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COMPARATIVE CLINICAL CHARACTERISTICS OF PATIENTS WITH VARIOUS FORMS OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE, ACCORDING TO THE CLINICAL CLASSIFICATION

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SUMMARY

Objective: to conduct a comprehensive analysis of the clinical, functional, hemodynamic profile of patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) according to the Russian Registry.

Materials and methods: The study involved 30 patients with Eisenmenger syndrome, 25 patients with PAH associated with prevalent systemic-to-pulmonary shunts and 26 patients with PAH after defect correction. All patients had been entered in the Russian registry (NCT03707561). A comparative analysis of clinical, functional, hemodynamic parameters was held. The diagnosis was established by the algorithm proposed in the Russian guidelines for the diagnosis and treatment of PH (2016).

Results: The patients of three subgroups of PAH-CHD were comparable in age and sex. The time from the onset of symptoms to the final diagnosis in the first and second PAH-CHD subgroups was significantly longer: on average, it took three years to establish the diagnosis, whereas in patients with PAH after defect correction, on average, after 9 months the correct diagnosis was made (p=0,0006). Patients with Eisenmenger syndrome were characterized by significantly high values of mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) according to right heart catheterization (mPAP (81,0 [72,0;92,0] mm Hg against 52,0 [41,0;75,0] mm Hg, p=0,001 and PVR 2329,0 [1333,0;2778,0] dyn*sec*cm-5 vs. 954,5 [591,0;1439,0] dyn*sec*cm-5, p=0,02) compared with the second subgroup of PAH-CHD, and significant decrease in arterial blood oxygen saturation (SpO2) (90,0 [85,0;93,0]% vs. 94,5 [92,5;96,0]% and 96,0 [92,0;98;0]%) compared with patients of the other subgroups (p=0,002).

Conclusions: Patients with PAH-CHD are a heterogeneous population, the division of which is presented in the clinical classification, and therefore have a different course of the disease. Analyzing the data of patients with PAH-CHD, we found various clinical, functional, physical and hemodynamic features of these patients. With comparable 6MWT and FC (WHO), patients with Eisenmenger syndrome have the highest values of PAP and PVR, as well as lower values of arterial blood oxygen saturation compared to other subgroups of PAH-CHD. In the group of patients with PAH associated with prevalent systemic-to-pulmonary PVR was significantly less compared to other groups of PAH-CHD. In patients with PAH after defect closure, the correlation between 6MWT and FC (WHO) and the area of the right atrium was detected. The obtained data can be useful in the choice of management of these patients.

Keywords: *pulmonary arterial hypertension, congenital heart disease, Eisenmenger syndrome, PAH after defect correction.*

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INTRODUCTION

According to Guidelines of the European Society of Cardiology for diagnosis and treatment of PH dated 2015 and Russian Guidelines dated 2016, a diagnosis of PAH is made when the mean pulmonary artery pressure (mPAP) is increased by 25 and more mm Hg at rest according to findings of the right heart catheterization (RHC) and is one of the most serious complications of congenital heart disease (CHD). PAH-CHD is the third most prevalent pathology after idiopathic PAH (IPAH) and PAH associated with connective tissue diseases in the European countries and the second most prevalent pathology according to the data of the Russian Registry [1,2,3].

The Guidelines of the European Society of Cardiology for Diagnosis and Treatment of PH dated 2015 and the Russian Guidelines dated 2016 suggested a clinical classification of PAH-CHD which distinguished four main groups: 1) Eisenmenger syndrome, 2) PAH associated with prevalent systemic-to-pulmonary shunts, 3) PAH in patients with small/coincidental defects, 4) PAH after defect correction [1,3].

The Guidelines of the European Society of Cardiology for Diagnosis and Treatment of PH dated 2009 provided an anatomical and pathophysiological PAH-CHD classification for more accurate characterization of a specific patient with CHD (Table 1) [4].

One should emphasize PAH-CHD heterogeneity depending on the clinical variant by the above clinical classification.

The objective of the present study was to analyze the parameters of the clinical, functional, hemodynamic profile of patients with PAH-CHD as a complex according to the clinical classification.

MATERIALS AND METHODS OF THE STUDY

The study included in total of 81 patients following inclusion/exclusion criteria. The study involved 30 patients (22 females and 8 males) with PAH-CHD and Eisenmenger syndrome, 25 patients with PAH-CHD and prevalent left-to-right shunt (21 females and 4 males) and 26 patients (23 females and 3 males) with PAH after defect correction (residual PAH) who were hospitalized for the management to the Department of Pulmonary Hypertension and heart diseases of the Federal State Budget-funded Institution National Medical Research Center of Cardiology of MoH of Russia in the period from 01.01.2016 to 01.01.2019. All patients were included in the Russian registry (NCT03707561) [7].

The inclusion criteria were the age above 18 years; verified diagnosis of PAH associated with simple CHD; a signed informed consent for participation in the study.

The exclusion criteria were the age under 18 years, pulmonary artery wedge pressure (PAWP) more than 15 mm Hg according to findings of RHC; PAH of other established etiology; PH of other etiology (left heart diseases, pulmonary diseases, mixed pathology); coronary heart disease confirmed by findings of MSCT of the coronary arteries or coronary angiography; cerebrovascular events over the last 6 months; pregnancy, lactation; diseases of musculoskeletal system preventing 6MWT; severe hepatic function disorders (Child-Pugh score of more than 9, class C); severe renal function disorders (GFR of less than 15 ml/min), demand of hemodialysis.

PAH-CHD diagnosis was made by an algorithm suggested in the Russian Guidelines for Diagnosis and Treatment of PH (2016) and European Guidelines of ESC/ERS 2015 [1,3].

Table 1. Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (modified in Venice, 2003)

1. Type
1.1. Simple pre-tricuspid shunts
1.1.1 Atrial septal defect (ASD)
1.1.1.1 Ostium secundum
1.1.1.2 Sinus venosus
1.1.1.3 Ostium primum
1.1.2 Total or partial unobstructed anomalous pulmonary venous return
1.2. Simple post-tricuspid shunts
1.2.1 Ventricular septal defect (VSD)
1.2.2 Patent ductus arteriosus (PDA)
1.3. Combined shunts
1.4. Complex congenital heart disease
1.4.1 Complete atrioventricular septal defect
1.4.2 Truncus arteriosus
1.4.3 Single ventricular physiology with unobstructed pulmonary blood flow
1.4.4 Transposition of the great arteries with ventricular septal defect (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5 Other
2. Dimension
2.1. Hemodynamic (specify Qp/Qs)
2.1.1 Restrictive (pressure gradient across defect)
2.1.2 Nonrestrictive
2.2. Anatomical
2.2.1 Small to moderate (atrial septal defect ≤ 2.0 cm and ventricular septal defect ≤ 1.0 cm)
2.2.2 Large (atrial septal defect > 2.0 cm and ventricular septal defect >1.0 cm)
3. Direction of shunt
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional
4. Associated cardiac and extracardiac abnormalities
5. Repair status
5.1 Inoperable
5.2 Palliated [specify type of surgery, age at surgery]
5.3 Repaired [specify type of surgery, age at surgery]

Transthoracic Echo was performed using the Vivid E9 ultrasonic device of expert class (GE Healthcare, USA). The M5S-D sensor was used for recording images in 2D mode and the 4V-D sensor was used for recording images in 3D mode. The functional status was assessed using the 6-minute walk test (6MWT).

Statistical analysis of the obtained data was performed with the

Table 2. Demographic characteristics of patients with PAH-CHD

	Eisenmenger syndrome (n=30)	PAH-CHD with prevalent left-to-right shunt (n=25)	Residual PAH (n=26)
Age, years	35.5 [28.0; 53.0]	36 [21.0; 51.0]	35.5 [23.0; 48.0]
Gender: Females Males	 22 (73%) 8 (27%)	 21 (84%) 4 (16%)	 23 (88%) 3 (12%)
BMI, kg/m^2	22.5 [19.7; 25.0]	20.7 [19.0; 23.0]	23.4 [21.1; 26.6]

help of STATISTICA 10.0 program (StatSoft, USA). The data are presented as mean and standard deviation and also median, 25% and 75% percentiles. The following statistical methods were used for assessment of the obtained results: Mann-Whitney U-test, analysis of statistical significance of sigh differences in independent and dependent samples using t-test, chi-squared test.

RESULTS

When analyzing the demographic characteristics of patients with PAH-CHD we see that all groups were comparable by age and gender. BMI was also comparable in the three groups (Table 1).

All patients with PAH-CHD had simple heart disease: atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA) and/or partial anomalous pulmonary venous connection (PAPVC). In the patient group with Eisenmenger syndrome, 13% of patients had ASD, ASD was combined with PAPVC in one of these patients, 57% of patients with VSD and 33% of patients with PDA. Two patients had a combination of VSD and PDA. The defect size was 2.0 [1.8; 2.4] cm.

ASD was the predominant defect in the patient group with PAH-CHD with left-to-right shunt; it was observed in 17 (68%) patients; ASD was combined with PAPVC in four patients. VSD was revealed in 16% of patients; it was combined with PAPVC in one case and with PDA in 16%. The defect size was 2.1 [1.9; 2.37] cm.

Patients of residual PAH group underwent defect correction at different age. Median of the age, when a defect was closed, was 7.5 [5.0; 23.0] years. This group included 7 patients (27.0%) after closing ASD, 11 patients (42.3%) after VSD correction and 8 patients (30.7%) after the surgical treatment of PDA. It should be mentioned that closing ASD, resulting in the development of severe PAH, was performed at the mature age and median was 50.0 [22.5; 54.5] years. Median of the age of VSD and PDA correction was 5.0 [4.0; 9.5] years (Fig. 1).

Thus, VSD was confidently the most prevalent defect resulting in PAH in patients with large defects with left-to-right shunt that in patients with Eisenmenger syndrome (p=0.0001) and residual PAH (p=0.008). PAPVC was observed more often in patients of group 2 than in patients of group 1 (p=0.04) and group 3 (p=0.01). VSD was the prevailing defect resulting in Eisenmenger syndrome (p=0.0009) and residual PAH (p=0.03) as compared to PAH-CHD group 2.

When analyzing the age of symptom manifestation in patients with Eisenmenger syndrome we revealed that it was 17.0 [8.0; 25.0] years that proved to be confidently lower than in patients with predominant left-to-right shunt, i.e. 27.0 [15.0; 38.0] years and it was also 27.0 [23.0; 44.0] years (p=0.03) in patients with residual PAH. The period from the manifestation of the symptoms to verification of the diagnosis of PAH in patients with Eisenmenger syndrome coincided with that in PAH-CHD group and left-to-right shunt and was approximately 3 years. The period of diagnosis verification was 9 months (p=0.0006) in the PAH group after defect correction.

Dyspnea was the main symptom at the beginning of the disease in all three groups; it was 93.3%, 92% and 92.31%, respectively. Such complaints as chest pain (20% vs. 3.3%) (p=0.004) and palpitation (36% vs. 13.3%) (p=0.04) developed significantly more often in group 2 at the manifestation of PAH that in case of Eisenmenger syndrome. Besides that, palpitation was observed significantly more often in patients of group 3 (7.69%) than in patients of group 1 (13.3%) (p=0.01). Hemoptysis and asthenia were seen significantly more often in patients with Eisenmenger syndrome than in case of residual PAH (13.3% vs. 0%, p=0.02 and 36.7% vs. 11.54%, p=0.03, respectively) (Fig. 2).

When analyzing clinical symptoms in case of the long-term course of PAH-CHD it was revealed that dyspnea was the main symptom in 100% of cases in all three groups. The comparison of other symptoms did not reveal any significant difference in the three groups (Fig. 3).

The study of the mean duration of clinical symptoms in different PAH-CHD groups revealed that dyspnea was the most long-term symptom. So, the maximum complaint of dyspnea was observed in patients with PAH-CHD with left-to-right shunt and was 15.0 [9.0; 23.9] years. This complaint disturbed patients with Eisenmenger's syndrome for a little bit shorter period: 9.13 [3.2; 17.37] years, and patients with residual PAH: 7.79 [3.0; 10.5] years. But any significant difference was not found. Besides that, the most long-term complaints included asthenia (3.5 [1.95; 12.3] years, 1.5 [1.0; 4.0] years, 2.0 [1.0; 3.0] years, respectively), palpitation (2.0 [1.0; 3.0] years, 2.0 [1.0; 4.0] years, 1.75 [1.0; 3.0] years, respectively), syncope (3.0 [3.0; 3.17] years, 1.33 [1.0; 2.33] years, 1.0 [1.0; 1.0] years, respectively). The duration of syncope was significantly longer in Eisenmenger syndrome than in the case of residual PAH (p=0.004) (Table 3).

When analyzing the rate of concomitant diseases in patients with PAH-CHD we paid attention to the fact that CHF was observed in more than a half of patients in each group (53.3%, 52% and 53.8%, respectively). Arrhythmia such as atrial fibrillation/flutter was seen more often in group with PAH associated with large defects and left-to-right shunt (28%); above disturbances were found more often in patients with residual PAH (26.9%) than in case of Eisenmenger syndrome (10%) but they did not reach a significant difference (Fig. 4).

Figure 4. Rate of concomitant diseases in patients with PAH-CHD

The initial assessment of the functional class found that patients were comparable by the functional class in all three groups and most patients belonged to FC 3 (WHO) (70% in the group with Eisenmenger syndrome, 60% in the group with PAH-CHD with left-to-right shunt and 64% in the group with residual PAH). Three groups were comparable by the distance in 6MWT (377.5 [330; 450] m, 350 [300; 431] m and 363 [318; 416] m, respectively).

The patient group with Eisenmenger syndrome had significantly decreased SpO2 both at rest – 86.5 [82.0; 91.0]% and after exercise – 72.5 [64.0; 84.0]% as compared to patients with PAH-CHD with left-to-right shunt (94 [93.0; 96.0]% and 90 [82.0; 94.0]%) and residual PAH (97 [95.0; 98.0]% and 97 [91.0; 97.0]%) (p=0.0002). Besides that, significant decrease of SpO2 was found after exercise in patients of group 2 as compared to patients after closing defects (p=0.008).

When assessing the structural and functional heart condition, we revealed a typical echocardiographic picture in all patients with PAH-CHD: right ventricular (RV) hypertrophy and dilation with signs of its volume and pressure overload, decreased left ventricular (LV) volume, pulmonary trunk and its branches dilation.

The comparative analysis found significantly higher values of eccentricity index and right ventricular diameter (RV) in patients with PAH-CHD and left-to-right shunt as compared to patient group with Eisenmenger syndrome (1.8 [1.5; 2.0] and 1.35 [1.2; 1.6], respectively, p=0.02 and 4.05 [3.7; 4.6] cm and 3.6 [3.05; 3.85] cm, respectively, p=0.02). But significantly larger right ventricular anterior wall thickness (RV AWT) was observed in patients with Eisenmenger syndrome (1.1 [0.8; 1.2] cm) as compared to group 2 (0.9 [0.8; 1.0] cm), p=0.03, and group 3 (0.8 [0.7; 1.1] cm), p=0.01. Besides that, significantly higher mean pulmonary artery pressure values were recorded in patients with Eisenmenger syndrome (73 [65; 75] mm Hg) as compared to patients with PAH-CHD with left-to-right shunt (56 [45; 66] mm Hg), p=0.03 and residual PAH (55 [48; 67] mm Hg), p=0.04. The significantly greater right ventricular area was observed in patients with residual PAH as compared to patients with Eisenmenger syndrome (21.7 [18.0; 30.0] and 19.0 [17.5; 22.0] cm2, p=0.005). A significant difference between TAPSE was also seen in patients of groups 2 and 3 (1.7 [1.45; 2.05] and 1.35 [1.15; 1.65], p=0.03). Patients with PAH after defect correction had greater inferior vane cava (IVC) dilation as compared to other groups (p=0.03) (Table 4).

Chest X-ray in all patients showed signs of pulmonary hypertension including increased Moore and Lupi coefficients, dilated descending

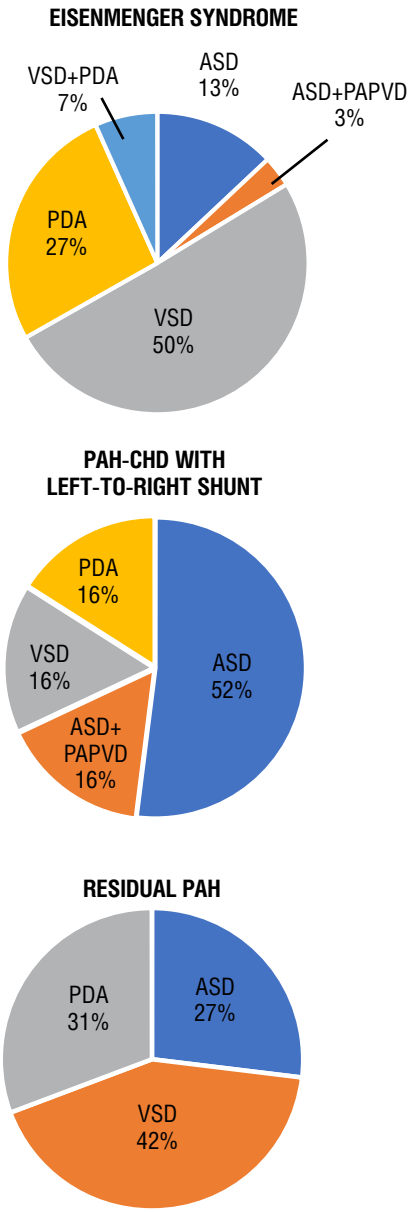

Figure 1. Percentage of simple CHD in different forms of PAH

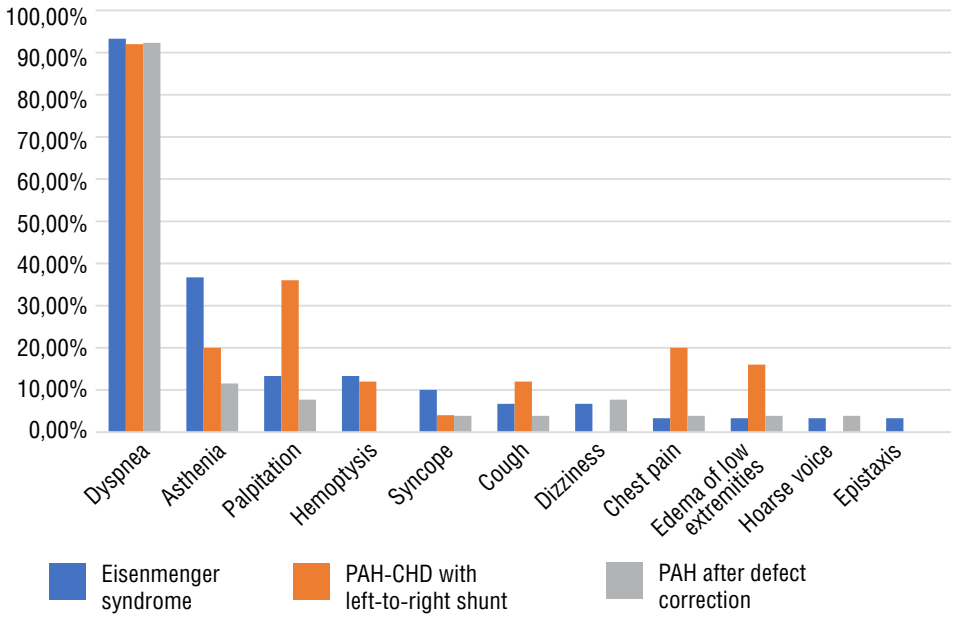

Figure 2. Main symptoms at the beginning of the disease in patients with PAH-CHD

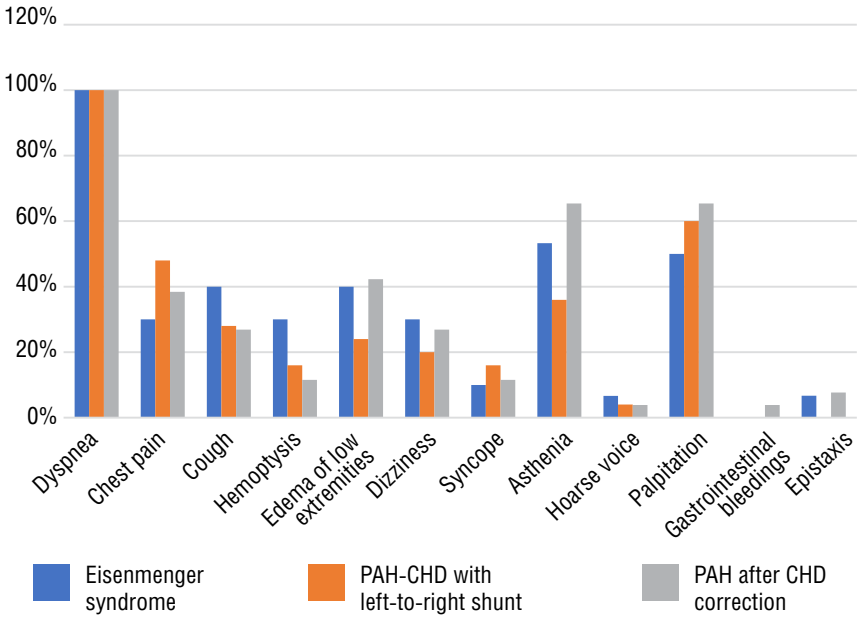

Figure 3. Clinical symptoms in case of long-term course of PAH-CHD

Table 3. Duration of clinical symptoms in patients with PAH-CHD

Clinical symptoms	Eisenmenger's syndrome	PAH-CHD with left-to-right shunt	PAH after CHD correction
Dyspnea, years	9.13 [3.2; 17.37]	15.0 [9.0; 23.9]	7.79 [3.0; 10.5]
Chest pain, years	0.56 [0.1; 1.0]	0.5 [0.5; 1.0]	0.04 [0.04; 0.04]
Cough, years	0.5 [0.5; 0.5]	0.1 [0.1; 0.1]	0.05 [0.05; 0.1]
Hemoptysis, years	0.5 [0.4; 0.6]	0.5 [0.5; 0.5]	0.5 [0.5; 0.5]
Edema of low extremities, years	1.7 [1.0; 2.0]	0.5 [0.5; 0.5]	0.25 [0.25; 0.33]
Dizziness, years	1.0 [1.0; 3.0]	1.17 [1.0; 3.0]	2.0 [1.0; 2.0]
Syncope, years	3.0 [3.0; 3.17]	1.33 [1.0; 2.33]	1.0 [1.0; 1.0]
Asthenia, years	3.5 [1.95; 12.3]	1.5 [1.0; 4.0]	2.0 [1.0; 3.0]
Palpitation, years	2.0 [1.0; 3.0]	2.0 [1.0; 4.0]	1.75 [1.0; 3.0]

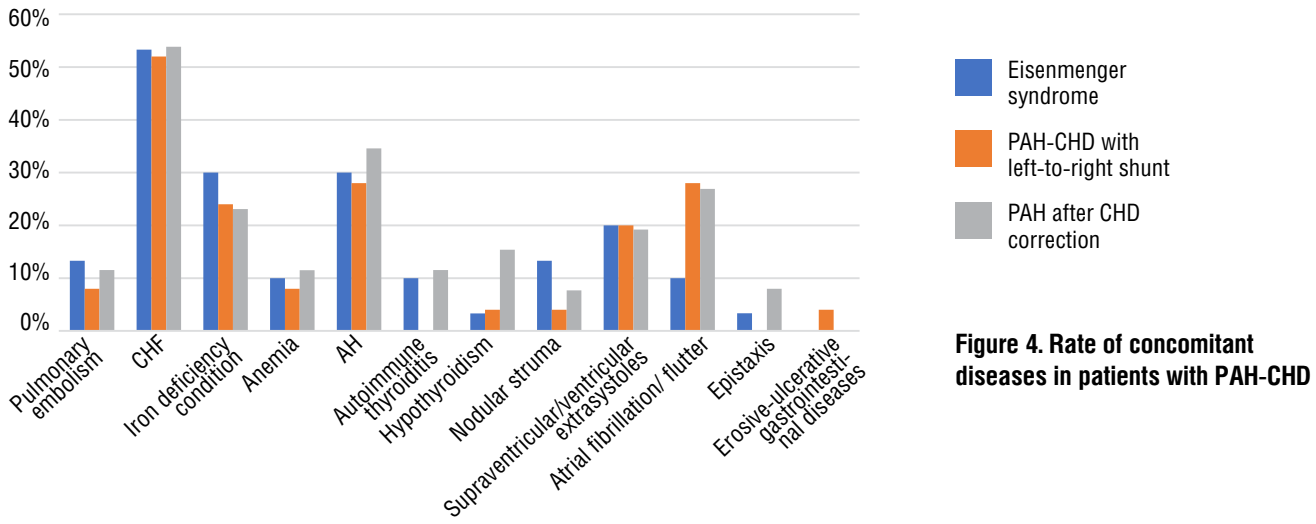

Figure 4. Rate of concomitant diseases in patients with PAH-CHD

branch of the right pulmonary artery. These measurements were statistically insignificant when compared between groups. The significant increase of cardiothoracic index was found in patients with residual pulmonary hypertension as compared to patients with Eisenmenger syndrome (55 [53; 59.5]% vs. 50.5 [48; 55]%, p=0.007).

According to RHC findings, all patients included in the study had criteria of precapillary PH (mPAP ≥25 mm Hg, PAWP <15 mm Hg). The investigation of the central hemodynamic parameters in patients with Eisenmenger syndrome revealed significantly higher sPAP (117.5 [102.0; 131.0] mm Hg vs. 91.0 [73.0; 98.0] mm Hg, p=0.0006), mPAP (81.0 [72.0; 92.0] mm Hg vs. 52.0 [41.0; 75.0] mm Hg, p=0.001), dPAP (57.0 [42.0; 64.0] mm Hg vs. 36.0 [24.0; 57.0] mm Hg, p=0.05) and also lower arterial blood oxygen saturation (SpO2) (90.0 [85.0; 93.0]% vs. 94.5 [92.5; 96.0] and 96.0 [92.0; 98.0]) as compared to patients of groups 2 and 3 (p=0.002) in contrast to patients with PAH-CHD with left-to-right shunt. We also observed significantly higher pulmonary vascular resistance (PVR) in patients with Eisenmenger syndrome (2329.0 [1333.0; 2778.0] dyn*s*cm-5 vs. 954.5 [591.0; 1439.0] dyn*s*cm-5) as compared to group 2, p=0.02 (Table 5).

The results obtained by correlation analysis of 6MWT distance (6MDWT) and parameters of the instrumental investigation revealed a negative correlation between 6MDWT and right root width (r=-0.56, p=0.03) and also 6MDWT and RV diameter (r=-0.44, p=0.04) in the group with PAH-CHD with left-to-right shunt. It was also found that the larger the right atrium area (r=0.51), Moore index (r=0.84), Lupi index (r=0.53), right root width (r=0.64) were, the worse FC (WHO) (p<0.05) was.

The residual PAH group had a negative correlation between 6MDWT and RA area (r=-0.52, p=0.008), positive correlation between FC (r=0.43, p=<0.05) and RA area and also negative correlation between 6MDWT and presence of effusion in the pericardial cavity (r=-0.48, p=0.04).

DISCUSSION

S. Ramjug et al. used in their study used both classification types in 240 patients with PAH-CHD and showed that anatomical-pathophysiological subdivision characterized with post-tricuspid defects as ones having better survival rate as compared to patients with pre-tricuspid or complex defects (p<0.05). The comparison of the survival rate of these patients according to the clinical classification

Table 4. Echocardiographic parameters in patients with PAH-CHD

Parameters	Eisenmenger syndrome (n=30)	PAH-CHD with left-to-right shunt (n= 25)	Residual PAH (n=26)	P
S RA, cm^2	19.0 [17.5; 22.0]* 888	20.0 [16.0; 29.0]	21.7 [18.0; 30.0]*	0.005*
RV diameter, cm	3.6 [3.05; 3.85]*	4.05 [3.7; 4.6]*	3.7 [3.3; 4.4]	0.02*
RV AWT, cm	1.1 [0.8; 1.2]*	0.9 [0.8; 1.0]*	0.8 [0.7; 1.1]*	0.03* 0.01*
TAPSE, cm	1.6 [1.35; 1.95]	1.7 [1.45; 2.05]*	1.35 [1.15; 1.65]*	0.03*
Ao, cm	3.1 [2.9; 3.4]	3.0 [2.8; 3.3]*	3,3 [2,9; 3,4]*	0.02*
LA, cm	3.5 [3.2; 3.9]	3.6 [2.9; 4.2]	3.5 [3.2; 4.0]	0.8
LV EDD, cm	4.1 [3.8; 4.5]	4.0 [3.7; 4.5]	4.5 [3.8; 5.0]	0.1
PA trunk, cm	3.6 [3.4; 4.0]	4.0 [3.4; 4.4]	3.3 [3.0; 4.2]	0.1
PASP, mmHg	100 [85.0; 115.0]	95.5 [78.5; 112.5]	90.5 [72.0; 109.0]	0.4
mPAP, mmHg	73.0 [65.0; 75.0]*	56.0 [45.0; 66.0]*	55.0 [48.0; 67.0]*	0.03* 0.04*
PADP, mm Hg	49.5 [43.5; 55.0]	48.5 [38.0; 62.0]	44.0 [27.0; 51.5]	0.3
IVC, cm	1.95 [1.8; 2.2]*	1.8 [1.7; 2.0]*	2.0 [1.8; 2.5]*	0.03*

*Note: * - statistically significantly differing parameter values. Data is presented as median, 25th and 75th distribution quartiles. Ao – aorta; LA – left atrium; LV EDD – left ventricular end-diastolic dimension; RV diameter – right diameter; RPA – right pulmonary artery; LPA – left pulmonary artery; PASP – pulmonary artery systolic pressure; mPAP – mean pulmonary artery pressure; PADP – pulmonary artery diastolic pressure; TAPSE – tricuspid annular plane systolic excursion), IVC – inferior vena cava*

Table 5. Parameters of right heart catheterization in patients with PAH-CHD

Parameters	Eisenmenger syndrome (n=30)	PAH-CHD with left-to-right shunt (n= 25)	Residual PAH (n=26)	P
sPAP, mm Hg	117,5 [102,0;131,0]*	91,0 [73,0;98,0]*	82,0 [79,0;101,0]	0,0006*
mPAP, mm Hg	81,0 [72,0;92,0]*	52,0 [41,0;75,0]*	62,0 [57,0;66,0]	0,001*
dPAP, mm Hg	57,0 [42,0;64,0]*	36,0 [24,0;57;0]*	46,0 [42,0;53,0]	0,005*
mRAP, mm Hg	5,5 [3,0;9,5]	11,0 [7,0;15,0]	6,5 [2,0;9,0]	0,08
PAWP, mm Hg	8,0 [6,5;10,0]	10,0 [5,5;12,0]	5,5 [5,0;6,0]	0,4
CO, l/min	3,4 [2,45;4,2]	4,0 [2,9;6,4]	3,4 [3,2;3,7]	0,3
CI, l/min/m^2	2,0 [1,6;2,7]	2,1 [1,9;2,9]	1,9 [1,8;2,0]	0,4
PVR, dyn•sec•cm-5	2329,0 [1333,0;2778,0]*	954,5 [591,0;1439,0]*	1339,0 [882,0;1475,0]	0,02*
SvO2 ,%	65,5 [57,5;73,6]	69,5 [68,5;73,5]	61,5 [51,0;64,0]	0,05
SaO2, %	90,0 [85,0;93,0]*	94,5 [92,5;96,0]*	96,0 [92,0;98;0]*	0,002*

*Note: * – statistically significantly differing parameter values. sPAP – systolic pulmonary artery pressure; mPAP – mean pulmonary artery pressure; dPAP – diastolic pulmonary artery pressure, mRAP – mean right atrium pressure; PAWP – pulmonary artery wedge pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance; SvO2 – mixed venous blood saturation; SaO2 – blood oxygen saturation.*

did not reveal any significant differences although the survival rate was higher in all four groups than that in patients with IPAH [5].

A. Manes et al. compared patients according to the clinical classification PAH-CHD and concluded that patients with small defects and patients with PAH after defect correction had the worst prognosis [6].

The objective of our study was to perform the complex analysis of the clinical, functional and hemodynamic profile of patients with PAH-CHD: Eisenmenger syndrome, PAH-CHD due to prevalent left-to-right shunt, residual PAH to reveal the features of clinical symptoms and hemodynamic parameters in these patient groups. So, it was shown than making a diagnosis of PAH-CHD (groups 1 and 2) required on average 3 years what was evidence of the necessity to diagnose pulmonary arterial hypertension earlier.

The period of diagnosis verification was 9 months in the PAH group after defect correction. But one should pay attention to the age of defect correction which resulted in severe PAH in this patient category. So, a median of the age of ASD correction was 50.0 [22.5; 54.5] years and that of the age of VSD and PDA correction was 5.0 [4.0; 9.5] years. These findings show that it is necessary to diagnose and correct CHD earlier to achieve the success of the procedure. According to R. Kozlik-Feldmann et al., simple post-tricuspid shunts such as VSD and PDA should be corrected within the first two years of life to avoid pulmonary vascular system remodelling. And the full hemodynamic assessment and also estimation of oxygen transport and utilization are required for adults with pre-tricuspid left-to-right shunts (ASD, PAPVD) before considering a surgery [7].

Our study revealed that dyspnea was the leading symptom in all patients with PAH-CHD (93.3%, 92% and 92.31%). Besides that, the fact called attention that CHF was present in more than a half of patients in each group (53.3%, 52% and 53.8%, respectively) what is similar to the data obtained by C. Vijarnsorn et al. where dyspnea in combination with CHF was revealed in 62% of patients with PAH-CHD [8]. Hemoptysis and syncope were characteristic symptoms of patients with Eisenmenger syndrome what was comparable with the data obtained by C.S. Broberg et al. The authors pay attention to the fact that the clinical picture in patients with Eisenmenger syndrome can include hemoptysis, syncope and manifestations of right ventricular heart failure in addition to central cyanosis, dyspnea and fatigue [9].

It is known that adults with PAH-CHD have lower exercise tolerance. So, according to our findings, most patients with PAH-CHD (70%, 60% and 64%, respectively) belonged to FC 3 (WHO) what was in agreement with the data obtained by A. Manes et al., where FC 3 (WHO) included 68%, 50% and 59% in the same groups [6].

Three groups were comparable by 6MWT in our study (377.5 [330; 450] m, 350 [300; 431] m and 363 [318; 416] m, respectively) what was higher than values revealed by E. Kehmeier et al. (280±178 m) and was most likely associated with the effective PAH-specific therapy in our patients [10]. These values are a little bit lower than parameter values obtained by A. Manes et al. (367±108 m, 420±128 m and 415±136 m, respectively) [6].

Our findings of RHC showed significantly higher sPAP, mPAP, dPAP, PVR values and lower arterial blood oxygen saturation levels in PAH-CHD group with Eisenmenger syndrome what was in agreement with the results obtained by C. Vijarnsorn et al. who revealed higher mPAP and PVR as compared to other groups of the clinical classification of PAH-CHD [8], results of A. Manes et al. [6] and REVEAL register [11]. The high mPAP and PVR values with simultaneous almost normal mRAP may be evidence supporting the hypothesis on better right ventricle contractility in this patient group.

PVR was lower in the group with PAH-CHD with left-to-right shunt as compared to other groups what also does not contradict the results obtained by A. Manes et al. [6] and maybe evidence of the milder course of pulmonary vascular diseases in this group.

CONCLUSIONS

Patients with PAH-CHD are a heterogeneous population, the division of which is presented in the clinical classification, and therefore have a different course of the disease. Analyzing the data of patients with PAH-CHD, we found various clinical, functional, physical and hemodynamic features of these patients. With comparable 6MWT and FC (WHO), patients with Eisenmenger syndrome have the highest values of PAP and PVR, as well as lower values of arterial blood oxygen saturation compared to other subgroups of PAH-CHD. In the group of patients with PAH associated with prevalent systemic-to-pulmonary PVR was significantly less compared to other groups of PAH-CHD. In patients with PAH after defect closure, the correlation between 6MWT and FC (WHO) and the area of the right atrium was detected. The obtained data can be useful in the choice of management of these patients.

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