Medium-term Effects of Enhanced External Counterpulsation in the Structural and Functional Parameters of Blood Vessels in Patients with Coronary Artery Disease

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Aim. To study the mid-term effects of enhanced external counterpulsation (EECP) in the structural and functional parameters of blood vessels, exercise tolerance and quality of life indicators in patients with verified coronary artery disease (CAD).
Material and methods. Patients (n=70) with verified stable CAD (angina pectoris class II-III) complicated by chronic heart faillure class II-III (NYHA) were included in the study. Data from 65 patients (48 to 74 years old; 45 men and 20 women) are included in the final analysis. All patients had a course of EECP (35 hours procedures with a compression pressure of 220-280 mm Hg). All patients at baseline, 3 and 6 months later had a 6 walk minute test (6WMT), an assessment of the clinical status, quality of life of patients (Minnesota Living with Heart Failure Questionnaire, SF-36). Computer nailfold video capillaroscopy, photoplethysmography with pulse wave recording and contour analysis, applanation tonometry to assess central aortic systolic pressure and radial augmentation index were performed to assess the structural and functional state of large and microcirculatory vessels.
Results. Significant improvement in exercise tolerance both after 3 and after 6 months (increase in distance in 6WMT by 44.6% after 3 months and 34.3% after 6 months, $p < 0.05$), improved quality of life (increased overall score on the SF-36 questionnaire from 50.3±8.1 to 59.8±8.8, $p<0.05$), an increase in the left ventricular ejection fraction were found. Significant improvement in indicators showing the function of the endothelium of both large vessels (phase shift: from 5.6 [2.45; 7.3] to 6.8 [3.1; 8.1] m / s) and microcirculatory vessels (occlusion index: from 1.51 [1.21; 1.7] to 1.66 [1.2; 1.9]), as well as a decrease in functional disorders of the capillary bed of the skin (% of perfused capillaries, density of the capillary network in the test with reactive hyperemia) were found after 3 months. However, after 6 months, there were no significant changes in these parameters compared to the baseline value. No significant change in indicators showing structural remodeling of both large vessels and microcirculatory vessels was found.
Conclusion. The positive effect of the EECP course on the functional status (exercise tolerance) and quality of life in patients with stable coronary artery disease complicated by chronic heart faillure was found both after 3 and 6 months. Positive dynamics of the functional state of large vessels and microvasculature was found only after 3 months.

Key words: enhanced external counterpulsation, ischemic heart disease, endothelial function, vascular effects, quality of life.

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Introduction

According to the World Health Organization, cardiovascular diseases are still the main cause of mortality and disability throughout the world, and among them coronary artery disease (CAD) occupies a leading position [1]. The optimization of drug therapy and the increase in the number of revascularization procedures in recent decades have led to a decrease in the mortality of these patients and an increase in their life expectancy. But the limited duration of effective functioning of stents and bypasses, as well as the lack of proven advantages in influencing the prognosis compared to the conservative strategy, inevitably led to an increase in the proportion of people with refractory angina pectoris [2]. Also, the course of coronary artery disease in these patients is often complicated by chronic heart failure. Also, we can't fail to mention the group of patients which are not suitable candidates for these procedures (stenting and bypass grafting) due to the presence of concomitant diseases, anatomical features of coronary lesions or previous interventions.

The depletion of the potential of conservative and invasive strategies is a major driver of the search for a treatment that can complement these two strategies. One of these methods is enhanced external counterpulsation (EECP). It's an effective method of treating patients with coronary artery disease and chronic heart failure. Studies have already demonstrated the effect of EECP on exercise tolerance, myocardial contractility and quality of life in these patients [3]. EECP is one of the safest and most effective methods of treating patients with coronary artery disease, including those with complicated chronic heart failure [4,5]. The relatively low cost and the possibility of outpatient use are also the indisputable advantages of this method of therapy.

The principle of operation of the EECP device was described in detail earlier [6]. One of the main goals of the method is its impact on the coronary reserve. The improvement in collateral perfusion is due to several factors. The opening of previously formed collaterals occurs due to the release of vasodilators (nitrogen monoxide, etc.), the increased levels of which are found in the blood plasma of patients even several months after the end of the EECP course [7]. The formation of new collaterals (angiogenesis) is due to an increase in shear stress during procedures [8,9]. The consequence after the EECP course is an increase in the volumetric rate of myocardial perfusion without increasing the load on the heart. Increasing the functional reserve of the myocardium improves exercise tolerance and increases the ischemic threshold [10]. The cardiac effects of EECP, as well as its effect on exercise tolerance and quality of life in patients with coronary artery disease and chronic heart failure, have been studied in many researches, but the vascular effects, which are the main goal of this method, have not been sufficiently studied.

The aim of this work is to study the medium-term effects of EECP on the structural and functional parameters of blood vessels, exercise tolerance and quality of life indicators in patients with verified coronary artery disease.

Material and methods

This study was conducted on the basis of the cardiology department of the University Clinical Hospital №1 (Sechenov University). The study included 70 patients (from 48 to 74 years old; 50 men and 20 women) with verified coronary artery disease (angina pectoris of II-III functional class) who received optimal drug therapy (ACE inhibitors, beta-blockers, antithrombotic therapy, statins, nitrates), which didn't change during the study. The patients underwent a course of EECP, which included 35 1-hour sessions with a compression pressure of 220-280 mm Hg. Features of study design, inclusion and exclusion criteria were described in detail in our previous work [11].

All patients before the start of the course (Visit 1), as well as 3 months later (1.5 months after the end of the EECP course; Visit 2) and 6 months later (Visit 3) underwent a comprehensive examination (Fig. 1), which included a physical examination, general and biochemical blood tests, electrocardiography (ECG), measurement of blood pressure on both hands and echocardiography. The 6-minute walk test was performed to assess the dynamics of exercise tolerance. The dynamics of the clinical status of patients was determined according to the scale for assessing the clinical condition (modified by V. Yu. Mareev). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) and SF-36 (The Short Form [36] Health Status Survey) were used to determine the dynamics of patients' quality of life.

In addition, Computer nailfold video capillaroscopy (Capillaroscan-1; New Energy Technologies, Russia) was performed to assess the structural and functional state of large blood vessels and microcirculatory vessels. The parameters of the structural state of the capillary network (density of the capillary network at rest and after the test with venous occlusion), and the functional state of the capillary network (density of the capillary network after the test with reactive hyperemia, percentage of capillary recovery, percentage of perfused capillaries) were studied. Photoplethysmography (FPG; Angioscan-

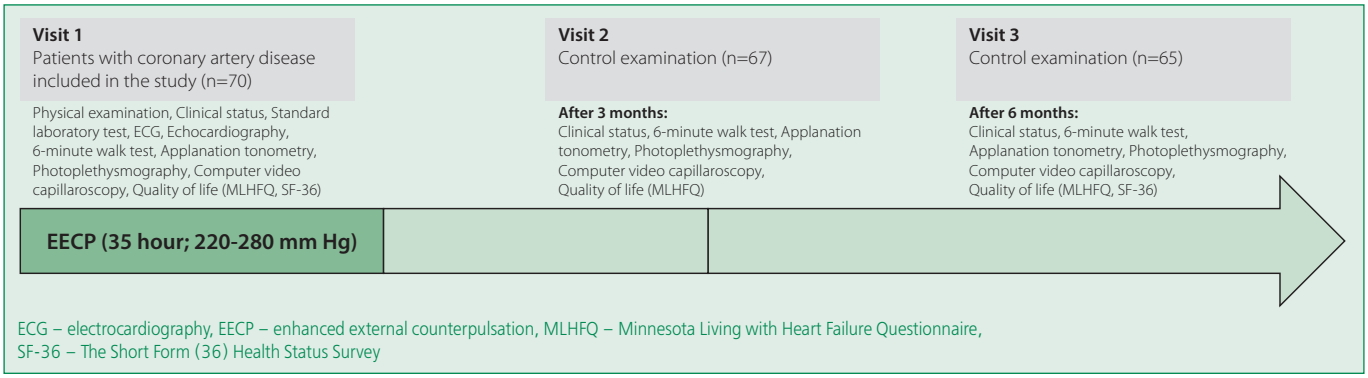

Figure 1. Study design

01; Angioscan, Russia) was used to study the structural and functional state of the wall of large vessels (aorta, brachial, radial arteries) and the functional state of microcirculatory vessels (arterioles) [12]. Applanation tonometry using «A-pulse CASPro» (HealthSTATS, USA) was performed to assess the central aortic systolic pressure (CASP) and the radial augmentation index (RAI).

During the study (6 months), 5 patients dropped out (3 patients at visit 2 and 2 more patients at visit 3). Data from 65 patients were included in the final analysis.

Statistical analysis. Statistical data processing was carried out using Statistica 6.0. The correspondence of the observed distribution of quantitative values to the normal distribution law was assessed using the Shapiro-Wilk's test. The Student's t-test for independent samples was used with a normal distribution of quantitative data. The Mann-Whitney's test was used with a distribution other than normal. The Student's t-test for dependent samples or the Wilcoxon's test were used when comparing quantitative data in dependent samples, respectively. Comparison of categorical data was carried out using the chi-square test (in independent samples) or the McNemar's test (in dependent samples). Data are presented as M±SD or Me [25%; 75%]. The statistical significance level was chosen at $p<0.05$.

Results

Clinical and demographic characteristics of patients are presented in Table 1.

After 6 months (and, on average, 4.5 months after the end of the EECP course), a statistically significant improvement in exercise tolerance was preserved, achieved at 2nd visit (after 3 months), as well as an improvement in the patients' state according to clinical status assessment scale, and improvement in the patients' quality of life according to the MLHFQ and SF-36 questionnaires and an increase in the contractile function of the left ventricle (Table 2). At the same time, a statistically insignificant correction of these indicators relative to the levels at the 2nd visit was found.

Also, the improvement in the patients' quality of life (according to the SF-36 questionnaire) after 6 months was due to positive dynamics not only from physical factors, but also from emotional factors (Fig. 2).

According to the results of applanation tonometry, the tendency (statistically insignificant dynamics) to decrease in central aortic systolic pressure and RAI persisted after 6 and 3 months (Table 3). According to the results of capillaroscopy and photoplethysmography, a statistically significant positive dynamics of indicators was found at visit 2, reflecting endothelial dysfunction of large blood vessels and microcirculatory vessels (phase shift, occlusion index), as well as functional disorders of the capillary bed of the skin (% of perfused capillaries, density of the capillary network in the sample with reactive hyperemia) (Table 3). But on visit 3, the levels of these indicators were corrected, which leveled the statistical significance of the differences in comparison with their initial values. No statistically significant dynamics were found at visits 2 and 3 compared to the baseline values despite positive changes in the indicators reflecting the remodeling of both large blood vessels and microcirculatory vessels (radial augmentation index, stiffness index, reflection index) (Table 3).

The present study found no adverse events during treatment with EECP, and treatment tolerance at a compression pressure of 220-280 mm Hg was satisfactory.

Discussion

EECP has been widely used for the treatment of patients with coronary artery disease and chronic heart failure for more than two decades. Traditionally, patients with coronary artery disease, including those

Table 1. Clinical and demographic characteristics of patients (n=65)

Parameter	Value
Age, years	65.2±8.9
Men, n (%)	45 (69.2)
Chronic heart failure, n (%)	65 (100)
Arterial hypertension, n (%)	41 (63.1)
Diabetes mellitus, n (%)	14 (21.5)
Smoking, n (%)	9 (13.8)
History of myocardial infarction, n (%)	18 (27.7)
History of revascularization, n (%)	54 (83.1)
Body mass index, kg/m^2	27.4 [22.0;30.3]

Data are presented as M±SD or Me [25%; 75%], unless otherwise indicated

complicated by chronic heart failure, receive one EECP course annually, which includes 35 hour procedures. According to the current guidelines for the treatment of patients with chronic coronary syndrome [4], this treatment method has a recommendation class IIb and an evidence level B. The latter statement is mainly based on the data of the MUST-EECP randomized controlled trial [14], which has become a classic work in this direction. After 35 hours of EECP, patients with refractory angina pectoris (n=59) compared with the placebo-counterpulsation group (n=65) showed a statistically significant increase in exercise tolerance (the time to reach ST elevation ⩾1 mm increased by 12.5% versus 1.2%, p<0.01), an insignificant decrease in the need for additional intake of nitroglycerin preparations (69.2% versus 23.2%, p>0.7), as well as a statistically significant improvement in the quality of life after 12 months of observation.

In this work, a statistically significant increase in distance in the 6-minute walk test was found - by 44.6% after 3 months and by 34.3% after 6 months. The difference from baseline was still statistically significant despite a slight decrease in effect after 6 months.

According to meta-analysis of studies evaluating the medium-term effects of EECP in patients with stable coronary artery disease, including chronic heart

Table 2. Change in the studied indicators during the study (n=65)

Parameter	Initially	After 3 months	After 6 months
Distance in the 6-minute walk test, m	213 [190; 275]	308 [253; 337]*	286 [244; 348]*
Dynamics of the patients' state according to CSAS, scores	6.5±1.9	4.35±1.23*	5.0±1.42*
Dynamics of the patients' quality of life (MLHFQ), scores	52.0±6.4	39±7.21*	40.4±8.7*
Dynamics of the patients' quality of life (SF-36, overall score[a]), scores	50.3±8.1	–	59.8±8.8*
Ejection fraction, %	41.8 [36.5; 47.4]	45 [39.2; 51.2]*	43.3 [39.3; 50.5]*

Data are presented as M±SD or Me [25%;75%]

*p<0.05 compared to baseline data

[a] the total score was calculated as the average of 8 components of the SF-36 questionnaire [13]

CSAS – clinical status assessment scale, MLHFQ – Minnesota Living with Heart Failure Questionnaire, SF-36 – The Short Form (36) Health Status Survey

Table 3. Changes in indicators of the structural and functional state of blood vessels

Parameter	Initially	After 3 months	After 6 months
Central aortic systolic pressure, mm Hg	131.5±16.1	129±15,4	126,8±16,2
Radial augmentation index, %	97.5±25.2	96.1±21.1	95.9±23.5
Phase shift, m/s	5.6 [2.45; 7.3]	6.8 [3.1; 8.1]*	6.1 [3.1; 7.9]
Occlusion index	1.51 [1.21; 1.7]	1.66 [1.2; 1.9]*	1.57 [1.23; 1.85]
Stiffness index, m/s	8.78±1.63	8.8±1.7	8.81±1.6
Reflection index, %	38.7±11.2	38.5±11.3	38.4±12.0
% of perfused capillaries	89.1 [76.4; 91.2]	91.3 [85.8; 94]*	90.6 [80; 92.2]
Density of the capillary network (at rest), n	44.3±12.6	44.7±11.6	44.2±12.3
Density of the capillary network (venous occlusion), n	52.5±14.7	56.8±14.4	55±15.2
Density of the capillary network (reactive hyperemia), n	44.9±14.7	56±15.2*	51±16.3

Data are presented as M±SD or Me [25%; 75%]

*p<0.05 compared to baseline

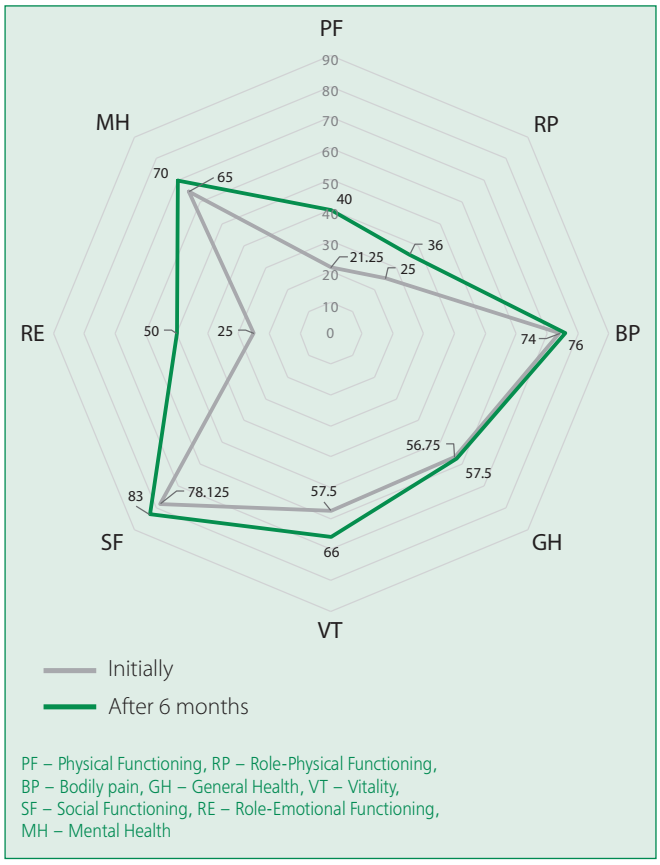

Figure 2. Changes in quality of life components (SF-36) in patients during the study (6 months)

failure, a positive effect (decrease in the functional class of angina pectoris by at least 1 unit) was found in 84-86% of patients [15,16].

The improvement in the quality of life (according to the MLHFQ and SF-36 questionnaires) also turned out to be statistically significant in the studied periods, and its change turned out to be more persistent in comparison with other effects (Table 2).

The study by R. Jan demonstrated a statistically significant improvement in the quality of life (SAQ-7 questionnaire) in patients with coronary artery disease (n=220) after 3 months of follow-up after treatment with EECP (35 hours) [17]. The quality of life was assessed at various times after a single course of EECP.

According to the Expert Consensus on the Clinical Use of EECP in the Elderly (Chinese Medical Association, Editorial Board of the Chinese Journal of Geriatrics, China Society of Biomedical Engineering), early studies on EECP focused on its hemodynamic effects. The uniqueness of hemodynamic changes in EECP is emphasized (an increase in diastolic pressure in the aorta by 26-157%, an increase in cardiac output by an average of 25%, an increase in intracoronary diastolic pressure by 16% and an increase in the volumetric flow rate of coronary blood flow by an average of 109%) [18]. Subsequently, the attention of scientists began to focus on the vascular effects that underlie the antiatherosclerotic action of EECP and its influence on the processes of remodeling and endothelial function. EECP increases the shear stress of blood vessels by 30-60 dyne/cm^2, improves endothelial function (an increase in endothelium-dependent vasodilation and nitric oxide levels with a simultaneous decrease in endothelin-1 levels, as well as an increase in telomeric repeat binding factor levels), inhibits oxidative stress (decreases levels of tumor necrosis factor-alpha, chemotactic protein-1 monocytes, mitogen-activated protein kinase p38, nuclear factor-kappa B and adhesion molecules), and also stimulates angiogenesis. The main areas of application of this method are atherosclerosis-associated diseases and associated conditions and complications.

The positive effects we noted on the part of indicators that reflect the functional component of both large blood vessels (phase shift) and microcirculatory vessels (occlusion index,% of perfused capillaries) were statistically significant only at the visit 3 months later (1.5 months after the end of the EECP course). Subsequently, their dynamics relative to the initial values was already insignificant in the absence of a therapeutic effect. Also, we didn't find statistically significant dynamics on the part of indicators that reflect structural vascular remodeling.

L. Xu et al. demonstrated an improvement in hemodynamic conditions in the aorta and coronary bed during EECP using geometric models based on CT angiography and pulse wave sphygmogram. The authors found a statistically significant improvement in the time-average shear stress of the vessel wall (from 12.3% to 6.7%) and the oscillatory shear index (from 6.8% to 2.5%) with an initially more pronounced stenosis (⩾75% of the area) [19].

The study by D.B. Kulchitskaya et al. patients with coronary artery disease complicated by chronic heart failure showed an improvement in myogenic and neurogenic tonus of arterioles after myocardial revascularization (n=60) after a EECP course (35 hours) according to laser Doppler flowmetry [20].

The positive vascular effects of EECP were found by C.W.S. Hoong et al. also in patients with concomitant diabetes mellitus with initially more severe endothelial dysfunction. An increase in the reactive hyperemia index by 20.8% (p=0.0178) was recorded using peripheral arterial tonometry [21].

But the duration of vascular effects, according to various authors, turned out to be quite different. For example, M. Hashemi et al. showed that functional vascular effects disappear within 1 month after the

end of the EECP course [22]. C. Luo et al. found an improvement in peak coronary diastolic blood flow and coronary blood flow reserve after 8 weeks, and this improvement persisted after 6 months [10].

We also note that EECP treatment is well tolerated. No undesirable phenomena were found in our work. According to E. Wu et al. EECP has also been described as a safe and well tolerated treatment method [23]. A very strict process of selecting patients for treatment with this method is also important, with the exception of a fairly wide list of contraindications. According to the same authors, more pronounced functional impairments, signs of left ventricular systolic dysfunction and fewer types of revascularization are considered the main predictors of response to EECP treatment. At the same time, an increase in exercise tolerance (according to the results of a 6-minute walk test) also improves the patients' quality of life with refractory angina pectoris [24].

In most studies of EECP in patients with coronary artery disease, including complicated chronic heart failure, the study of the effects (0-12 months after the end of treatment) was carried out after a standard single course (35 hours per year) and didn't consider this method as a regular one. In our own experience, this category of patients lacks the effects of EECP for a whole year. And most of the patients have effects for no more than 6 months. For example, this can be compared with the effectiveness of a course of ACE inhibitors, where the effect of the treatment course is always limited. Therefore, one of the tasks of our work was to demonstrate the "not infinite" effect of EECP. But we note the longest-lasting impact of this method on patients' quality of life. In general, the variability of non-vascular effects (exercise tolerance, quality of life) was significantly higher than vascular effects in terms of severity and duration. This can be explained by the diversity of the functional phenotypes of patients (the ratio of the functional reserve of the coronary bed and the muscular system).

Most researchers talk about the need to study the long-term effects of EECP. The present work was part of a randomized, placebo-controlled study of the long-term effects of EECP in patients with coronary artery disease, including complicated chronic heart failure.

Study limitations:

The interpretation of the results of this work suggests that we should take into account the peculiarities of its design (non-randomized), although it was part of a randomized study. We also need to take into account the fact that some patients had fairly regular cardio loads (we couldn't exclude them for ethical reasons), which could also affect the studied indicators.

Conclusion

The vascular and non-vascular effects of EECP identified by us in patients with coronary artery disease confirm the need to include this method in the treatment program for such patients. But the instability of the effects (several months) after a single EECP course requires longer studies in patients with coronary artery disease, including complicated chronic heart failure, as well as studying other treatment regimens using this method.

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