

Enhanced external counterpulsation improves systolic blood pressure in patients with refractory angina

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Background Enhanced external counterpulsation (EECP) is a noninvasive treatment of patients with refractory angina. The immediate hemodynamic effects of EECP are similar to intra-aortic balloon pump counterpulsation, but EECP's effects on standard blood pressure measurements during and after treatment are unknown.

Methods We evaluated systolic blood pressure (SBP) and diastolic blood pressure (DBP) for 108 consecutive patients undergoing EECP. Baseline SBP, DBP, and heart rate were compared for each patient before and after each EECP session, at the end of the course of EECP, and 6 weeks after the final EECP session.

Results One hundred eight patients (mean age 66.4 ± 11.2 years, 81% male) completed 36.5 ± 5.1 EECP sessions per patient. Overall, based on 3,586 individual readings, EECP resulted in a decrease in mean SBP of 1.1 ± 15.3 mm Hg at the end of each EECP session ($P < .001$), 6.4 ± 18.2 mm Hg at the end the course of EECP ($P < .001$), and 3.7 ± 17.8 mm Hg 6 weeks after the final EECP session ($P = .07$), with no significant change in DBP or heart rate. Stratifying by baseline SBP, a differential response was demonstrated: SBP increased in the 2 lowest strata (<100 mm Hg and $101-110$ mm Hg) and decreased in the remaining strata ($P < .001$). Stratified differences were sustained after individual EECP sessions, at the end of the course of EECP, and 6 weeks after the final EECP session and were independent of changes in cardiovascular medications.

Conclusions Enhanced external counterpulsation improved SBP in patients with refractory angina. On average, EECP decreased SBP during treatment and follow-up; but for patients with low baseline SBP (<110 mm Hg), EECP increased SBP. The improvements in SBP may contribute to the clinical benefit of EECP. (*Am Heart J* 2008;156:1217-22.)

Enhanced external counterpulsation (EECP) is an approved treatment for patients with coronary artery disease (CAD) and Canadian Cardiovascular Society (CCS) class III to IV angina.¹ Enhanced external counterpulsation consists of sequential inflation of 3 sets of pneumatic cuffs on the lower extremities where inflation is synchronized with the onset of diastole and deflation occurs at the onset of systole.² Clinical benefits of EECP include reduction in CCS angina class, increased time to exercise-induced ischemia, decreased nitroglycerin use, and better quality of life.²⁻⁴ Precise mechanisms accounting for the clinical benefits of EECP are not completely understood but include improved endothelial function, reduced aortic impedance, enhanced coronary artery collateral blood flow, and improved hemodynamics.^{2,5,6} The immediate hemodynamic

effects of EECP are similar to intra-aortic balloon pump counterpulsation.⁷ Standard blood pressure measurements during and after EECP have not been formally studied. Clinically, we observed that patients undergoing EECP experienced a decrease in blood pressure during the treatment. Therefore, our hypothesis was EECP therapy would lower blood pressure and we systematically investigated the effects of EECP on standard blood pressure measurements during the course of therapy and at 6-week follow-up.

Methods

We reviewed records of 108 consecutive patients who completed at least 30 EECP sessions for refractory angina (CCS class III-IV) with or without heart failure (New York Heart Association class II-III) at Hennepin County Medical Center and the Minneapolis Heart Institute at Abbott Northwestern Hospital (both in Minneapolis, MN). Clinically stable patients were eligible for EECP if they had significant coronary artery disease with (1) limited or no conventional revascularization option and (2) ongoing angina despite optimal medical therapy. Exclusions were acute coronary syndrome within 4 weeks; cardiac catheterization within 2 weeks; clinically significant valvular heart disease; acute myocarditis; presence of abdominal aortic aneurysm and/or severe peripheral arterial disease; $>1+$ pretibial

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Submitted April 22, 2008; accepted July 31, 2008.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2008.07.024

edema; history of deep venous thrombosis, phlebitis or stasis ulcer; arrhythmia that would interfere with EECF triggering; and pregnancy. The study satisfied the exemption from informed consent for institutional review boards at both institutions.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were obtained before the first EECF session (baseline), before and at the end of each EECF session, after the final EECF session, and at 6 weeks after the final EECF session. Enhanced external counterpulsation technicians obtained blood pressure measurements with standard calibrated sphygmomanometers (handheld) and determined HR by assessing the radial pulse. Canadian Cardiovascular Society angina and New York Heart Association class were determined by the same physician-investigator (B.A.B. and T.D.H.) at each institution at baseline, after the final EECF session, and 6 week follow-up.

Data were analyzed by stratifying patients according to baseline SBP into the following subgroups: ≤ 100 mm Hg ($n = 16$), 101 to 110 mm Hg ($n = 26$), 111 to 120 mm Hg ($n = 20$), 121 to 130 ($n = 27$), 131 to 140 ($n = 7$), and ≥ 141 mm Hg ($n = 12$); and baseline DBP into the following subgroups: ≤ 60 mm Hg ($n = 37$), 61 to 70 mm Hg ($n = 39$), 71 to 80 mm Hg ($n = 22$) and ≥ 81 mm Hg ($n = 10$). Blood pressure ranges for each stratum were selected before analyzing the overall effects of EECF therapy on blood pressure.

Cardiovascular medications were recorded at baseline, at each EECF session, at the completion of a course of EECF, and 6 weeks after the final EECF session by the EECF technician. Medications of interest included long-acting nitrates, β -blockers, calcium channel blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, vasodilators, and diuretics. Dose changes as well as the addition or discontinuation of cardiac medications were documented. To assess whether changes in blood pressure during EECF resulted in clinically necessary adjustments in cardiovascular medications, we performed regression analyses. Regression analyses were also performed with respect to age, gender, baseline weight, left ventricular ejection fraction (LVEF), and the interaction of covariates.

Continuous data are expressed as mean \pm SD, and non-continuous variables are presented as percentages. Analysis of variance with pairwise multiple comparisons (Student-Newman-Keuls method) assessed the significance of mean changes per session, from baseline to end of treatment, and from baseline to 6-week follow-up, and was supplemented by linear regression analyses. Normality and equal variance tests were performed as a part of the analysis of variance. Changes in SBP and DBP per session were compared with a paired Student *t* test. Proportions were compared by χ^2 analyses. All *P* values were considered statistically significant when $\leq .05$. SigmaStat software (version 2.0, Jandel Scientific Software, San Rafael, CA) was used for all analyses.

Results

The baseline characteristics were typical for patients with refractory angina undergoing EECF⁸ (Table I). A total of 3,586 SBP, DBP, and HR readings were analyzed. The average SBP at baseline was 120.4 ± 19.3 (range 88-192) mm Hg, baseline DBP was 66.0 ± 10.4 (range 44-96) mm Hg, and baseline HR was 66.2 ± 10.6 (range 40-103) beat/min.

Table I. Baseline characteristics for 108 patients undergoing EECF for refractory angina

Demographic parameter	Baseline value
Age, years \pm SD (range)	66.4 \pm 11.2 (35-90)
Male, no. (%)	87 (81)
Systolic hypertension, no. (%)	79 (74)
Dyslipidemia, no. (%)	93 (85)
Multivessel Disease, no. (%)	94 (87)
Baseline CCS angina class	3.3 \pm 0.6
Prior revascularization, no. (%)	104 (96)
CABG alone, no. (%)	22 (20)
≥ 1 PCI alone, no. (%)	23 (21)
CABG and PCI both, no. (%)	59 (55)
Peripheral vascular disease, no. (%)	24 (22)
Heart failure, no. (%)	19 (17)
Ejection fraction, % \pm SD (range)	48.5 \pm 12.5 (19-76)
EECF treatment sessions completed	36.5 \pm 5.1

CABG, Coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Individual EECF sessions

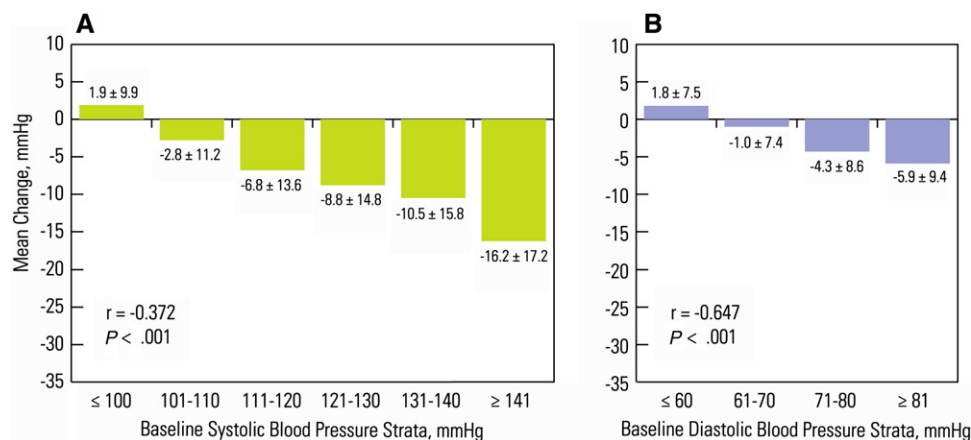
Overall, there was a 1.1 ± 15.3 mm Hg mean decrease in SBP after an individual treatment session ($P < .001$). Systolic blood pressure decreased ≥ 20 mm Hg in 10.9% of sessions. Systolic blood pressure was <100 mm Hg before EECF in 20.9% of sessions and after EECF in 23.2% of sessions ($P < .001$).

Enhanced external counterpulsation significantly lowered SBP per session in each baseline stratum from 101 to 110 mm Hg to ≥ 141 mm Hg, whereas in the lowest stratum (≤ 100 mm Hg), a rise in SBP was observed (Figure 1, A). There was a significant difference between each pair of strata ($P < .05$) except the 121 to 130 mm Hg and the 131 to 140 mm Hg strata ($P = .066$). Linear regression of each person's average per session change in SBP on baseline SBP was statistically significant ($r = 0.372$, $P < .001$). This association cannot simply be regression to the mean. Each person's baseline SBP is the measure taken before the first EECF session: it affects only the first session's change in SBP pre to post, which is averaged with many other per-session SBP changes to produce that person's average per-session change in SBP.

Overall, DBP did not decrease for individual treatment sessions (mean change 0.2 ± 7.8 mm Hg, $P = .3$). However, DBP decreased ≥ 10 mm Hg in 11% of sessions. DBP was <60 mm Hg before EECF in 30.4% of sessions and after EECF in 32.9% of sessions ($P < .001$). Similar to SBP, DBP increased in the lowest baseline stratum and decreased in the other strata (Figure 1, B). There was a significant difference between the mean values of each pair of strata ($P < .05$). Linear regression of the individual changes in DBP on baseline DBP was statistically significant ($r = 0.647$, $P < .001$).

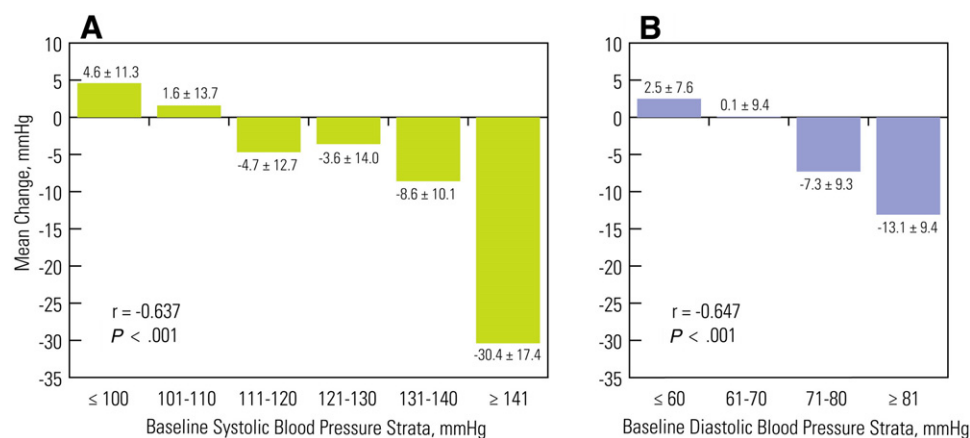
Overall, HR did not change (-1.1 ± 5.5 beat/min, $P = .3$) with each session. Heart rate was also not significantly changed after accounting for SBP and DBP strata ($P = .9$ and $P = .5$, respectively).

Figure 1



Changes in blood pressure after individual EECp sessions, stratified by baseline blood pressure.

Figure 2



Changes in blood pressure after completing a course of EECp, stratified by baseline blood pressure.

After completion of EECp

Overall, there was a 6.4 ± 18.2 mm Hg mean decrease in SBP after a course of EECp, resulting in a mean SBP of 114.0 ± 16.0 (86-150) mm Hg ($P < .001$). However, SBP increased in the 2 lowest baseline SBP strata (≤ 100 and 101-110 mm Hg) and decreased in the remainder of the strata (Figure 2, A). Comparing baseline SBP strata, there were significant ($P < .05$) differences between ≤ 100 mm Hg and ≥ 141 mm Hg, 101 to 110 and ≥ 141 mm Hg, 111 to 120 and ≥ 141 mm Hg, 121 to 130 and ≥ 141 mm Hg, and 131 to 140 and ≥ 141 mm Hg strata. Linear regression of each person's change in SBP, baseline to completion of EECp, on baseline SBP was statistically significant ($r = 0.637$, $P < .001$).

Overall, there was a trend toward decreased DBP with a mean reduction of 1.8 ± 10.1 to 64.3 ± 9.7 (46-92) mm Hg ($P = .07$). The DBP changes were similar to those for SBP

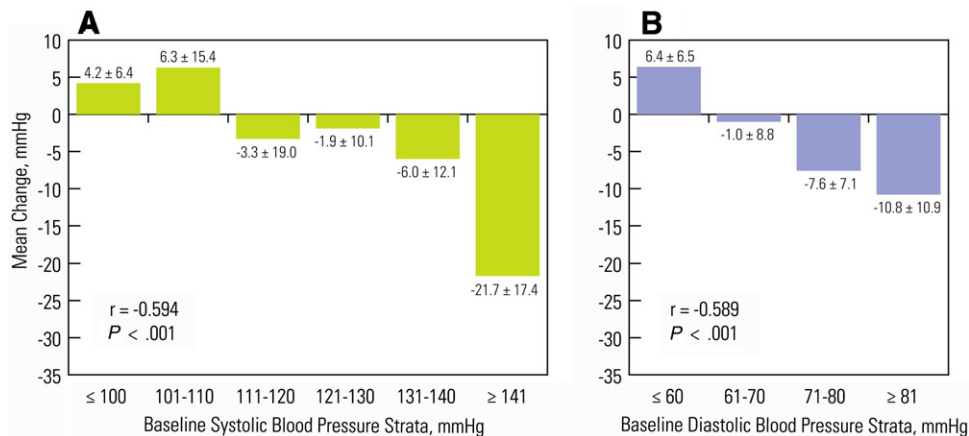
with an increase in the 2 lowest baseline strata and a reduction in the other strata (Figure 2, B). Comparing baseline DBP strata, there were significant differences between the mean values of each pair of strata ($P < .05$), except for ≤ 60 and 61 to 70 mm Hg strata, and 71 to 80 and ≥ 81 mm Hg strata. Linear regression of the individual changes in DBP on baseline DBP was statistically significant ($r = 0.647$, $P < .001$).

Overall, HR did not change (-0.5 ± 9.0 beat/min, overall mean 66.8 ± 9.9 [range 50-93] beat/min, $P = .5$). Heart rate was also not significantly changed after accounting for SBP and DBP strata ($P = .7$ and $P = .9$, respectively).

Six weeks after EECp

Six-week follow-up (41 ± 5.2 days) was available for 94 patients (87%). Overall, the mean SBP was 117.7 ± 17.0

Figure 3



Changes in blood pressure 6 weeks after EECP, stratified by baseline blood pressure.

Table II. Distribution of changes in cardiovascular medications (baseline to 6-week follow-up) and mean baseline LVEF

	≤100 mm Hg	101-110 mm Hg	111-120 mm Hg	121-130 mm Hg	131-140 mm Hg	≥141 mm Hg	P
Δ Meds (% patients)	31.3	46.2	35.0	45.0	28.6	33.3	.975
↑ Meds (% patients)	12.5	30.8	15.0	25.0	14.3	16.7	.371
↓ Meds (% patients)	18.8	15.4	20.0	20.0	14.3	16.7	.999
No Δ meds (% patients)	68.8	53.8	65.0	55.0	71.4	66.7	.994
BL LVEF (% ± SD)	49.2 ± 13.9	45.5 ± 23.1	50.3 ± 10.1	51.0 ± 13.3	46.1 ± 11.2	48.5 ± 10.3	.856

Δ represents change; ↑ increase; ↓, decrease. BL, Baseline.

(90-166) mm Hg, 3.7 ± 17.8 mm Hg lower than baseline ($P = .07$). The mean DBP was 65.6 ± 9.5 (49-94) mm Hg, 0.8 ± 13.8 mm Hg lower than baseline ($P = .5$). The differential blood pressure effects observed at the end of a course of EECP were maintained at 6 weeks for both SBP and DBP (Figure 3, A and B).

Comparing baseline SBP strata, there were significant ($P < .05$) differences between ≤ 100 and ≥ 141 mm Hg, 101 to 110 and ≥ 141 mm Hg, 111 to 120 and ≥ 141 mm Hg, and 121 to 130 and ≥ 141 mm Hg. Linear regression of each person's change in SBP, baseline to 6 weeks, on baseline SBP was statistically significant ($r = 0.594$, $P < .001$).

Comparing baseline DBP strata, there were significant differences ($P < .05$) for all comparisons except for 71 to 80 and ≥ 81 mm Hg strata. Linear regression of the individual changes in each DBP on baseline DBP was statistically significant ($r = 0.589$, $P < .001$).

Overall, HR did not change (-1.3 ± 9.8 beat/min, overall mean 65.6 ± 9.5 [42-94] beat/min, $P = .3$). Heart rate was also not significantly changed after accounting for SBP and DBP strata ($P = .3$ for both).

Angina

After a course of EECP, patients experienced a significant reduction in mean CCS angina class (3.3 ± 0.6 to 2.0 ± 1.0 ,

$P < .0001$), and significantly fewer patients were CCS class III (25% compared to 62% at baseline) or class IV (7% compared to 37% at baseline) ($P < .001$). Improvements in angina were similar across SBP and DBP strata (range from -1.05 ± 0.78 to -1.31 ± 1.25 class, $P = .9$).

Independence of blood pressure changes

Univariate regression analyses showed no association of blood pressure changes with age, gender, baseline weight, LVEF, or medication changes, nor did a multivariate regression including all of these ($P > .12$ for all tests). Changes in cardiovascular medications and the distribution of the mean baseline LVEF across SBP strata are illustrated in Table II. Similar stratification of these 2 covariates by DBP did not yield any significant differences.

Discussion

In patients with refractory angina, EECP decreased SBP at the end of each EECP session, at the end of a course of EECP, and 6 weeks after the final EECP session. Diastolic blood pressure and HR were not significantly different. A differential response was demonstrated according to baseline SBP before initiation of EECP. Patients in the 2 lowest baseline SBP strata (< 110 mm Hg) before EECP

showed an increase in SBP that was sustained at the end of a course of EECP and at 6-week follow-up. Therefore, the major clinical implications of this study are as follows: (1) on average, EECP decreased systolic blood pressure over the course of therapy; (2) however, in patients with low baseline SBP (<110 mm Hg), EECP did not decrease SBP and appears to be safe; (3) improvement in SBP may contribute to the clinical benefit of EECP.

The precise mechanisms linking immediate hemodynamic effects to clinical benefit in EECP are incompletely understood. Intracoronary measurements during EECP show an increase in diastolic pressure and flow similar to an intra-aortic balloon pump,⁷ and diastolic augmentation has been proposed as a primary reason for clinical improvement through increased endothelial shear stress and stimulation of nitric oxide production. Both elevation of plasma nitric oxide and reduction of endothelin-1 have been demonstrated during EECP and up to 3 months after treatment.⁹ Enhanced external counterpulsation also inhibits intimal smooth muscle proliferation, a major feature of adverse vascular remodeling, by modifying shear stress.^{10,11} Increased endothelial shear stress produces circulating angiogenic growth factors, which have vasodilatory properties.¹² Both increased levels of vascular endothelial growth factor and enhanced angiogenesis have been shown after EECP in dogs.¹³ Finally, EECP has recently been shown to increase the number and colony-forming capacity of circulating endothelial progenitor cells,¹⁴ which contribute to improved vascular function in cardiovascular disease.¹⁵ Our results with standard blood pressure measurements may represent a physiologic response that integrates the above mechanisms, reflecting both improved endothelial function and vasoreactivity. It is important to emphasize that there was no significant change in HR at any time point during the study; therefore, a straightforward decrease in sympathetic tone (by lying supine) does not explain our observations.

Enhanced external counterpulsation has also been shown to enhance ventricular performance with an increase in both LVEF and cardiac index in patients after a course of EECP.¹⁶ These changes may be attributable to increased myocardial oxygen supply and decreased ventricular afterload. In our study, the increases in SBP and DBP for patients in the lowest baseline strata are intriguing. Prior invasive studies of hemodynamic responses to EECP included patients with higher mean SBP (114 ± 19 mm Hg) and DBP (71 ± 10 mm Hg) at baseline.⁷ To our knowledge, this study is the first to report longitudinal blood pressure changes in a group of patients undergoing EECP with baseline SBP <100 mm Hg and baseline DBP <60 mm Hg. In patients with heart failure, SBP less than 110 mm Hg correlates strongly with increased mortality in hospital¹⁷ and ambulatory¹⁸ settings. Underlying mechanisms responsible for improved blood pressure after EECP may correspond to improved outcomes; EECP improves functional capacity and quality

of life in subsets of patients with heart failure.¹⁹ Because pharmacological therapy is often maximized in refractory angina patients, both relative hypotension and hypertension can be clinically challenging. This study suggests that EECP may facilitate blood pressure control by increasing it in patients with relative hypotension and decreasing it in patients with relative hypertension.

There are several limitations to this study. First, no control group (patients treated for refractory angina not receiving EECP) is available for comparison. Second, because of the wide variety of cardiovascular medications, we chose to simplify adjustment as “increased” or “decreased” rather than try to detail the wide variety of medications adjustments. Notably, 61% of all patients had no medication changes during the study. Third, blood pressure assessment at 6-week follow-up was based on chart review from clinic visits and was available for only 94 (87%) of 108 patients. Finally, for changes from baseline to end of therapy or 6-week follow-up—but not average per-session blood pressure changes—we cannot entirely exclude that our results stratifying on baseline blood pressure represent regression to the mean. However, the association of blood pressure change with baseline is consistent for change per-session, at the end of EECP, and at 6-week follow-up. At a minimum, there is no evidence to suggest that patients with relative hypotension (SBP <110 mm Hg) had a decrease in blood pressure with EECP. This group of patients deserves further study in a larger prospective trial. Despite these limitations, these are the first available data on blood pressure change over the course of EECP therapy and in follow-up for patients with refractory angina.

In conclusion, EECP lowered SBP in patients with refractory angina. However, there was a differential effect on blood pressure depending on baseline SBP. The differential effect on blood pressure may represent favorable changes in cardiac output, endothelial function, and vasoreactivity that ultimately improve clinical outcomes.

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