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The effects of enhanced external counterpulsation on time- and frequency-domain measures of heart rate variability ☆

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Abstract

Background and Purpose: We hypothesized that symptom improvement from enhanced external counterpulsation (EECP) is related to improved heart rate variability (HRV).

Methods: This prospective, multicenter study enrolled 27 patients with angina who underwent 48-hour ambulatory electrocardiogram monitoring at baseline, immediately after 35 hours of EECP, and at 1 month. Primary end points included change in time-domain (SD of normal-to-normal intervals) and frequency-domain HRV.

Results: Twenty-four patients completed the full course of EECP therapy and 3 ambulatory electrocardiograms. There were no significant changes in time-domain HRV measures after EECP. Patients younger than 65 years and those with heart failure had improved SD of normal-to-normal interval after EECP (P = .02). Although frequency-domain HRV measures did not change in the overall cohort, patients with diabetes had improved daytime low-frequency power (P = .016).

Conclusions: There was no significant change in the time- or frequency-domain HRV measures after EECP. In diabetic individuals, there was an increase in low-frequency HRV, which has been associated with reduced mortality.

Introduction

It is estimated that more than 13 million Americans have coronary artery disease, which causes more deaths, disability, and economic loss in Westernized nations than any other groups of diseases.[1] Although most of the 6.4 million patients with angina may be managed medically, others require invasive revascularization with percutaneous coronary intervention and/or coronary artery bypass graft surgery.[1] Despite significant advances in medical and revascularization strategies, many patients still have debilitating chronic angina.

Enhanced external counterpulsation (EECP) is a noninvasive counterpulsation technique that has been shown to reduce angina pectoris,[2] extend time to exercise-induced ischemia,[3] and improve quality of life[4] in patients with symptomatic stable angina. Enhanced external counterpulsation was cleared for marketing by the Food and Drug Administration in 1995 for use in stable and unstable angina, acute myocardial infarction, and cardiogenic shock, and in 2002 for use in congestive heart failure. The Center for Medicare and Medicaid services approved coverage of EECP in 1999 for use in patients with angina refractory to maximal medical therapy and not readily amenable to percutaneous and/or surgical coronary revascularization.

The physiologic mechanism of benefit with EECP remains unclear. Proposed mechanisms have included promotion of coronary artery collateral development, angiogenesis, a training-like effect, and improved endothelial function.[5,6] Each of these possible mechanisms remains unproven. We hypothesized that treatment with augmented diastolic aortic pressure may modulate the

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carotid baroreceptors, resulting in an improved balance of coronary autonomic tone. If sympathetic tone to the coronary vascular bed is reduced, coronary vasodilation may result in improved coronary blood flow and enhancement of coronary collateral flow.

Heart rate variability (HRV) has been extensively studied as a noninvasive marker of autonomic tone,[7,8] and HRV has been shown to provide prognostic data in post–myocardial infarction[9-11] and heart failure patients.[12] Other cardiac interventions, such as β-blockers[13,14] and biventricular pacing,[15] have shown improvements in autonomic tone in patients with ischemic heart disease. We sought to test the hypothesis that EECP may improve autonomic function. We performed a prospective, multicenter cohort study involving serial ambulatory electrocardiographic Holter monitor recordings on patients before and after EECP therapy to measure changes in the time- and frequency-domain measures of HRV.

Methods

Study patients

This prospective, multicenter cohort study enrolled adult subjects undergoing EECP for refractory angina. Patients were recruited from 4 EECP centers in the United States. All patients had chronic stable angina due to coronary artery disease diagnosed by coronary angiography or noninvasive echocardiographic or scintigraphic stress testing. Exclusion criteria included sinus node dysfunction due to sick sinus syndrome, atrial fibrillation, supraventricular tachycardia, bradycardia requiring pacemaker therapy, heart transplantation, coronary revascularization within 6 months, or prior EECP treatment. Any patient with a contraindication to EECP was not enrolled, including decompensated heart failure, moderate-to-severe aortic insufficiency, myocardial infarction within 2 weeks, frequent ventricular ectopy (>10 premature ventricular complexes per minute), symptomatic peripheral vascular disease, uncontrolled hypertension (>180/110 mm Hg), pregnancy, or bleeding diathesis.

Study design

Medication changes were discouraged during the study period. Although medication class use was recorded, the doses of medications were not recorded. Within 1 week before EECP, subjects underwent a 48-hour Holter monitor recording using the Rozinn 151 cassette-based recorder (Biomedical Systems, St Louis, MO). Patients then underwent a 35-hour course of EECP therapy, consisting of daily 1-hour treatment sessions, 5 days per week, over a total of 7 weeks. Patients then underwent repeat 48-hour Holter recordings immediately upon finishing the 35-hour course of EECP, and again 1 month later. The study protocol was approved by the institutional review boards at each of the 4 study sites, and all subjects provided written informed consent.

Holter recording analysis

A Holter technician blinded to any clinical data or the timing of the recorder performed the quantitative analysis using the DelMar model 563 scanner at a 128-Hz sampling rate from the analog tape (Biomedical Systems). An interpolation function checked each interval in the analysis beat stream against the next interval in the stream to determine if a condition warranting beat interpolation exists. These conditions may exist because of the removal of nonnormal beats or artifact from the beat stream. Ectopic beats and artifact areas were interpolated after meeting a qualifying interpolation ratio threshold of more than 1.8 times the preceding RR interval. The SD of all normal-to-normal intervals (SDNN; milliseconds), SD of the averages of normal-to-normal intervals in all 5-minute segments (milliseconds), and the square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals (milliseconds) were assessed for the time-domain analyses. Daytime (7:00 AM-10:00 PM) and nighttime (10:00 PM-7:00 AM) frequency-domain analyses were performed by averaging the mean of the power (square milliseconds) in the low- (0.04-0.15 Hz) and high-frequency (0.15-0.40 Hz) ranges. The frequency-domain variables were recorded in 5-minute intervals and then averaged each hour. The normalized low-frequency power was defined as (low × 100)/(low + high).

Statistical analysis

The statistical analysis includes only those patients who completed EECP therapy and the 3 Holter tests. Data are presented as percentages for categorical variables or as mean values and SDs for continuous variables. Repeated-measures analysis of variance was used to assess changes in Holter values over time at baseline, post-EECP, and at 1 month. For repeated-measures skewed data, the Friedman statistic was used. Pairwise *t* testing was used to compare changes from baseline to post-EECP, and baseline to 1 month. A statistical multiple comparison procedure was not used in analyzing these pilot study results. Multivariable linear regression was used to identify predictors of SDNN. The sample size was calculated using the following variables: 22 participants had a 90% power to detect a 20% change in the mean time-domain measure of HRV from baseline to post-EECP with a 2-tailed α of .05. Two-tailed *P* values of less than .05 were defined as significant.

Results

Baseline characteristics

Of the 27 patients enrolled in the study, 24 patients completed the full course of EECP and the Holter studies at the 3 time points, thus forming the study cohort for this analysis. The baseline demographic and clinical characteristics are presented in Table 1 and are typical of patients currently undergoing treatment with EECP for chronic angina. Nine patients (38%) were older than 65 years. Two thirds of the patients had class III angina, whereas one third had class IV angina. Diabetes was reported in 10 patients and heart failure in 6 patients. Only one of the patients with heart failure also had diabetes. None of the patients were considered suitable candidates for interventional revascularization. Cardiac medications included β-blockers (88%), angiotensin-converting enzyme inhibitors (65%), angioten-

Table 1
Baseline demographics and clinical characteristics (n = 24)

Variable	Value
Age ± SD (y)s	62 ± 10
Male, n (%)	17 (71%)
Multivessel coronary disease, n (%)	18 (76%)
Hypertension, n (%)	21 (88%)
Dyslipidemia, n (%)	21 (88%)
Diabetes, n (%)	10 (44%)
Heart failure, n (%)	6 (25%)
LVEF ≤40%, n (%)	5 (21%)
Current smoking, n (%)	3 (13%)
Prior PCI, n (%)	21 (88%)
Prior CABG, n (%)	15 (63%)
Prior myocardial infarction, n (%)	15 (63%)

LVEF indicates left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.

sin receptor blockers (9%), calcium channel blockers (52%), and hypolipidemic agents (96%).

Clinical response to EECP

The mean duration of treatment was 37 ± 5 hours of EECP treatment. There were no significant adverse events during the EECP treatment course or in the 1-month period after treatment. After EECP, 5 patients were free of angina, 16 (67%) had class I to II angina, 2 had class III, and 1 subject had class IV angina. The number of weekly anginal attacks decreased by 9.1 ± 7.9 episodes after EECP ($P <$ .001). Twenty-two patients (91%) decreased their anginal severity by 1 class or more after EECP. There were no significant changes in the use of different classes of cardiac medication after EECP. During the study period, β-blocker use decreased from 90% to 86%, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker use increased from 70% to 77%, long-acting nitrate use decreased from 90% to 79%, and hypolipidemic agent use increased from 90% to 100% (all P = not significant) comparing baseline to 1 month post-EECP.

Standard Holter outcomes

For each of the three 48-hour Holter recordings, at least 47 hours were included in the analysis for the artifact-free data analysis. The mean, minimum, and maximal heart rates were unchanged in comparing the 3 Holter time points. The mean number of premature atrial complexes and episodes of supraventricular tachyarrhythmias was unchanged. There was no change in the number of premature ventricular complexes per hour: median of 0.48 (interquartile range, 0.10-1.5) at baseline, median of 0.48 (interquartile range, 0.03-3.2) post-EECP, and median of 0.53 (interquartile range, 0.08-4.4) at 1 month (P = .73). There were no changes in the incidence of ventricular couplets or nonsustained ventricular tachycardia between the 3 Holter studies. There were no episodes of second- or third-degree atrioventricular block observed.

One patient had ST-segment depression during the Holter recordings. This patient had ST-segment depression episodes in each of his 3 Holter tests, with no significant change in the duration or severity of the ST-segment depression episodes after EECP.

Time-domain measures of HRV

Overall, SDNN was 101 ± 27 at baseline, 106 ± 33 immediately post-EECP, and 102 ± 31 at 1 month (P = .53; Table 2, Fig. 1). Likewise, there were no significant changes in averages of normal-to-normal intervals in all 5-minute segments (90 ± 26 at baseline, 91 ± 35 post-EECP, and 93 ± 33 at 1 month; P = .62) or the square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals (21 ± 7 at baseline, 24 ± 9 post-EECP, and 21 ± 6 at 1 month; P = .81).

Baseline SDNN was lower for those with heart failure and for those with diabetes mellitus compared to those without (Table 2). Among the subgroup with heart failure, there was improved SDNN immediately after EECP (101 ± 26) compared to baseline (81 ± 27; P = .02). However, the SDNN returned to the baseline value at 1 month. A similar effect was seen with those patients younger than 65 years. There was no difference in SDNN before or after EECP based on either baseline or post-EECP angina class. A multivariable analysis using a general linear model showed diabetes and heart failure to be statistically significant independent predictors of lower SDNN at all time points.

Table 2
Time-domain measures of HRV using the SDNN (milliseconds)

Group	n	Baseline	Post-EECP	1 mo	P^a	P^b	P^c
All patients	24	101 ± 27	106 ± 33	102 ± 31	.53	.27	.82
Age <65 y	15	97 ± 30	110 ± 35	100 ± 31	.08	.02	.57
Age ≥65 y	9	107 ± 19	100 ± 31	105 ± 33	.77	.45	.81
No diabetes	14	108 ± 26	117 ± 28	109 ± 34	.18	.06	.75
Diabetes	10	90 ± 26	85 ± 24	90 ± 25	.71	.43	.95
No heart failure	18	107 ± 26	108 ± 36	107 ± 33	.99	.89	.98
Heart failure	6	81 ± 27	101 ± 26	86 ± 22	.12	.02	.53

MI indicates myocardial infarction.

[a] P value for repeated-measures analysis of variance across the 3 time points.

[b] P value for paired t test immediate post-EECP to baseline.

[c] P value for paired t test 1 month post-EECP to baseline.

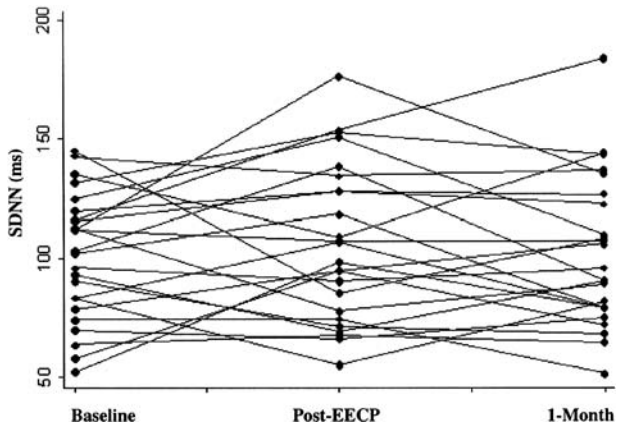

Fig. 1. Time-domain SDNN (milliseconds) at baseline, post-EECP, and at 1 month.

Frequency-domain measures of HRV

In the total cohort, the normalized daytime power in the low-frequency range had a modest, nonstatistically significant increase after EECP, and the increase was mainly maintained out to 1 month. A similar pattern was seen in the normalized low-frequency/high-frequency ratio (Table 3; Fig. 2A). There were no significant changes in the nighttime normalized frequency-domain measures of HRV.

Diabetic individuals had lower normalized low-frequency daytime power compared to those without diabetes at each of the 3 time points ($P < .05$; Table 3). In diabetic individuals, there was a significant increase in the daytime normalized low-frequency power ($P = .016$) and the low-to-high frequency ratio ($P = .053$) from baseline to post-EECP (Fig. 2B). There were no significant differences in the frequency-domain measures of HRV in those with heart failure (Fig. 2C).

Discussion

In this study, EECP was associated with improved anginal frequency and severity. Although there was no overall effect on autonomic tone by the time-domain HRV measures, patients younger than 65 years and those with heart failure had a significant increase in HRV immediately after EECP. Diabetic individuals had a significant increase in the low-frequency domain HRV measures immediately after EECP, whereas those with heart failure had no significant change in the frequency-domain HRV measures. The absence of a significant overall change in the time- or frequency-domain HRV measures suggests that improved autonomic tone is unlikely to play a significant role in symptom relief after EECP. It is possible that patient subsets such as those with diabetes or heart failure may have improved HRV after EECP.

Heart rate variability provides a noninvasive measure of sympathetic tone and vagal modulation of normal beat-to-beat intervals.[7,8,16] Increased sympathetic signaling is reflected by a decrease in HRV and is associated with a poor prognosis and increased adverse cardiac events in patients with cardiovascular disease and the general population.[9-12] Interventions used in the management of cardiovascular disease such as β-blockers,[13,14] biventricular pacing,[15] digoxin,[17] and exercise[18] increase HRV. There remains controversy and inconsistent results regarding the effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on HRV.[19-21]

Enhanced external counterpulsation causes significant increase in the central aortic diastolic pressure and a reduction in central aortic systolic pressure.[22] Such changes may be associated with changes in autonomic tone.[23] We hypothesized that EECP therapy may improve autonomic modulation, manifested as an increase in the time-domain measures of HRV. Our data do not support this hypothesis. However, we did observe an increase in daytime normalized low-frequency power and a decrease in normalized high-frequency power from the frequency-domain HRV analysis in diabetic individuals. Studies have shown that low-frequency HRV reflects primarily sympathetic modulation,[24] whereas high-frequency HRV reflects parasympathetic modulation.[25] A recent study has demonstrated that lower levels of daytime normalized high-frequency HRV is associated with a reduced mortality rate in patients after myocardial infarction.[26] The observed reduction in the normalized high-frequency HRV measures after EECP may be associated with improved outcomes in these patients. These observations are based on a cohort of patients with preserved HRV at baseline and should not be generalized to those with abnormally depressed HRV.

There are several reasons that may have limited our ability to detect a change in the time-domain assessment of HRV. First, β-blockers were prescribed in 88% of the study subjects. This high rate of β-blockers may have reduced sympathetic signaling such that further improvement with EECP was not easily appreciated. β-Blockers are associated with increased HRV in healthy subjects,[27] patients with heart failure,[28,29] those with recent and remote myocardial infarction,[30-32] and those with stable chronic coronary artery disease.[33]

Second, improvements in autonomic tone after EECP therapy may be difficult to achieve in study subjects with HRV similar to that observed in the general population. The mean SDNN in this study cohort (101 milliseconds) is similar to that of a cohort of 2501 patients followed in the Framingham study

Table 3
Normalized frequency-domain measures of HRV for entire cohort (n = 24), the diabetic cohort (n = 10), and the heart failure cohort (n = 6)

Variable	Daytime			*P*	nighttime			*P*
	Baseline	Post-EECP	1 mo		Baseline	Post-EECP	1 mo	
Entire cohort (n = 24)								
Normalized LF	59 ± 17	63 ± 17	64 ± 12	.28	56 ± 18	58 ± 14	59 ± 14	.52
LF/HF ratio	2.7 ± 1.9	3.1 ± 2.0	3.0 ± 1.9	.41	2.6 ± 1.6	2.6 ± 1.6	2.5 ± 1.2	.91
Diabetic cohort (n = 10)								
Normalized LF *	51 ± 16**	59 ± 9**	57 ± 9**	.08	49 ± 21	56 ± 13	55 ± 14	.23
LF/HF ratio***	1.7 ± 0.9**	2.1 ± 0.7**	1.9 ± 0.7**	.20	1.9 ± 1.5	2.2 ± 0.9	2.2 ± 1.1	.70
Heart failure cohort (n = 6)								
Normalized LF	55 ± 21	65 ± 15	62 ± 16	.41	54 ± 20	56 ± 19	61 ± 14	.66
LF/HF ratio	2.3 ± 1.5	3.5 ± 2.1	2.9 ± 1.8	.33	2.3 ± 1.7	2.8 ± 2.5	2.8 ± 1.3	.76

LF indicates low frequency; HF, high frequency.

* $P = .016$ (daytime LF from baseline to post-EECP) and $P = .053$ (from baseline to 1 month).

** $P < .05$, testing diabetic vs nondiabetic patients.

*** $P = .051$ (daytime LF/HF from baseline to post-EECP) and $P = .19$ (from baseline to 1 month).

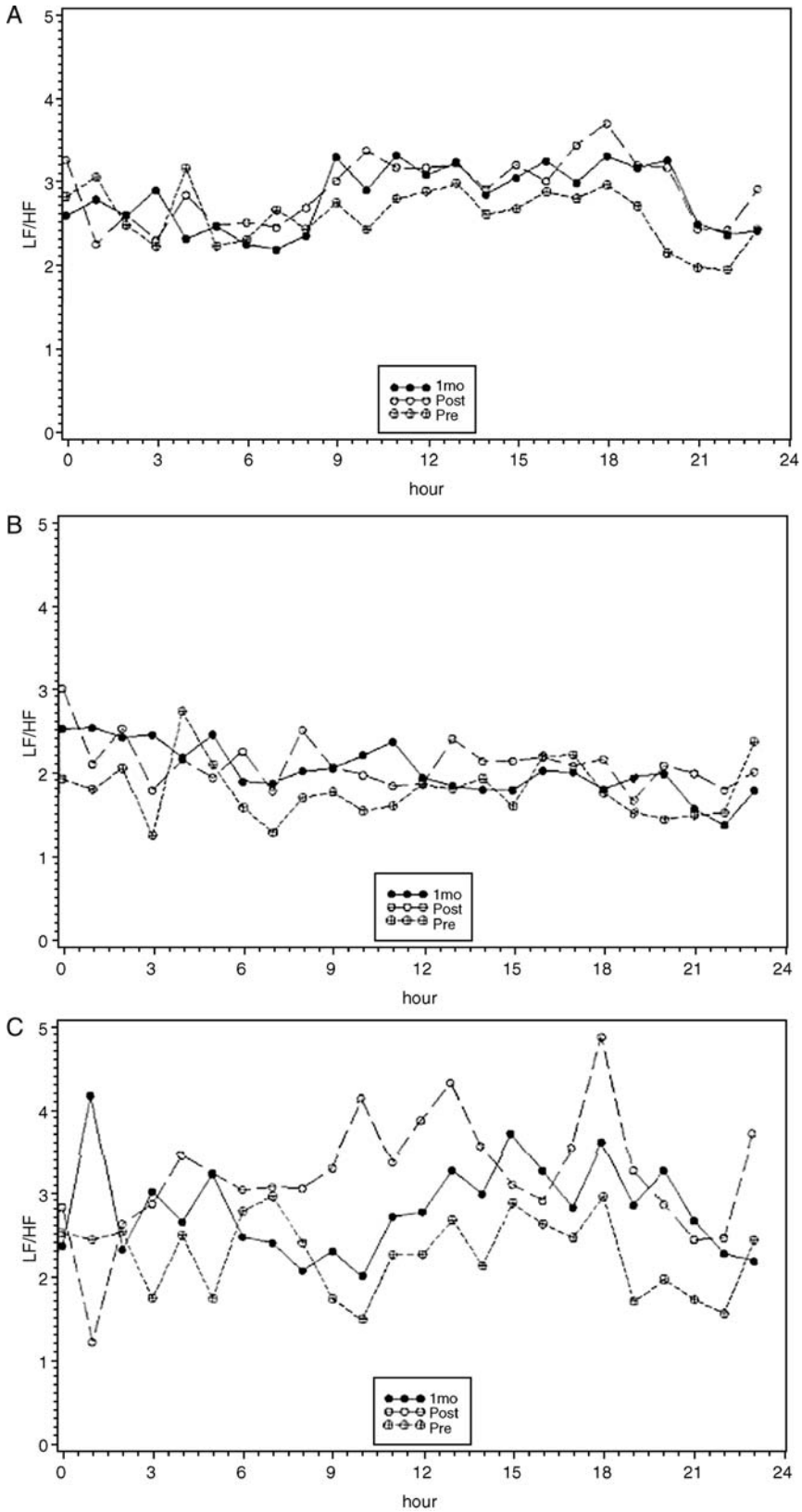

Fig. 2. Frequency-domain low-to-high frequency ratio measure of HRV for the entire cohort (A), those with diabetes (B), and those with heart failure (C).

measured from a mean analysis time of 94 minutes (91 milliseconds in men, 86 milliseconds in women).[34] A high SDNN of more than 100 milliseconds is associated with favorable outcomes.[7,35] Yi et al[36] performed 24-hour Holter monitors on 64 patients with dilated cardiomyopathy. An SDNN of less than 50 milliseconds was associated with progression of heart failure and reduced left ventricular performance. In a study of 433 patients with class I to III heart failure symptoms, an SDNN of less than 50 milliseconds was associated with 51% mortality at 482 days follow-up, whereas

an SDNN of more than 100 milliseconds was associated with only a 6% mortality rate.[37] Other investigators have consistently observed that SDNN of less than 100 milliseconds in patients with heart failure is independently associated with adverse cardiac event rates.[38,39]

There are several limitations to this study. First, the sample size is relatively small. We did recalculate the sample size required to detect a 20% improvement in the SDNN using our observed SD of 27 milliseconds. Using a 2-sided α of .05, this study had a 95% power to detect this change from the 24 study subjects. Next, we may have decreased our ability to detect improved HRV in this population of patients with a normal HRV before EECP. The use of the DelMar model 563 Holter scanner and the beat detection software may have limitations in the accuracy of uniform beat detection. The use of the 1.8 qualifying interpolation ratio threshold may have removed important heart rate pattern information. This study was not powered to assess changes in mortality, heart failure hospitalization, and myocardial infarction.

Conclusions

Enhanced external counterpulsation decreased the frequency and severity of angina in patients with stable chronic coronary artery disease without measurable changes in the time-domain measures of HRV. Patients younger than 65 years and those with heart failure had improved time-domain HRV immediately after EECP. In the total cohort, there was no significant change in the frequency-domain measures of HRV. In diabetic individuals, the normalized low-frequency domain increased after EECP. These changes did not persist 1 month later. Increased low-frequency domain power has been associated with improved mortality in myocardial infarction survivors. Because of the absence of improvement in the time- and frequency-domain HRV measures in the total cohort, it is unlikely that the antianginal benefits of EECP are attributable to improved autonomic tone.

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