Clin. Cardiol. 27, 689–692 (2004)

Enhanced External Counterpulsation Does Not Alter Arterial Stiffness in Patients with Angina

FRANCES DOCKERY, M.D., CHAKRAVARTHI RAJKUMAR, PH.D., CHRISTOPHER J. BULPITT, M.D., ROGER J. HALL, M.D.,*
JENS PEDER BAGGER, M.D.*

Section of Geriatric Medicine and *Department of Cardiology, Imperial College, Hammersmith Hospital, London, U.K.

Summary

Background: Enhanced external counterpulsation (EECP) is a noninvasive treatment for angina that acutely augments diastolic pressure and reduces cardiac afterload. However, the mechanism of the sustained clinical benefit seen with this therapy is not known.

Hypothesis: The study aimed to determine whether EECP leads to an improvement in arterial stiffness.

Methods: In all, 22 men and 1 woman with angina (age 63.6 ± 6.7 years, mean ± SD) were studied prior to and after 35 h of EECP therapy over 7 weeks. We measured carotid-radial (C-R) pulse wave velocity (PWV), and aortic augmentation index (AI) was derived from radial and carotid artery waveforms using applanation tonometry. Seventeen patients underwent treadmill exercise testing before and after the 7 weeks of EECP.

Results: After EECP therapy, despite a significant improvement in treadmill exercise time and a reduction in systolic and diastolic blood pressures, there was no significant change in any arterial stiffness parameters: Mean C-R PWV was 8.4 ± 0.8 m/s at baseline and 8.0 ± 1.2 m/s after 7 weeks of EECP, mean change: – 0.4, 95% confidence interval (CI): −1.0, + 0.2, p = 0.17. Mean radial-derived AI was 25.7 ± 10.4% before and 24.6 ± 10.8% after, mean change: + 1.1%, 95% CI: −2.3, + 4.5, p = 0.53. Median AI-carotid was 31.5% before and 28.7% after; median change: −0.5, interquartile range: −9.5, + 3.5, p = 0.32. Nineteen patients returned for 6-month recordings; neither blood pressure nor arterial stiffness readings were significantly different from baseline.

Conclusion: Enhanced external counterpulsation therapy does not significantly alter arterial stiffness. Other than an initial reduction in blood pressure, the sustained clinical benefit seen with this therapy is unlikely to be effected through alterations in arterial wall mechanical properties.

Key words: enhanced external counterpulsation, arterial stiffness, hemodynamics, augmentation index

Introduction

Enhanced external counterpulsation (EECP) is an effective, noninvasive therapy for refractory angina, resulting in reduced myocardial ischemia and increased exercise capacity.[1–3] The benefits seem to be sustained in some patients for up to 5 years.[4] There is much uncertainty surrounding the precise mechanism of both short-term and sustained clinical benefits seen with EECP. Studies to date mainly address the central effects; there may be increased coronary collateral vessel development resulting from diastolic augmentation and release of angiogenic growth factors.[5–7] Urano *et al*. demonstrated improved left ventricular diastolic filling following EECP.[3] Improved coronary[7] and, more recently, peripheral endothelial function have been demonstrated up to 1 month after therapy.[8] Left ventricular diastolic function and endothelial function are related to arterial stiffness,[9, 10] but no study to date has examined the effect of EECP on large artery stiffness. Arterial stiffness or compliance can be measured noninvasively by a number of methods, including pulse wave velocity (PWV) and pulse wave analysis.[11] The pulse wave travels faster in a stiffer artery, hence a higher PWV. Pulse wave analysis allows for measurement of the augmentation of the systolic pressure peak (the augmentation index [AI]) due to peripheral wave reflection. The speed of wave reflection is determined, at least in part, by aortic and large artery PWV. Increased arterial stiffness widens the pulse pressure, causing an increased left ventricle load and reduced coronary perfusion.[12, 13] Aortic PWV has been shown to be an independent marker of cardiovascular mortality in hypertensive subjects,[14] and both radial and aortic PWV are associated with the degree of coronary artery disease.[15, 16] It is important to note that arterial stiffness can be modified by several factors, including exercise and antihypertensive drugs.[17, 18] We hypothesized that repeated counterpulsation in EECP treatment would have a significant beneficial impact on arterial wall stiffness, which might contribute to the sustained clinical benefits seen with EECP. To this end we measured arterial stiffness in a group of patients with stable angina before and after a course of EECP treatment.

Address for reprints:

Jens Peder Bagger, M.D.
Department of Cardiology
Imperial College School of Medicine
Hammersmith Hospital
London W12 0NN, U.K.
e-mail: p.bagger@ic.ac.uk

Received: August 2, 2004
Accepted: October 1, 2004

Methods

This work was a side project of a clinical trial of EECP therapy effects on dobutamine-induced wall motion scores in a cohort of 26 subjects, methods and results of which are reported elsewhere.[19]

Briefly, consecutive patients referred to this hospital with medically refractory stable angina Canadian Cardiovascular Society (CCS) class II–IV, who were considered unsuitable for revascularization or declined this treatment, were invited to participate. Of the original 26 subjects who underwent dobutamine stress echo,[19] 23 also agreed to have arterial stiffness measures performed before and after treatment. Two further subjects who had EECP treatment and arterial stiffness readings but not a dobutamine stress echo were also included here, bringing our cohort to 25 subjects. All had angiographically confirmed coronary artery disease and/or a history of myocardial infarction. Exclusion criteria were myocardial infarction or revascularization (coronary artery bypass graft or balloon angioplasty) in the preceding 3 months, unstable angina, aortic insufficiency, hypertrophic cardiomyopathy, overt heart failure, atrial fibrillation, uncontrolled hypertension (systolic blood pressure [SBP] > 180 or diastolic blood pressure [DBP] > 110), aortic aneurysm, severe peripheral vascular disease, deep vein thrombosis, lower limb skin disorder, or bleeding diathesis. The study was approved by the Regional Ethics Committee and all patients gave written informed consent.

Enhanced External Counterpulsation Therapy

The EECP equipment (Vasomedical, Inc., Westbury, N.Y., USA) is described elsewhere.[2] Briefly, it consists of an air compressor, a computer console, three pressure cuffs for each leg, and a treatment table. Cuffs are inflated to 300 mmHg pressure sequentially from the calves upward at the onset of diastole. At the end of diastole, the cuffs are quickly deflated releasing the external pressure during systole. The sequence is synchronized with the cardiac cycle. Patients had 1 h of treatment daily for a total of 35 h. A finger plethysmograph was used to measure the diastolic augmentation (DA) ratio during EECP. The aim was to achieve a DA ratio of 1.5–2.0 which reflects improved hemodynamic effects.[20]

Arterial Stiffness Measures

Patients lay supine for the duration of the study. The average of three sitting brachial blood pressure readings (Omron 705CP) was taken just prior to the recordings. Two measures of arterial stiffness were used: PWV and AI. The Sphygmocor system (Atcor Medical, Sydney, Australia) was used for all recordings. Aortic AIs were derived using a generalized transfer factor from the radial and the carotid arterial pulse wave tracings as described previously.[21] Augmentation index is defined as the difference between the first and second systolic peaks of the arterial waveform expressed as a percentage of the pulse pressure. The waveforms were recorded by applanation tonometry using a micromanometer (Millar Instruments, Houston, Texas, USA). The probe is used to flatten the artery gently and the arterial waveform is recorded.

Carotid-radial PWV is calculated from transit distance / transit time. The transit time between electrocardiographic (ECG)-carotid pulse and ECG-radial pulse was recorded using a three-lead ECG and simultaneous arterial applanation tonometry as described previously.[17, 21] These times are subtracted automatically to give the carotid-to-radial pulse transit time (or time interval). Distances between these sites (sternal notch to carotid/radial artery) were measured as straight lines on the body surface and subtracted similarly.

Exercise Treadmill Test

Seventeen of the patients underwent standard Bruce protocol exercise treadmill test at baseline and on completion of the 7-week treatment period. Six patients were unable to exercise because of poor mobility. This took place just after the arterial stiffness readings on both occasions in all patients.

Statistical Analysis

The Statistical Package for Social Sciences for windows version 10.0 (SPSS, Inc., Chicago, Ill., USA) was used for all analyses. Paired Student's *t*-test was used to compare readings between visits 1 and 2. In the group in which 6-month readings were also taken, analysis of variance (ANOVA) was used to compare readings between the three visits. Analysis of covariance (ANCOVA) was used to adjust changes in arterial stiffness parameters for concomitant changes in blood pressure. Appropriate nonparametric tests were used for non-normally distributed data. Data are presented as mean ± standard deviation (SD), or median (range). Interquartile ranges rather than 95% confidence intervals (CI) are given for non-normally distributed data. A p value ≤ 0.05 was considered significant for all tests.

Results

Baseline Characteristics (Table I)

Two subjects did not complete EECP treatment, leaving 23 subjects for analysis. All subjects remained on the same medications throughout the 7-week period. The DA ratio taken at the start of the first session increased from 0.6 ± 0.5 at baseline to 1.4 ± 0.8 just prior to the final session ($p < 0.001$). Nineteen subjects were available for a 6-month visit (3 declined, 1 was an in-patient elsewhere). From the 7 to 24 week period, one subject was started on an angiotensin-converting enzyme inhibitor (ACEI), one subject had discontinued an ACEI, and one had discontinued a calcium-channel blocker.

Treadmill Exercise Test

In the 17 subjects who underwent this test on both visits, 13 (57%) had ≥ 1 mm ST-segment depression at baseline, and 14 (61%) did after EECP treatment ($p = 0.67$); however, there was

TABLE I Baseline patient characteristics (n = 23)

	No. (%)
Male	22 (96)
Age (mean ± SD years)	63.7 ± 6.7
Previous MI	17 (74)
Previous CABG	18 (78)
History of heart failure	5 (22)
Hypertension	8 (35)
Diabetes	8 (35)
Ex-smoker	8 (35)
Medications	
Beta blocker	14
Diuretic	8
Lipid-lowering drug	19
Nitrates	22
Aspirin	23
Calcium-channel blocker	19
Angiotensin-converting enzyme inhibitor	8

Abbreviations: SD = standard deviation, MI = myocardial infarction, CABG = coronary artery bypass graft.

a significant improvement in total exercise time (from 349 [164–540] at baseline to 416 [216–601] s after 7 weeks, median change 60, interquartile range 36, 114, p = 0.001).

Blood Pressure and Arterial Stiffness Readings (Table II)

Both brachial SBP and DBP blood pressures decreased significantly after 7 weeks of EECP (SBP from 138 ± 18 to 132 ± 20, mean 6 mmHg, 95% CI: 1, 12, p = 0.03; DBP from 79 ± 9 to 73 ± 10, mean 6 mmHg 95% CI: 2, 10, p = 0.01).

Despite the decrease in blood pressure, there was no significant change in any arterial stiffness parameters (Table II). The changes, though nonsignificant, in C-R PWV and AI-carotid were adjusted for the concomitant change in blood pressure using ANCOVA. The adjusted p value for C-R PWV was 0.52 and for AI-C it was 0.36.

A separate analysis of arterial stiffness data, including only those patients who improved on exercise treadmill test (n = 15), also failed to show any significant difference in any arterial stiffness results from baseline to 7 weeks (p ≥ 0.18 for all).

In the 19 subjects who presented for 6-month readings, arterial stiffness and blood pressure readings tended to return to baseline values (p ≥ 0.38 by ANOVA for all, Fig. 1). Systolic and diastolic blood pressures were no longer significantly different from baseline values (SBP: 139 ± 19 at baseline vs. 137 ± 20 mmHg at 6 months, p = 0.76, DBP: 78 ± 9 vs. 76 ± 10, p = 0.53 from ANOVA).

Discussion

This study demonstrates that effective EECP therapy in patients with refractory angina does not cause any significant alteration in arterial stiffness as measured by AI and radial PWV. Changes in arterial elasticity may take time to be effected, which is why we performed a 6-month reading in 19 of the 23 subjects; however, this also failed to show any change from baseline. The group achieved adequate diastolic augmentation and significant clinical improvement as measured by exercise treadmill test. Though unexpected, this is an interesting result in terms of understanding the mechanism of action of EECP. It would support the theory that the benefits are exerted solely thorough central cardiac effects including increased coronary collateral vessel development and coronary endothelial function, as much current evidence suggests,[3, 5–7] rather than through a concomitant improvement in central or peripheral arterial function. However, we did observe a significant decrease in blood pressure in our group at the end of the 7 weeks of EECP, although this was not reflected by any improvement in arterial stiffness measures. It is unclear why this decrease occurred; it may have been due to a nonspecific placebo effect for which we had no control group or, as suggested by Lawson *et al.*, due to a decrease in systemic vascular resistance (SVR).[22]

Masuda *et al.* attributed an increased nitric oxide release observed in their study following EECP to a possible improvement in peripheral endothelial function, but this was not

TABLE II Hemodynamic data; all values are mean ± SD or median (range)

	Baseline	7 Week	p Value
Brachial SBP (mmHg)	138 ± 18	132 ± 20	0.03
Brachial DBP (mmHg)	79 ± 9	73 ± 10	0.01
Pulse rate (beats/min)	63 ± 14	61 ± 12	0.25
C-R PWV (m/s)	8.4 ± 0.8	8.0 ± 1.2	0.17
AI—radial-derived (%)	25.7 ± 10.4	24.6 ± 10.8	0.53
AI—carotid-derived (%)	31.5 (11.5–55.5)	28.7 (7.5–46)	0.32

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, C-R = carotid-radial, PWV = pulse wave velocity. AI = aortic augmentation index, SD = standard deviation.

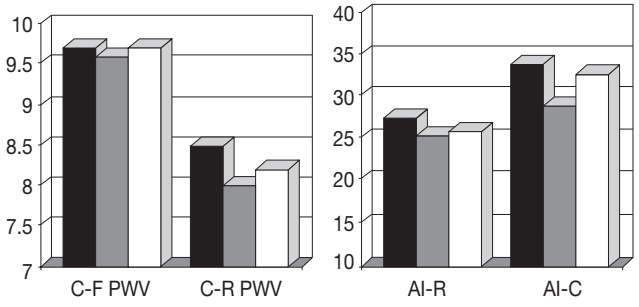

FIG. 1 Arterial stiffness measured in the 19 patients who had readings at baseline ■ and at 7 ■ and 24 □ weeks; p ≥ 0.38 for all by analysis of variance. C-R = carotid-radial, PWV = pulse wave velocity, AI-R = radial-derived aortic augmentation index, AI-C = carotid-derived aortic augmentation index.

measured directly.[7] More recently, Bonetti *et al.* did demonstrate an improvement in peripheral endothelial function that persisted up to 1 month after treatment.[8] Although related to endothelial function, arterial stiffness may vary in an endothelial-independent manner in different subjects.[23] On the other hand, several studies have demonstrated increased myocardial perfusion with associated release of endothelial growth factors, improved coronary endothelial function, and decreased neurohumeral factors, which may reflect improved ventricular hemodynamics.[3, 5–7] Hence, the bulk of the evidence to date suggests that EECP exerts its sustained clinical benefits through improvements in cardiac status, rather than benefitting the peripheral vascular system. Our study result supports this theory by failing to demonstrate any measurable change in central or peripheral arterial stiffness immediately or 4 months post completion of EECP therapy.

There are several limitations to this study: the group may have been too small to show any subtle improvement in arterial stiffness; however, with even fewer subjects, various interventional studies have shown significant changes in arterial stiffness using similar methods.[24, 25] In any case, a subtle change may not be clinically relevant and would be very unlikely to explain the sustained clinical benefits of EECP therapy. We did not have a measure of central arterial stiffness such as aorto-femoral PWV, but if there had been marked improvement, a significant change in AI would have been expected, although we cannot rule out this possibility. The aortic AI was derived using a transfer function applied to the radial or carotid pulse wave tracing, the validity of which has recently been questioned; however, there is a close linear correlation between the nontransformed and the derived values,[26] and our methodology was the same for all three visits with patients acting as their own controls.

Conclusion

Other than an initial decrease in blood pressure, the sustained clinical benefit seen with EECP is unlikely to be effected through alterations in mechanical properties of the arterial wall.

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