment (high-high group).

Patients with low DA ratios both at the beginning and end of EECP were older, and fewer were women (Table 1). This group had a longer history of coronary disease and was more likely to have a history of hypertension, diabetes, noncardiac vascular disease, and current smoking. There were no meaningful differences with respect to cardiac medications among the 4 groups. Patients with low DA ratios also were more likely to have multivessel coronary disease, prior percutaneous or surgical coronary revascularization, and more frequent anginal episodes (Table 2). Patients with high DA ratios both at the beginning and end of treatment were more likely to be candidates for revascularization and had the lowest baseline angina class.

Significant independent predictors of a DA ratio below the median during the first hour of EECP included female gender (odds ratio [OR] 2.34; 95% confidence interval [CI] 1.88 to 2.91, p <0.001), noncardiac vascular disease (OR 1.89; 95% CI 1.5 to 2.31, p <0.001), age ≥65 years (OR 1.73; 95% CI 1.45 to 2.07, p <0.001), smoking (OR 1.65; 95% CI 1.35 to 2.01, p <0.001), heart failure (OR 1.39; 95% CI 1.14 to 1.69, p <0.001), diabetes mellitus (OR 1.38; 95% CI 1.15 to 1.66, p <0.001), hypertension (OR 1.24; 95% CI 1.03 to 1.49, p <0.001), and prior coronary artery bypass surgery (OR 1.22; 95% CI 1.01 to 1.46, p <0.001). These same variables were significant independent predictors of a low DA ratio during the final hour of EECP.

Among those with an initial DA ratio below the median, independent predictors of improving the final DA ratio to above the median were smoking (OR 1.82; 95% CI 1.34 to 2.49, p <0.001), hypertension (OR 1.51; 95% CI 1.11 to 2.05, p <0.001), and multivessel disease (OR 1.51; 95% CI 1.08 to 2.12, p <0.001). Among those with an initial DA ratio above the median, independent predictors of worsening the final DA ratio to below the median were smoking (OR 2.64; 95% CI 1.80 to 3.87, p <0.001), female gender (OR 2.35; 95% CI 1.59 to 3.49, p <0.001), β-blocker use (OR 1.83; 95% CI 1.29 to 2.61, p <0.001), multivessel disease (OR 1.66; 95% CI 1.12 to 2.47, p <0.001), diabetes mellitus (OR 1.48; 95% CI 1.08 to 2.03, p <0.001), and age ≥65 years (OR 1.47; 95% CI 1.08 to 2.01, p <0.001).

Immediately after EECP, patients in the low-high group had the greatest reduction in angina class, whereas those in the high-low group had the least reduction in angina class (Figure 1; Table 3). Data on 6-month clinical outcomes were available from 78% of patients included in the initial cohort. These findings were sustained at 6 months of follow-up. There were no significant differences among the 4 groups in clinical events, such as death, myocardial infarction, unstable angina, congestive heart failure, coronary revascularization, repeat EECP, or cardiac hospitalization.

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The median peak DA ratio increased from 0.7 during the first hour of EECP up to 1.0 during the last hour of treatment. This increase in DA during the treatment

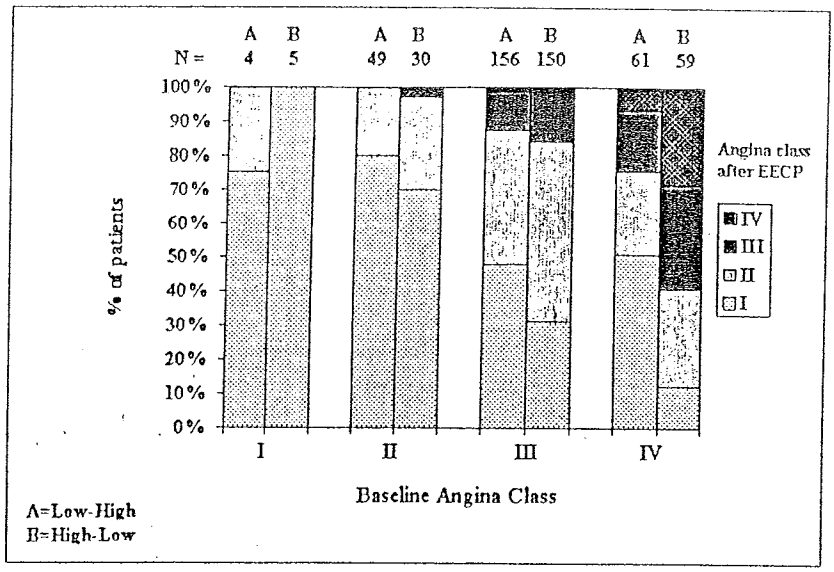

FIGURE 1. The change in angina class from baseline to after EECP is shown, stratified by baseline angina class. Data are shown for 2 groups: those with low diastolic augmentation at the beginning of EECP and high augmentation at the end of treatment (Low-High; group A), and those with high augmentation at the beginning of EECP and low augmentation at the end of treatment (High-Low; group B). The p value between groups A and B is <0.01 by Cochran-Mantel-Haenszel statistics.

TABLE 3 Immediate and Six-Month Clinical Outcomes After EECP and Pattern of DA

Variable	Post-EECP (6 mo)	Pattern of DA: Low-Low (n = 1,009) (n = 757)	Low-High (n = 281) (n = 217)	High-Low (n = 250) (n = 206)	High-High (n = 946) (n = 756)
Decrease in mean angina class					
Baseline to 35 h of EECP*		1.54	1.72	1.38	1.44
Six mo†		1.59	1.67	1.47	1.53
Patients with decrease in ≥2 angina classes					
Baseline to 35 hours of EECP†		44.6%	49.3%	37.3%	44.0%
Six mo†		46.1%	53.9%	38.9%	45.9%

*p <0.001; †p <0.01; ‡p <0.05.

course is likely attributable to an improvement in vascular compliance. This beneficial hemodynamic effect with an increase in DA during therapy may reflect a beneficial effect of EECP on endothelial function.

Moreover, the magnitude of the symptomatic benefit with EECP was related to the pattern of how the DA ratio changed during therapy. Patients who had an increase in DA ratio from the beginning to the end of EECP had a greater reduction in angina class. In contrast, patients who started EECP with an above-average DA ratio, but finished EECP with a below-average DA ratio had the lowest reduction in angina class. It appears that patients most likely to benefit from EECP also have the greatest increase in DA ratios during therapy, reflecting a beneficial increase in vascular compliance.

This study identified several independent predictors of achieving higher DA at the beginning and end of EECP treatment. Male gender, age <65 years, nonsmoking, and no history of diabetes, heart failure, noncardiac vascular disease, or prior bypass surgery were independent predictors of having a higher DA both at the beginning and end of EECP. These findings are consistent with those from prior studies.[3] Patients with these clinical characteristics are less likely to have peripheral vascular disease, attenuating the pressure transmission from the lower extremity pneumatic cuffs to the upper extremities (where finger plethysmography is performed) and the coronary arteries. Known noncardiac vascular disease was twice as likely to occur among patients who had DA ratios below the median at the beginning and end of treatment (35.5%) than among those with DA ratios above the median at both time points (17.8%, p <0.001). In some cases, the degree of DA may be dependent on patient factors. Patient discomfort, for example, may limit the cuff pressure applied. In general, EECP therapists attempt to obtain the maximum DA obtainable by finger plethysmography.

In summary, among 2,486 patients enrolled in the IEPR who underwent EECP therapy for symptomatic coronary artery disease, the median DA ratio increased from 0.7 to 1.0 from the beginning to the end of treatment. Patients who had the greatest increase in the DA ratio had the greatest reduction in angina class, whereas those with a relative decrease in the DA ratio had the lowest reduction in angina class immediately after EECP and at 6 months of follow-up. These data suggest that improved vascular tone during EECP treatment may play a mechanistic role in the relation between DA and clinical benefit with EECP.

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