

Effects of Enhanced External Counterpulsation on Carotid Circulation in Patients with Coronary Artery Disease

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Key Words

Coronary artery disease • Carotid hemodynamics •
Enhanced external counterpulsation • Arterial stiffness •
Arterial resistance

Abstract

Background: Enhanced external counterpulsation (EECP) is a noninvasive method previously shown to improve measures of myocardial ischemia in patients with coronary artery disease. However, the concomitant effects of EECP on large and small arterial properties have been poorly examined. In a randomized controlled study, we investigated whether arterial stiffness and resistance of the carotid circulation are altered by EECP. **Methods:** Thirty patients with angiographically demonstrated coronary artery disease were randomized into two groups to receive either 'sham' or active EECP therapy for 35 1-hour sessions. The β stiffness index was calculated by the $\ln(P_s/P_d)/DD$ equation where P_s and P_d = systolic and diastolic blood pressure, and DD = the ratio between carotid pulse and diastolic diameter, measured by ultrasound sequential frames during the cardiac cycle. Carotid vascular resistance was calculated as the ratio between mean arterial pressure and mean common carotid blood flow. **Results:** No significant between-group differences

were seen in clinical characteristics or carotid hemodynamics at baseline. The β stiffness index and carotid vascular resistance were significantly reduced after 35 h of active EECP ($p < 0.01$), and the decrease was significantly different when compared with controls ($p < 0.05$ for β stiffness index and $p < 0.001$ for carotid vascular resistance). These reductions persisted after multiple covariate adjustment. **Conclusions:** This study suggests that EECP exerts clear arterial effects on large and small vessels of the carotid circulation. The combined effects on arterial stiffness and vascular resistance are of particular interest in cardiovascular disease involving reduction in blood flow, in which techniques that increase regional blood flow may be beneficial.

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Introduction

Enhanced external counterpulsation (EECP) is a noninvasive method currently used in the treatment of coronary artery disease and heart failure. EECP involves sequential inflation at the onset of diastole and rapid deflation just prior to the beginning of systole of compressive air cuffs wrapped around the lower extremities [1–3]. Inflation produces an acute increase in diastolic blood pres-

sure, raising the coronary perfusion pressure, and increases venous return, while deflation produces a decrease in systolic pressure, reducing cardiac afterload; together, these effects raise cardiac output [4, 5]. Besides these hemodynamic effects, the long-term improvement in coronary artery disease symptoms has been attributed to coronary collateral development and recruitment [6], to enhancement of ventricular function and to peripheral effects similar to those of physical exercise [7–9]. As yet, there are no published studies examining the possible action of EECP on the mechanical properties of the arterial wall. This is surprising as coronary artery disease and several cardiovascular risk factors including diabetes, smoking and hypertension are characterized by dysfunction of the properties of large arteries [10–13]. These alterations have pathophysiological relevance because arterial wall properties play a key role in the modulation of important parameters, such as arterial impedance, left ventricular afterload and myocardial oxygen consumption. The conduit function of the large arteries, which relates to the regulation of steady blood flow and depends mainly on the changes in small arteries, has also been poorly investigated after EECP therapy. Based on its known hemodynamic effects, including afterload reduction, shear stress increase and increase in venous return, this randomized, controlled investigation hypothesized that the application of EECP would improve arterial function and carotid artery circulation in patients with stable coronary artery disease.

Methods

Subjects

Thirty patients (28 males and 2 females), 44–85 years old, with stable coronary artery disease (CAD) demonstrated by angiographically proven stenosis greater than 50% in at least one major coronary artery or a documented history of myocardial infarction were included in the study. Fifteen patients had previous myocardial infarction, 16 had undergone prior coronary angioplasty and 7 had undergone prior coronary artery bypass grafting. Patients were treated according to secondary prevention guidelines [14], except for nitrate derivatives that could interfere with nitric oxide (NO) pathway assessment. All medications remained unchanged for the duration of the study. Patients were excluded if they had congestive heart failure, significant valvular heart disease, myocardial infarction or revascularization in the preceding 3 months, left ventricular ejection fraction less than 35%, blood pressure above 180/110 mm Hg, a permanent pacemaker, atrial fibrillation or ventricular premature beats that would interfere with EECP triggering, peripheral vascular occlusive disease, phlebitis, deep vein thrombosis, hemorrhagic diathesis, severe renal failure, were pregnant, or were enrolled in another research program. The study was placebo controlled by assigning CAD patients to receive

at random either active or ‘sham’ counterpulsation as described below. Approval of the local ethics committee was granted for this study and informed consent was obtained from all subjects after they were given a detailed description of the protocol.

EECP and Study Design

The EECP therapy system (Vasomedical, Westbury, N.Y., USA) consisted of an air compressor, a control console, a treatment table and an integrated set of air cuffs designed to be wrapped around the patient’s lower extremities. The cuffs are sequentially inflated from the calf to the lower thigh to the upper thigh and buttock at the onset of diastole, followed by a rapid, simultaneous deflation just prior to the beginning of systole. Pressures applied to the cuffs range from 0 to 300 mm Hg. Pressures in this study were 75 mm Hg in the sham control group and about 300 mm Hg in the active group. All subjects underwent 35 h of either sham or active counterpulsation. In the latter group, the pressure applied to the cuffs was increased until a diastolic augmentation ratio greater than 1.0 was achieved, indicated by a peak diastolic pressure greater than peak systolic pressure. Blood pressure changes were monitored by finger plethysmography.

Clinical and Biochemical Parameters

Body mass index was calculated as the ratio of weight to height squared. Resting brachial blood pressure was measured by an automated recorder (Omron HEM 705CP, Tokyo, Japan) as the average of two consecutive measurements. Current smoking was defined as daily consumption of at least 1 cigarette for at least 3 months. Fasting blood lipids (after precipitation of low-density lipoprotein and very low-density lipoprotein for high-density lipoprotein measurement) and fasting glucose were measured by enzymatic methods. Platelet cyclic GMP (cGMP) content was measured at baseline and after 1, 17 and 35 h of EECP therapy by radioimmunoassay (Perkin-Elmer, Boston, Mass., USA) as reported previously [15, 16].

Arterial Measurements

Arterial parameters were measured at baseline and after 1, 17 and 35 h of EECP therapy. Echo-Doppler studies were performed with a high-resolution ultrasound imager (Ultramark 5000, Advanced Technologies Laboratory) [17]. The right and left common carotid arteries were examined with a 7.5- to 12-MHz probe, 3 cm proximal to the bifurcation of the vessels. A longitudinal scan of both arteries allowed visualization of the lumen-intima and media-adventitia interfaces of the proximal and distal wall. When the two parallel echogenic lines were clearly visible on the monitor along at least 1 cm, a succession of images (sequence) was acquired to determine the instantaneous waveform of arterial diameter. The images, along with simultaneous ECG acquisition, were transferred to a computer and digitized for off-line analysis using an automated computerized program [18]. The maximum and minimum diameters were determined for each cardiac cycle and defined as the average of distances between the two leading edges of far- and near-wall lumen-intima interfaces. The diameter dimension was averaged over three or four successive cardiac cycles. A repeatability study in humans found the change between two repeated diameter measurements to be 9.4% [18].

Systolic and diastolic diameters and pressures were measured to estimate carotid elasticity. Diameters were calculated based on the average of right and left carotid measurements. Pressures were

Table 1. Clinical characteristics

Parameters	EECP	
	sham (control)	active
n	15	15
Age, years	61 ± 9	63 ± 10
Gender, M/F	14/1	14/1
Current smokers	0 (0)	1 (7)
Body mass index	26.9 ± 3.2	26 ± 3.1
Brachial systolic pressure, mm Hg	139 ± 18	132 ± 15
Brachial diastolic pressure, mm Hg	76 ± 9	78 ± 10
Total cholesterol, mmol/l	4.21 ± 0.92	4.12 ± 0.83
Low-density lipoprotein cholesterol, mmol/l	2.52 ± 0.60	2.40 ± 0.75
High-density lipoprotein cholesterol, mmol/l	1.20 ± 0.31	1.12 ± 0.27
Triglycerides, mmol/l	1.52 ± 1.11	1.34 ± 0.57
Blood glucose, mmol/l	6.67 ± 3.06	5.75 ± 1.33
Previous myocardial infarction	7 (47)	8 (53)
Previous coronary angioplasty	9 (60)	7 (47)
Previous coronary bypass	4 (27)	3 (20)

Data are given as means ± SD. Figures in parentheses are percentages.

the average of brachial blood pressure measured during right and left carotid artery echographic examination. Because these pressures have been reported to differ substantially from central pressure, [19] peripheral-to-central transfer function methods were noninvasively applied to estimate the central aortic pressure waveform, though only systolic and diastolic transformations were required in this study. The transformation methods have been validated in a population-based study, where regression analysis showed a high correlation for systolic, diastolic and pulse pressure [20]. We applied these results to transform systolic peripheral (SPP) and diastolic peripheral (DPP) blood pressures into central systolic (Ps) and diastolic (Pd) homologues as follows:

$$P_s = 1.01 \times SPP - 20.4 \text{ mm Hg,}$$

and

$$P_d = 1.17 \times DPP - 12.5 \text{ mm Hg}$$

Arterial distension (DD) was obtained from the difference between the maximum (D_{\max}) and minimum (D_{\min}) artery diameters divided by the minimum artery diameter:

$$DD = (D_{\max} - D_{\min})/D_{\min}$$

Measurement of both arterial distension and blood pressure enabled us to estimate the nondimensional pressure-independent β stiffness index as follows:

$$\beta = \ln(P_s/P_d)/DD$$

To estimate the conduit function, once the arterial diameter was determined as described above, blood flow velocity of the right common carotid artery ($\text{cm} \cdot \text{s}^{-1}$) was measured using the smallest possible Doppler sample volume (1 mm) placed at the center of the vessel. The angle between the ultrasound beam and the longitudinal vessel axis was 70° for all patients. Then, volumic blood flow ($\text{ml} \cdot \text{min}^{-1}$) was determined as the product of mean

blood flow velocity over 3 cardiac cycles and the cross-section ($\pi D^2/4$) of the vessel. Carotid vascular resistance was calculated as the ratio between mean arterial blood pressure (defined as one third of the sum of systolic blood pressure and twice the diastolic blood pressure) and mean blood flow of the common carotid artery ($\text{mm Hg} \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$).

Statistical Analysis

Results are expressed as means ± SD unless otherwise specified. log transformation was used for parameters with skewed distribution. Between-group differences were assessed by Student's t test. Pre- and post-EECP values were analyzed by the paired Student t test and ANOVA for repeated measurements. Univariate regression analyses were performed using the least squares method. Multivariate regressions were performed by general linear model using JMP (SAS) software. Statistical significance was set at $p < 0.05$.

Results

No significant between-group differences were seen in baseline clinical characteristics (table 1) or in baseline carotid hemodynamic values (table 2).

One patient in the sham control group withdrew from the study after 17 h of external counterpulsation due to worsening of a pre-existing ventricular arrhythmia that interfered with EECP triggering. No major complications occurred, and all the remaining patients finished the study. Systolic and diastolic pressure did not change after 1, 17 or 35 h of external counterpulsation in either group. However, in contrast to active counterpulsation, a slight

Table 2. Carotid hemodynamic baseline values

Parameters	EECP	
	sham (control)	active
Systolic pressure, mm Hg	109 ± 14	105 ± 12
Diastolic pressure, mm Hg	74 ± 8	75 ± 11
Pulse pressure, mm Hg	35 ± 10	30 ± 8
Mean pressure, mm Hg	86 ± 9	84 ± 10
Distention, × 10 ³	5.08 ± 2.5	4.14 ± 2.0
β stiffness index	10.5 ± 6.6	10.1 ± 7.2
Blood flow, ml · min ⁻¹	374 ± 84	382 ± 105
Vascular resistance, mm Hg · ml ⁻¹ · s ⁻¹	14.4 ± 3.6	13.9 ± 3.1

Data are given as means ± SD.

but significant increase from baseline in pulse pressure was observed in the control group at 1 and 35 h (4.6 ± 2 vs. 1 ± 1 and 4.3 ± 2 vs. -2 ± 2 mm Hg, respectively; $p < 0.05$); this increase was significantly different when compared with active counterpulsation ($p < 0.05$). Figure 1 shows that carotid distension was significantly increased at 1 h ($p < 0.05$), 17 h ($p < 0.01$) and 35 h ($p < 0.05$) only in patients receiving active counterpulsation, but the difference between groups was significant only after 1 h of external counterpulsation ($p < 0.05$). The β stiffness index was significantly reduced at 1 h ($p < 0.01$), 17 h ($p < 0.001$) and 35 h ($p < 0.01$) of active external counterpulsation, and this decrease was statistically different when compared with controls at 1 and 35 h ($p < 0.05$, respectively) (fig. 1). Also, in contrast to controls, mean carotid blood flow in patients receiving active counterpulsation increased significantly at 1 h ($p < 0.05$) and again more strongly at 35 h ($p < 0.001$), with a trend present at 17 h ($p < 0.07$). The difference between groups was significant at 17 h ($p < 0.05$) and 35 h ($p < 0.01$) (fig. 2). Carotid vascular resistance was concomitantly reduced in active counterpulsation at 17 h ($p < 0.05$) and 35 h ($p < 0.01$), showing a significant difference between groups in carotid vascular resistance at 17 h ($p < 0.01$) and 35 h ($p < 0.001$) (fig. 2). Adjustment for multiple covariates (age, sex, systolic and diastolic pressure, body mass index, smoking, glucose and low-density lipoprotein cholesterol) did not change the observed differences in arterial wall stiffness or vascular resistance between the study groups.

Patients undergoing active external counterpulsation had a nonsignificantly higher platelet cGMP content compared with controls (0.46 ± 0.36 vs. 0.26 ± 0.15 pmol/ 10^8 platelets, respectively) at baseline. From these values,

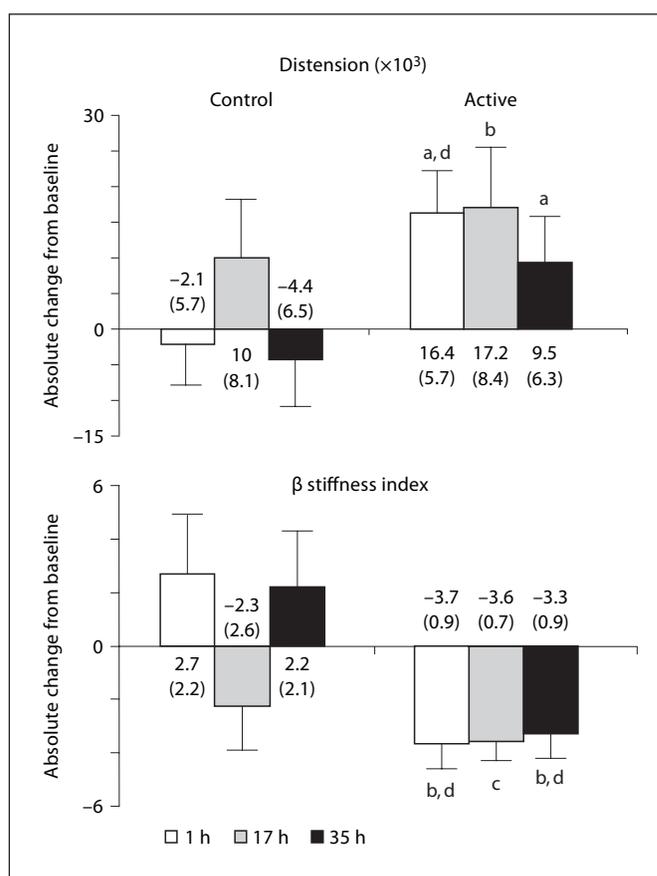


Fig. 1. Absolute change from baseline in carotid distension and stiffness during EECP treatment. Data are given as means ± SEM. ^a $p < 0.05$, ^b $p < 0.01$ and ^c $p < 0.001$ compared with values before EECP; ^d $p < 0.05$ compared with controls.

platelet cGMP contents increased at 1, 17 and 35 h of counterpulsation by 0.019 ± 0.02 , 0.058 ± 0.05 and 0.052 ± 0.05 pmol/ 10^8 platelets in controls and by 0.097 ± 0.02 ($p < 0.05$), 0.059 ± 0.08 and 0.087 ± 0.09 pmol/ 10^8 platelets in active patients, respectively. The difference between groups reached statistical significance only after 1 h of counterpulsation ($p < 0.05$). When all measurements of the β stiffness index versus platelet cGMP content were pooled in a linear regression analysis, a significant negative correlation coefficient was obtained in the overall population ($n = 115$; $r = -0.29$, $p < 0.01$), as well as in patients receiving active external counterpulsation ($n = 59$; $r = -0.32$, $p < 0.05$), but not in patients in the control group ($n = 56$; $r = 0.16$, n.s.) (fig. 3). No association was observed between carotid vascular resistance and cGMP platelet content either in the active or the control group.

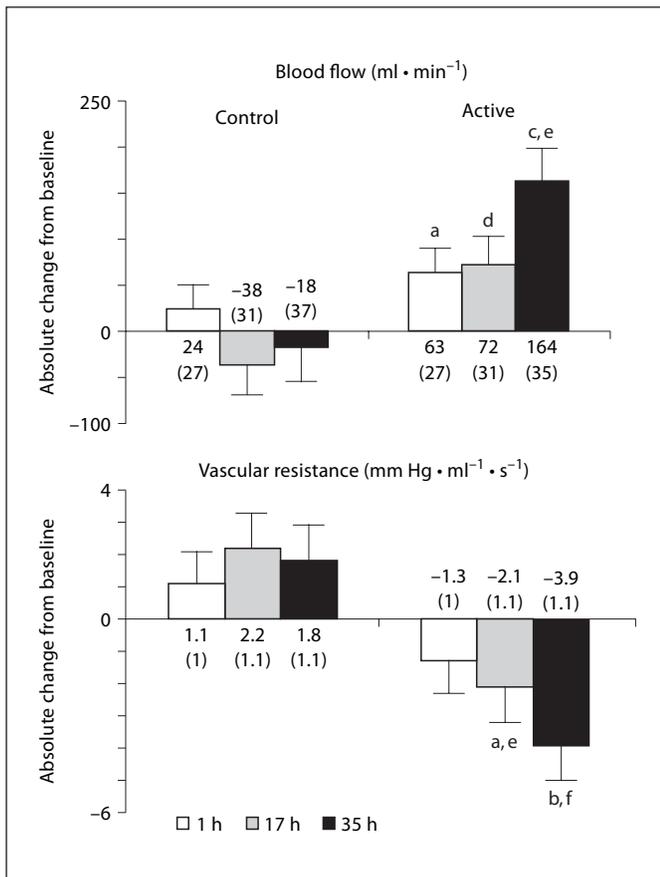


Fig. 2. Absolute change from baseline in carotid blood flow and vascular resistance during EECP treatment. Data are given as means \pm SEM. ^a $p < 0.05$, ^b $p < 0.01$ and ^c $p < 0.001$ compared with values before EECP; ^d $p < 0.05$, ^e $p < 0.01$ and ^f $p < 0.001$ compared with controls.

Discussion

This randomized, controlled study demonstrates that EECP therapy reduces carotid arterial stiffness and resistance in patients with stable CAD. Arterial stiffening, the sclerotic component of atherosclerosis, may participate in the complication (or development) of end organ damage by affecting arterial wall dynamics and left ventricular afterload [21]. It represents a systemic disorder that affects not only the coronary arteries [13], but the entire vasculature, including large and small vessels. Small vessels, as the major determinant of arterial resistance, play an important role in blood supply and distribution between tissues. In this study, arterial stiffness and resistance were assessed in the common carotid artery because of its particular suitability for ultrasonic investiga-

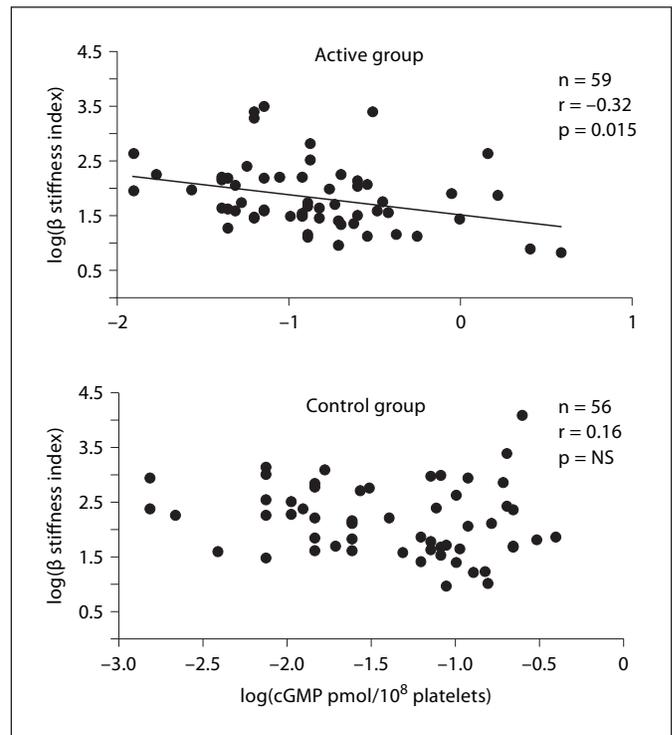


Fig. 3. Relationship of pooled platelets cGMP content and carotid arterial stiffness during 1, 17 and 35 h of EECP in active and control patients.

tion and its status as a preferential target for exploring vascular changes of cardiovascular disease and for pharmacological or nonpharmacological treatment. In addition, this artery is considered a 'sentinel' vessel for assessing the status of the coronary arteries [22]. Thus, a non-dimensional stiffness index providing a measure of elasticity independently of arterial pressure was applied to serve this goal. It was noninvasively derived via a logarithmic diameter-pressure relationship from the measurement of systolic-to-diastolic changes in arterial diameter at prevailing pressure [13]. While arterial distension, i.e. the ratio of pulse artery diameter and diastolic artery diameter, was obtained from the instantaneous carotid arterial diameter measured as the difference between the far and near wall displacements, arterial blood pressure was assessed at the brachial artery, which often overestimates central pulse pressure. Indeed, peripheral pressures are recorded routinely and assumed to be representative of central pressures, although morphological and absolute value changes are well known and attributed to wave propagation effects [21]. Significant differences were reported, mostly regarding systolic values

[19]. Different studies introduced the idea of a dynamic transfer function to extrapolate peripheral to central pressures across a variety of patient conditions [19, 20]. In the present study, peripheral pressures measured in the brachial artery were corrected to obtain the corresponding central pressures based on a regression analysis of a transfer function reported by Chen et al. [19] from a population-based study. For this, only systolic and diastolic values were required and not an estimation of the ascending aortic pressure wave. Indeed, systolic overestimation was considered constant for a wide pressure range, due to its tendency towards identity, whereas diastolic values remained practically unchanged for pressure values higher than 70 mm Hg. In any case, the β stiffness index, based on a log pressure scale, has been shown to remain unaltered by an acute 40 mm Hg change in systolic blood pressure [13] and might be considered independent of current distending pressure.

The conduit function of large arteries, which relates to the regulation of steady blood flow [23], was assessed by the concomitant measurement of the carotid artery diameter and blood flow velocity. Such a determination enables calculation of a semi-quantitative evaluation of vascular resistance of the carotid circulation by the ratio between mean arterial pressure and volumic blood flow.

One of the possible mechanisms by which EECp may reduce carotid arterial stiffness and resistance is by decreasing arterial pressure [24]. However, the decrease in carotid arterial stiffness cannot simply be the consequence of pressure reduction inside the arteries; indeed, an increase or a decrease in arterial pressure induces 'per se' a respective augmentation or reduction in arterial distension as the walls are more or less stretched. We observed that a significant increase in pulse pressure in the control group receiving sham counterpulsation did not modify the distention of the carotid artery, while a significant increase in distention was observed in patients receiving active EECp despite an unchanged pulse pressure. Such a result indicates that other mechanisms, independent of pulse pressure, may act on this large artery. The carotid artery includes elastic and collagenous fibers as well as smooth muscle that can alter arterial stiffness. EECp used in the present study was a short-term treatment, excluding any modification of the arterial wall structure. In the short term of 1–35 h of EECp administered during 7 weeks, only the smooth muscle may be actively modifiable by circulating or local vasoactive mediators acting on arterial stiffness. Increased shear stress generated by EECp may stimulate the release of different endothelium-derived mediators, including NO or C-type

natriuretic peptide, which can relax smooth muscle tone and subsequently reduce large artery stiffness. This hypothesis is supported by the observation that external counterpulsation improved endothelial function assessed by finger tonometry [25] or by flow-mediated dilation of the brachial artery [26]. It is well documented that the release of cGMP in response to natriuretic peptides or NO regulates smooth muscle tone and arterial wall changes [16, 27, 28]. The negative association between platelet cGMP contents and carotid stiffness in subjects receiving active external counterpulsation suggests that active EECp may relax the smooth muscle tone of the carotid artery and consequently decrease their arterial stiffness via the signaling product of NO/natriuretic peptide pathways. Another mechanism by which EECp may influence arterial properties involves its training effect [7]. It has been proposed that EECp might provide hemodynamic stimuli similar to those of physical exercise [8]. This was in line with some interventional studies showing improvement in coronary endothelium function by exercise [29] and an increase in aortic compliance after moderate intensity exercise [30]. The observation that EECp augments carotid blood flow and concomitantly reduces the regional vascular resistance independent of mean blood pressure modification suggests that small artery calibers were increased by changes in the tone of the vascular smooth muscle. It is interesting to note that contrary to carotid stiffness, there was no significant association between platelet cGMP and carotid resistance. A possible explanation is that besides endothelium-derived mediators, EECp as well as physical training may also activate autonomic influences (catecholamines) and/or metabolic vasodilator pathways.

In conclusion, this randomized, controlled study demonstrates that EECp exerts clear vascular relaxation effects both on large and small arteries of the carotid circulation. These effects are of particular interest in cardiovascular disease involving a reduction in blood flow, such as heart failure or ischemic cerebrovascular disease, in which techniques that increase regional blood flow may be beneficial.

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