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Right heart remodeling in patients with inoperable chronic thromboembolic pulmonary hypertension, after balloon angioplasty of the pulmonary arteries

Abstract

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a precapillary form of pulmonary hypertension (PH) that develops due to thrombotic mass obstruction of the pulmonary arteries. In the absence of appropriate treatment which aims to reduce the pressure in the pulmonary artery and pulmonary vascular resistance, the disease progresses leading to hypertrophy and then dilatation of the right heart chambers with right ventricular heart failure. Heart failure determines the extremely unfavorable prognosis of these patients. We aimed to study the dynamics of RV remodeling in patients with inoperable CTEPH (one year after final BPA) by using echocardiography.

Materials and methods: 22 consecutive patients with inoperable CTEPH who underwent BPA with echocardiography before, after 1 month and 12 month after final BPA were retrospectively studied.

Result: BPA led to significantly ameliorated right-sided heart failure symptoms and signs, and exercise capacity. The results obtained in the long-term period did not significantly differ from the results immediately after the BPA, which proves the persistent effect after BPA procedure.

Conclusion: Echocardiography is useful method for assess effectiveness of BPA. The BPA procedure not only stops the progression of right ventricular failure, thereby stabilizing the disease with a persistent long-term result.

Keywords: pulmonary hypertension, echocardiography, chronic thromboembolic pulmonary hypertension, balloon angioplasty of pulmonary arteries, thromboendarterectomy

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a precapillary form of pulmonary hypertension (PH),[1] which is usually a late complication of acute pulmonary embolism. Obstruction of the pulmonary artery branches with thrombotic masses and following significant small vessel arteriopathy which lead to an increase in pulmonary vascular resistance (PVR) and pressure in the pulmonary artery (PAP), that causes hypertrophy and then dilation of the right heart chambers with the development of right ventricular heart failure. Heart failure determines an unfavorable prognosis in this category of patients.[2] There is a chance for patients with CTEPH to be back to normal life-after successful operation of bilateral thrombendarterectomy (TEE) from the branches of the pulmonary artery, in most cases it is possible to normalize hemodynamic parameters and functional status. However, according to the international registry, only 63% of patients with CTEPH are recognized as suitable for TEE.[3] The remaining 37% are inoperable by the decision of the multidisciplinary team. Most often these are patients with a distal type of pulmonary vascular lesions and/or with severe concomitant pathology.[4,5]

Fast worldwide development of endovascular treatment methods led to the emergence in 2001 of a new treatment method - balloon angioplasty of the pulmonary arteries (BPA). First study results demonstrated that BPA is highly effective in patients with CTEPH. In addition to improving hemodynamic parameters and functional status of patients, it leads to an improvement in the function of the right ventricle (RV). RV myocardial reverse remodeling is confirmed by echocardiography, magnetic resonance imaging (MRI), and a decrease in the level of cerebral natriuretic peptide (BNP).[6] Evaluation of sizes of right heart chambers are included in the mortality risk assessment scale in patients with pulmonary arterial hypertension (PAH), which reflects the significance of these indicators. These indicators positive changes were called positive reverse remodeling of RV and these are the object of different studies, including present one.

Objective

To study the structural and functional changes of the right heart chambers in the long-term period in patients with inoperable CTEPH who underwent BPA procedure.

Material and methods

The study was conducted in the hypertension department of the National Medical Research Center of Cardiology, Moscow, Russia. All included patients signed written informed consent. Twenty-two patients with a diagnosis of inoperable CTEPH took part in the study. Patients were included in the study according to established criteria.

Criteria for inclusion in the study:

a. The presence of a diagnosis of an inoperable form of CTEPH;

b. Age over 18 years;

c. Functional class II-IV (according to WHO);

d. The technical ability to perform transluminal balloon angioplasty of the pulmonary arteries;

Study exclusion criteria:

a. The presence of pulmonary hypertension of another etiology;

b. System hypotension (systolic blood pressure <90 mmHg);

c. Severe concomitant pathology that can have an independent effect on the prognosis, including-an oncological process, an inflammatory process, the presence of severe anemia, severe dysfunction of the respiratory system, kidneys, liver; cerebrovascular events over the past 6 months;

d. Pregnancy, lactation;

e. Refusal of the patient from invasive intervention;

f. Any contraindication to endovascular intervention, including the presence of an allergic reaction to contrast medium;

The main characteristics of the included patients are presented in table 1. The diagnosis of CTEPH was made according to current guidelines, based on data from right heart catheterization (RHC), ventilation-perfusion lung scintigraphy, computer angiopulmonography or invasive angiopulmonography, as well as the exclusion of other forms of PH. Indications for PBA were determined by a multidisciplinary team, that included cardiologist, cardiovascular surgeon and endovascular specialist.[1]

Table 1 Baseline clinical and hemodynamic parameters of included patients

Parameter	M (Q1;Q3)
Age, year	56 (47;63,5)
Body surface area (BSA)	1.8 (1.7;2.0)
Functional class (FC) II/III/IV	05/11/6
6-min walking test distance, m	346 (297;411)
Dyspnea (Borg scale)	3 (3;4)
Systolic pulmonary artery pressure, mmHg	83 (73;91)
Mean pulmonary artery pressure, mmHg.	50 (43;54)
Diastolic pulmonary artery pressure, mmHG.	27 (19;34)
Right atrium pressure, mmHg	9 (7.5;10.8)
Arterial blood saturation, %	891 (749;1209)
Venous blood saturation, %	2.2 (1.7;2.4)
Cardiac index, l/min	92 (89;95)
Pulmonary vascular resistance, dyn*sec/cm[5]	62 (56;65)
Blood creatinine, mkmol/l	80 (72.25;94.5)
Brain natriuretic peptide, pg/ml	265 (74;575)

M (Q1;Q3) - median (25d percentil;75d percentil)

Right heart catheterization and balloon angioplasty of the pulmonary arteries

All included patients underwent the standard RHC procedure using a Swan-Gantz catheter 110 cm long with a diameter of 6F. Catheterization was performed before the first BPA, one month after the last BPA, and in the long term-1 year after the last BPA procedure. Cardiac output (CO) was determined by Fick indirect method. The BPA procedure was performed through the medial saphenous vein (v.basilica), with a vein diameter of more than 2 mm and the absence of an abnormal structure of the saphenous vein system. Before BPA procedure, all patients underwent diagnostic RHC to determination of hemodynamic parameters and selective angiopulmonography. The following parameters were measured and calculated: right atrium pressure (RAP), pulmonary artery pressure (systolic (sPAP), diastolic (dPAP) and mean (mPAP)), CO, CI, PVR). After completion of the diagnostic step, the long introducer was inserted into the trunk of the pulmonary artery, through which a guiding catheter was passed to the affected vessel. Next, a coronary conductor was guided through the guide catheter through the affected area. Series of dilations of the affected area were carried out with balloons of different diameters, starting from 2.0 mm to 4-6 mm. The required balloon size was determined during the procedure by quantitative angiography or by intravascular ultrasound. All patients underwent 6 BPA procedures.

Echocardiography

All patients underwent transthoracic echocardiography using an expert-grade ultrasound machine. The study was carried out in accordance with the local protocol with mandatory assessment of PAP, the size of the right atrium (the right atrium area, the thickness of the anterior wall of the RV, the size of the RV apically and in the area of the RV outflow tract, and the systolic function of the right ventricle-TAPSE, the size of the trunk of the pulmonary artery and its branches), the degree of regurgitation on the tricuspid and pulmonary valves, gradients on the tricuspid and pulmonary valves, pulmonary wedge pressure (PWP). The sPAP was calculated as maximum systolic gradient on the tricuspid valve (TV) plus RAP. The mPAP was calculated as average systolic gradient on the TV plus RAP. To determine the RAP, diameter of the inferior vena cava and its collapse on inspiration were evaluated. To calculate the PWP, we used the formula: PWP=1.24xE/E'+1.9, where E is the maximum speed of early diastolic filling of the LV, according to Doppler ultrasound, E' is the maximum speed of early diastolic displacement of the lateral segment of the mitral valve according to tissue myocardial dopplerography (TMD).

Statistical analysis

Statistical analysis was carried out using the free software calculation environment R (v.3.6.0) and additional tidyverse and DescTools packages. The following methods were used: nonparametric U Mann–Whitney test, paired t-test, X2 criterion and nonparametric correlations. The correlation between the data samples was evaluated with a significance level of 95%. The sets of quantitative indicators were described using the values of the median (Me), 25d and 75d percentile (Q1-Q3). The reliability of the used statistical estimates was taken as not less than 95%.

Results

Long-term results of pulmonary angioplasty were evaluated 1 year after the final pulmonary angioplasty. Fifty percent of patients at the time of inclusion in the study had functional class III, 68% of patients had mPAP exceeding 45 mm Hg, and 31% of patients had PVR exceeding 1100 dyn* sec/cm.[5] These data indicate the progressive status of the disease in the included patients. Analysis of the results showed significant improvement in all hemodynamic and functional parameters one month after the final BPA procedure, while maintaining the achieved results in the long-term period. Thus, the

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mPAP was initially 86(74;93) mm Hg and after the series of BPA it decreased to 56(48;69) mm Hg (p<0.001). After a year it increased slightly to 66(53;76) mm Hg (p<0.001). There was a statistically significant difference in sPAP one month after BPA (p<0.001) and after one year (in the long-term period) (p=0.022). There was no difference in sPAP after the BPA and in the long-term period (p=0.4). The same was shown for mPAP PVR, RAP, in 6-min walking test distance and BNP level. Despite the observed positive dynamics, there was no significant difference in saturation of arterial and venous blood, as well as in CI and dPAP (p=0.02; p=0.08; p=0.4; p=0.01, respectively). Detailed dynamics of the main hemodynamic and functional parameters are presented in Table 2.

Table 2 Dynamics of hemodynamic and functional status indicators after BPA, n=22

Parameter	Before BPA (n=22)	One month after last BPA (n=22)	1y after last BPA (n=22)	p
Systolic pulmonary artery pressure, mmHg	83 (73;91)*	55 (48;69)**	65 (53;76)***	0,001
Mean pulmonary artery pressure, mmg	50 (43;54)*	30 (27;38)**	35(30;47)***	0,001
Diastolic pulmonary artery pressure, mmHg	27 (19;34)*	19 (15;22)**	22 (18;29)***	0,01
Right atrium pressure, mmHg	9 (7,5;10,8)*	7 (5;8,25)**	8 (7;11,5)***	0,005
Pulmonary vascular resistance, dyn*sec/cm5	891 (749;1209)*	481 (431;618)**	579 (432;765)***	0,001
Cardiac index, l/min/m2	2,2 (1,7;2,4)*	2,2 (1,8;2,5)**	2 (1;3)***	0,4
Arterial blood saturation, %	92 (89;95)*	97 (91;98)**	95 (91;97)***	0,02
Venous blood saturation, %	62 (56;65)*	66 (57;68)**	67 (56;70)***	0,08
Functional class (WHO), %				
I	0	10 (50%)	7 (35%)	<0,001
II	5 (23%)	5 (25%)	7 (35%)	<0,001
III	11 (50%)	5 (25%)	6 (30%)	<0,001
IV	6 (27%)	0	0	<0,001
6-min walking test distance, m	346 (297;411)*	549 (458;623)**	560 (444;638)***	0,001
Dyspnea (Borg scale)	3 (3;4)*	3 (1,2;4)**	3 (2;4)***	0,03
Brain natriuretic peptide, pg/ml	265 (74;575)*	30 (19;71)**	32 (11;88)***	0,003

* - differences in the initial values with the values after BPA (after 2 months) (p<0.005).

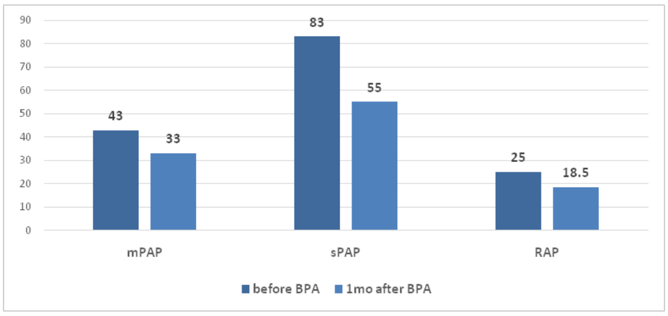
** - differences between the base values and the values in the long-term period (p<0.005).

*** - differences in values after the intervention with values in the long-term period (p=0.4-1).

Positive reverse remodeling of the right chambers of the heart was shown by echocardiography. After completion of all BPA sessions an improvement in all studied parameters was noted. There was also an improvement in right heart volume and pressure overload signs: a decrease of eccentricity index, a decrease of tricuspid valve insufficiency degree, a decrease of pulmonary artery trunk size, gradient on the tricuspid valve, and, consequently, the estimated sPAP and mPAP. Despite improvement in all studied parameters, the most significant were changes in the area of the right atrium, the anteroposterior size of the RV, and sPAP (Table 3). The results obtained in the long-term period did not significantly differ from the results immediately after the BPA, which proves the persistent effect after BPA procedure (Figure 1).

Table 3 Dynamics of right hear hemodynamic and functional characteristics after a series of BPA according to echocardiography

Parameter	Before BPA	One month after last BPA	1y after last BPA	p
Eccentricity index	1.7 (1.5;1.8)	1.2 (1.15;1.45)	1.2 (1.1;1.3)	0.006
Right atrium area cm^2	25 (22;30.5)	18.5 (16.5;21)	18 (16.5;21.5)	0.002
Thickness of the front wall of the RV, cm	0.6 (0.5;0.7)	0.5 (0.48;0.6)	0.5 (0.46;0.6)	0.08
Anterior-posterior size of RV, cm	3.75 (3.4;4)	3.35 (3.03;3.5)	3.25 (2.95;3.4)	0.001
Anterior-posterior size of RV, apically, cm	4.9 (4.4;5.4)	4.5 (4.15;4.8)	4.3 (4.05;4.6)	0.07
Systolic pulmonary artery pressure. mmHg	82 (71.5;90.8)	55 (47.2;64.8)	52 (45;67)	0.001
Mean pulmonary artery pressure. mmHg	43 (40;54.2)	33 (28.8;36.5)	33.5 (29.5;42.8)	0.03
Tricuspid regurgitation 3/2/1	8/11/3	1/9/12	1/8/13	0.01
TAPSE, cm	1.55 (1.4;1.92)	1.95 (1.8;2.3)	1.9 (1.7;2.4)	0.01
Diameter of pulmonary artery trunk, cm	3.15 (3;3.62)	3.2 (2.77;3.4)	2.9 (2.8;3.25)	0.01



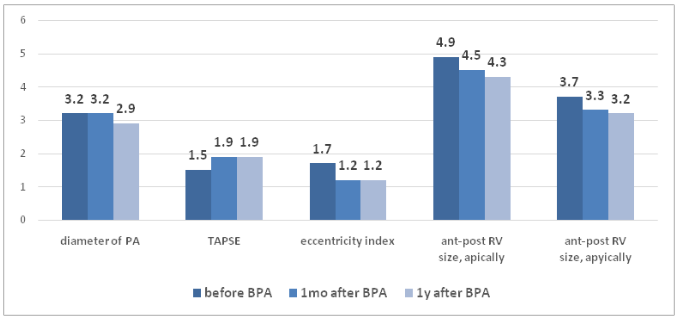


Figure 1 Dynamics of right hear hemodynamic and functional characteristics after a series of BPA according to echocardiography.

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Discussion

The main cause of disability in patients with pulmonary hypertension is right ventricular and then biventricular heart failure. A reverse remodeling of the right heart chambers immediate after the BPA was already proved earlier thus the objective of our study was to evaluate long-term results. Earlier Reesink et al.[7] have described RV reverse remodelling after successful TEE in CTEPH patients using MRI.[7] Also there are couple of studies which demonstrate the efficacy of BPA for RV reverse remodeling and dysfunction in patients with inoperable CTEPH.[6,8] All of them proved that BPA could be a safe and effective therapy for restoring RV function and structure immediate after the procedure. But nowadays there is no data of the persistence of the BPA effect for RV in the long-term period. In the present study, in order to assess the structural and functional changes in the heart muscle, we studied the dynamics of the most commonly used diagnostic method in the medical practice: echocardiography. According to the results of echocardiography, in all patients after the final BPA and in the long-term period, a significant improvement in all main parameters reflecting the state of the right heart chambers was shown. It proves the persistent long-term result of the BPA for RV. The revealed patterns confirm echocardiography as useful method not only for risk stratification, but also as indicator of the effectiveness of BPA. Several limitations of the present study should be mentioned. First, this study was performed retrospectively, without any control subjects. Moreover, the number of patients enrolled in the study was small what was primarily associated with epidemiology of inoperable CTEPH. Also we did not assess myocardial changes in the RV with MRI and did not compere the accuracy of our data with MRI. Therefore, future larger prospective studies need to be performed.

Conclusion

According to the results of this study, it was proved that BPA not only stops the progression of right ventricular failure, thereby stabilizing the disease, but also has a persistent long-term result. Positive reverse remodeling claims BPA as an instrument for improvement of disease prognosis.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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