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CLINICAL FEATURES OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL SYSTEMIC-TO-PULMONARY SHUNTS

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ABSRACT

Pulmonary arterial hypertension (PAH), associated with congenital heart disease (CHD) (PAH-CHD), despite the similarities of histological lesions, is a different from other forms of PAH. PAH-CHD is represented by a heterogeneous patient population with varying defect locations, concomitant diseases, indications and contraindications to surgical correction; also, some patients have a history of a defect closure. According to the European guidelines for the diagnosis and treatment of pulmonary hypertension 2015, there are four main groups in the clinical classification of PAH-CHD: 1) Eisenmenger's syndrome, 2) PAH associated with prevalent systemic-to-pulmonary shunts, 3) PAH with small/concidental defects, 4) PAH after defects correction. The evolution of the guidelines for the surgical correction of CHD has seen in recent years. Risk stratification has a great importance for further prognosis, response to treatment and timing of surgical correction. For optimal treatment carefulness and expertise in diagnosis and differential diagnosis should be exercised. A better understanding of clinical features, risk stratification and the assessment of the impact of a genetic background will help to determine the best clinical management, which is associated with better quality of life and improved survival in patients with PAH-CHD.

Key words: *pulmonary hypertension, congenital heart defects, the syndrome Eisenmenger, residual pulmonary hypertension*

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INTRODUCTION

Congenital heart diseases (CHD) with the presence of intra-cardiac or extra-cardiac shunts, associated with constant overload with an elevated volume in the pulmonary circulation, leads to an increase in pulmonary vascular resistance (PVR) and, consequently, to the development of pulmonary arterial hypertension (PAH). PAH can develop at any stage of the disease and is accompanied by a decrease in both tolerance to physical activity and the quality of life, as well as high morbidity and mortality [1]. Despite the similarity in terms of histological damage to the lungs, PAH associated with CHD (PAH-CHD) is markedly different from other forms of PAH and represents a heterogeneous population of patients with different localization of defects, comorbidities. Also, some patients previously underwent surgical correction of a heart defect. In recent years, progress has been made in the development of new treatment methods, which has had a significant impact on the clinical course of this disease. The expected increase in the number of adults with complex CHD presents practical interest since most such patients have an increased risk of developing PAH. In the case of the development of pulmonary hypertension, patients should be followed up at expert PAH centers. However, in routine practice physicians may also encounter such patients. [2]

CLASSIFICATION OF PAH-CHD

In 1897, Austrian cardiologist Victor Eisenmenger first described a patient with ventricular septal defect (VSD) with cyanosis and dyspnea since infancy and died at the age of 32 from massive hemoptysis [3]. The term "Eisenmenger syndrome" was proposed in 1965 by Paul Wood and is now widely used for all large systemic-to-pulmonary shunts with bi-directional flow of blood or pulmonary-to-systemic shunts leading to PAH [4].

The recommendations of the European Society of Cardiologists for diagnosis and treatment of PH 2009 presented an anatomo-pathophysiological classification of PAH-CHD (Table 1) to characterize each specific patient with CHD more accurately [5].

According to the recommendations of the European Society of Cardiology for Diagnosis and Treatment of pulmonary hypertension 2015, there are four main groups of PAH-CHD in the clinical classification: 1) Eisenmenger syndrome; 2) PAH associated with systemic-to-pulmonary shunts; 3) PAH with small or coincidental cardiac defects, 4) PAH after defect closure [6].

PATHOMORPHOLOGY OF PAH-CHD

The histopathological changes in the pulmonary vessels, accompanying PAH-CHD are generally indistinguishable from changes in idiopathic pulmonary hypertension (IPAH). These include hypertrophy of the media, fibrotic thickening of the intima and, with more severe PH, plexiform lesions, and necrotizing arteritis. Dysfunction of the endothelium leads to remodeling of the pulmonary vascular bed, which causes an increase in pulmonary vascular resistance (PVR).

There is a hypothesis on the possibility of having IPAH or genetic mutations in patients with severe PAH and minor defects, which is based on reports of the presence of IPAH in the relatives of such patients, and doubts that a small volume of a systemic-pulmonary shunt can lead to a significant overload of pulmonary circulation and endothelial dysfunction [7].

Table 1. Anatomico-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
1.3. Combined shunts (describe combination and define predominant defect)
1.4. Complex congenital heart disease
1.4.1. Complete atrioventricular septal defect
1.4.2. Truncus arteriosus
1.4.3. Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4. Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5. Other
2. Dimension (specify for each defect if >1 congenital heart defect)
2.1. Hemodynamic (specify Qp/Qs)
2.1.1. Restrictive (pressure gradient across the defect)
2.1.2. Nonrestrictive
2.2. Anatomic
2.2.1. Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
2.2.2. Large (ASD >2.0 cm and VSD >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. Unoperated
5.2. Palliated (specify type of operation[s], age at surgery)
5.3 .Repaired (specify type of operation[s], age at surgery)

EPIDEMIOLOGY AND GENETICS

It is well known that over the past decade, significant advances in the field of pediatric cardiovascular surgery have led to an increasing survival of patients with CHD. More than 90% of them now reach adulthood. The frequency of development of PAH is 5-10% among all patients with CHD and depends on the location and size of the defect. Thus, the occurrence of PAH in patients with a patent ductus arteriosus (PDA) can be expected in 3% of patients, with an ASD in 10-17%, in half of the patients with VSD, with complete atrioventricular septal defects – 90 % and in all patients with an atrioventricular canal [8]. It is believed that the risk of developing Eisenmenger syndrome is determined by the size of the systemic-to-pulmonary shunt and the volume of pulmonary blood flow, while larger defects are associated with a higher risk. Also, the location of the defect is very important, for example, a unrepaired ASD leads to the development of Eisenmenger syndrome in only 5-10% of cases,

while in the case of unrepaired VSD Eisenmenger syndrome develops in 50% of cases. The time to occurrence of PH differs significantly depending on the location of the defect. Thus, in patients with PDA or VSD, Eisenmenger syndrome occurs earlier than in patients with atrial septal defect. With more complex defects, such as a complete atrioventricular septal defect or an atrioventricular canal, PAH often develops early in life [9].

Finally, in some patients, severe PAH can be detected after surgical correction of CHD. However, early correction of CHD usually prevents the subsequent development of PAH. It has been proved that residual circulatory disorders in a pulmonary circulation in patients operated for CHD and complicated with PAH require diagnosis in time and adequate correction [10].

According to studies, the incidence of PAH in some patients with similar CHD differs. Screening for genetic mutations revealed that bone morphogenic protein receptor type 2 (BMPR2) mutation was observed in patients with PAH-CHD, although significantly less than in hereditary PAH or IPAH patients (6% vs 50% and 26%, respectively) [11].

Among all forms of PAH, the incidence of PAH-CHD occupies third place in Europe after IPAH and PAH associated with systemic diseases of connective tissue, and the second place among the countries of Asia and Russia [12]. However, in recent years, there has been an increase in the percentage of patients with PAH-CHD observed in expert centers in Europe. According to 7 UK PAH-centers, the prevalence of PAH-CHD was 30.2% in the PAH population that was equivalent to the number of patients with IPAH – 33.6%, and much higher than previous reports. The authors concluded that patients with PAH-CHD were more likely to be sent to specialized PAH-centers for follow-up [13]. According to the Dutch register, there is a shift in PAH-CHD subgroup distribution: as a result of early diagnosis and repair of CHD, the prevalence of Eisenmenger syndrome has declined, whereas the number of adult patients with PAH after defect closure appears to have increased (fig. 1) [14].

CLINICAL MANIFESTATIONS PAH-CHD

Among patients with congenital systemic-to-pulmonary shunts, there is a large heterogeneity in size and location of the shunt, the presence of complex defects and the indications for surgical correction. These changes may explain some important differences in these patients regarding response to therapy with vasodilators and clinical course of the disease. Clinical signs, such as reduced exercise tolerance, dyspnoea, and fatigue, may cause suspicion of PAH. Eisenmenger syndrome is characterized by the presence of an initial systemic-to-pulmonary shunt leading to the progression of PAH and reversion or bi-directional blood shunting

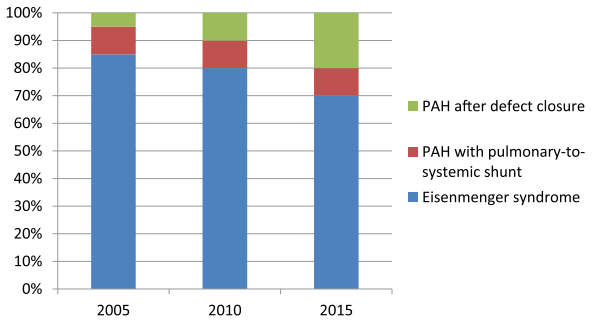

Figure 1. Changing subgroup distribution of PAH-CHD: patients on treatment at two CHD designated centers in the Netherlands from 2005 to 2015

and the development of cyanosis. Cyanosis causes patients with Eisenmenger syndrome to be highly symptomatic with poor quality of life and severe functional limitations [15]. Thus, the clinical picture, in addition to central cyanosis, dyspnoea, fatigue, may include hemoptysis, syncope, and manifestations of right ventricular heart failure. Reduction in saturation of arterial blood with oxygen leads to disruption of hemostasis, thrombocytopenia, due to which these patients are at risk of developing both bleeding and thrombosis. According to C.S. Broberg et al., parietal thrombosis of the proximal branches of the pulmonary artery associated with biventricular dysfunction and a decrease in the rate of pulmonary blood flow develops in 20% of patients and can lead to peripheral embolism and a partial lung infarction. The prognosis in such patients is one of the worst in the general population of adult patients with CHD, although it is better than in PAH with small or surgically corrected defects [16].

In patients with defects of medium and large sizes, while maintaining systemic-to-pulmonary shunting, there is no cyanosis at rest. In patients with small defects and high PVR, the clinical picture is very similar to IPAH. In patients with PAH after defect closure, the clinic develops immediately after the intervention or in several months/years with no residual defects [15].

Complications in the course of PAH-CHD are hemoptysis, pulmonary hemorrhage, acute pulmonary arterial thromboembolism, pulmonary artery dissection, cardiac arrhythmias, pulmonary edema, acute cerebrovascular accident / brain abscess, decompensation of chronic heart failure, syncopal conditions, hemostasis disorders, paresis of the vocal cords, hypertrophic osteoarthropathy, gout/ hyperuricemia, cholelithiasis, kidney dysfunction, infective endocarditis.

Transthoracic echocardiography is the most commonly used method in the initial evaluation on PAH-CHD to determine the location of cardiac defect, visualization of cardiac hemodynamics and provide an estimate of the pulmonary artery pressure (fig. 2)

In cases transthoracic echocardiography presents difficulties in diagnosing CHD (for example, partial abnormal drainage of pulmonary veins or PDA), transesophageal echocardiography becomes the verification method. With transoesophageal access, the high-frequency sensor is located close to the object, which provides excellent visualization.

Additional imaging techniques, such as magnetic resonance imaging (MRI) of the heart or computed tomography (CT), allow assessing the anatomical changes and the function of the right ventricle. The right heart catheterization should be considered for evaluation of hemodynamic parameters, as well as to support decisions on the possibility of shunt correction [17].

Laboratory tests are not useful in diagnosing PAH, but are necessary to determine the associated disorders, for example, thyroid disease and iron deficiency, and to provide information on disease severity and end-organ damage (circulating biomarkers such as brain-natriuretic peptide (BNP), N-terminal pro brain natriuretic peptide (NT-proBNP) and cystatin C) [18].

COMPLEx ISSUES OF SURGICAL CORRECTION

Recent advances in surgical and percutaneous techniques have allowed correction of defects with low preoperative risk. The timing of repair is crucial to avoid the development of PAH as early changes in pulmonary vascular bed are probably reversible if the shunt is closed. In general, patients with systemic-to-pulmonary shunts and normal PVR may safely undergo shunt closure. Hemodynamically insignificant shunts do not require closure. In the recent years, the evolution of recommendations for

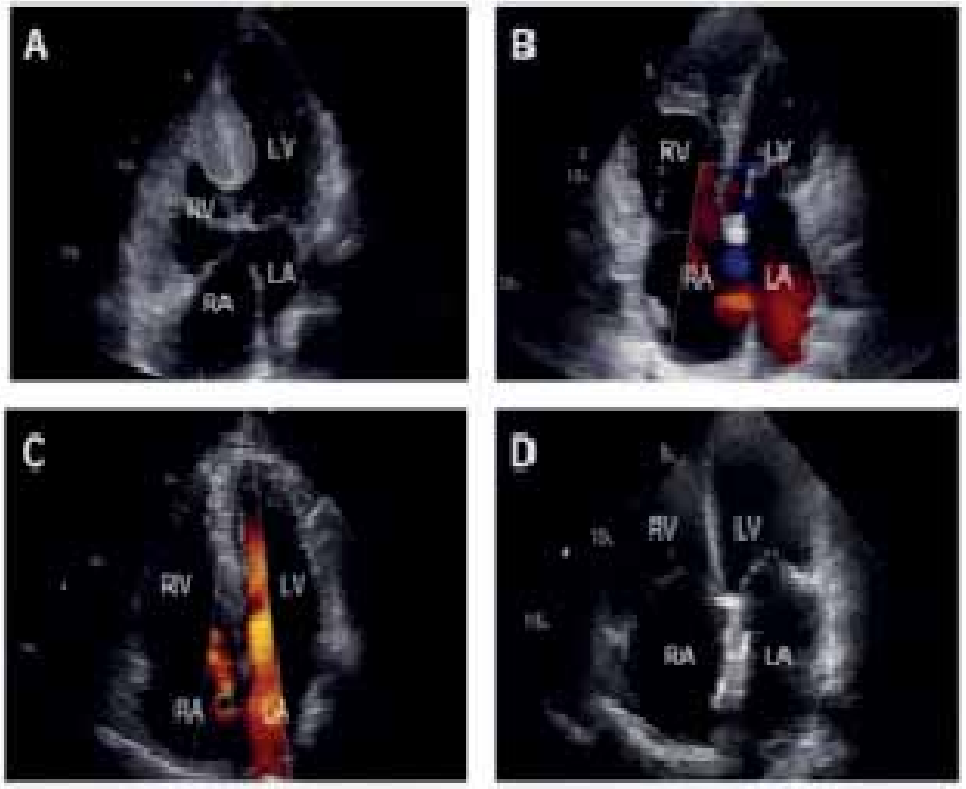

Figure 2. Transthoracic echocardiographic (apical four chamber view) images of the 4 clinical subgroups in pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD): (A) Eisenmenger syndrome: atrioventricular septal defect; (B) PAH associated with prevalent systemic-to-pulmonary shunt lesion: atrial septal defect with left-to-right shunt; (C) PAH associated with small or coincidental cardiac defect: secundum atrial septal defect; (D) PAH after defect closure: closed atrial septal defect. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.

the correction of CHD has been noted. If in 2008 it was proposed to operate almost all patients with systemic-to-pulmonary shunts, then in 2010 the indications for correcting the ASD became the ratio Qp / Qs >1,5, PVR <5 Wood units (I B), and to repair the VSD - Qp / Qs >1,5 (II a C). At present, the approaches to operability have been toughened, which are based on the evaluation of the PVR (PVR <2,3 Wood units) (II a C). The clinical solution for patients with border hemodynamic parameters remains the most complex issue (table 2) [18].

There is data on the possibility of partial closure of septal defects, for example, with flap patches or fenestrated occluding device, but recommendations defining the optimal fenestration size need further investigation [19].

A few studies demonstrated a good hemodynamic response to PAH-specific therapy allowing a successful surgical correction of the defect. However, only the results of the short-term postoperative period have been described; long-term results have not been published yet. Currently, this approach is not recommended.

It should be noted that significant proportion of patients who have udergone a successful correction of CHD in childhood may develop PAH years after the closure. According to the Dutch register, this risk is 15%. Accordingly, the decision to intervene should be based not only on technical capability but also on long-term prospects. A retrospective analysis revealed that the initial values of the PVR ≥5 Wood units, PVR index ≥6 Wood units•m2 and PVR / systemic vascular resistance ratio ≥0,33 contributed to the development of residual PAH in patients. However, the number of patients that did not develop PAH in a similar situation

Table 2. Evolution of guideline recommendations for correction in congenital heart disease with prevalent systemic-to-pulmonary shunts

Type	Correctable	AHA/ACC CHD Guidelines, 2008	ESC GUCH Guidelines, 2010	ESC/ERS PH Guidelines, 2015
ASD	Yes	All with RA and RV enlargement with or without symptoms	RV volume overload and PVR <5 WU regardless of symptoms	PVRi <4 WU•m^2 or PVR <2,3 WU
	No	Severe irreversible PAH and no L-R shunt	Eisenmenger syndrome	PVRi >8 WU•m^2 or PVR >4,6 WU
	Individual patient evaluation	Paradoxical embolism; Net left-right shunt, PVR <2/3 of SVR, PAP <2/3 of systemic levels or when responsive to pulmonary vasodilators or test occlusion of defect	Paradoxical embolism; PVR ≥5 WU but <2/3 of SVR or PAP <2/3 of systemic levels and net left-right shunt (Qp:Qs >1.5)	PVRi 4–8 WU•m^2 or PVR 2,3–4,6 WU
VSD	Yes	Qp:Qs ≥2 and LV volume overload; History of infective endocarditis	Symptoms of left-right shunting and no severe PVD; History of infective endocarditis; Asymptomatic with LV volume overload due to VSD	PVRi <4 WU•m^2 or PVR <2,3 WU
	No	Severe irreversible PAH	Eisenmenger syndrome or exercise-induced desaturation; VSD is small, not subarterial and no LV volume overload/PH	PVRi >8 WU•m^2 or PVR >4,6 WU
	Individual patient evaluation	Net left-right left-right shunt (Qp:Qs >1,5) and PAP <2/3 of SVR and PVR <2/3 of systemic levels; Net left-right shunt (Qp:Qs >1.5) and LV systolic/diastolic failure	Net L-R shunt (Qp:Qs >1,5) and PAP or PVR <2/3 of systemic levels	PVRi 4–8 WU•m^2 or PVR 2,3–4,6 WU

was not included in the report [20].

It is hard to predict the development of PAH after correction of the CHD. Therefore, a search for markers is currently underway. It was found that in patients who subsequently develop residual PAH, the number of circulating endothelial cells is higher compared to those after positive surgical correction. Animal models have demonstrated other potential markers for the development of PAH, such as inhibition of phosphodiesterase-1, activation of soluble guanylate cyclase and dichloroacetate, affecting reverse remodeling [17].

RISK STRATIFICATION

Stratification of risk is of great importance for clarifying the prognosis of disease progression, treatment response and the timing of intervention. In recent years, numerous predictors of mortality in PAH, such as a 6-minute walk distance, WHO functional class (FC), maximum oxygen uptake (VO_2 max), right ventricular failure, hemodynamic parameters, and biomarkers, have been identified and implemented in PAH guidelines for risk stratification and method of PAH treatment in general. Given the distinct differences between PAH-CHD and other forms of PAH, it is necessary to modify the widely used ESC/ERS guidelines table on disease severity, stability and prognostic parameters to PAH-CHD patients. One of such modifications has been proposed by M.A. Gatzoulis et al. for patients with Eisenmenger syndrome, though its predictive value has not been confirmed. The data indicate that FC, right ventricular failure, arrhythmias, NT-proBNP level, young age at presentation and complex cardiac anatomy are the predictors for the unfavorable outcome in PAH-CHD [21].

According to the results of the study M.M. Clavé et al., whose goal was to identify potential predictors of clinical outcomes in 67 patients with Eisenmenger syndrome, parameters such as initial FC (OR=3.07, 95% CI=1.01-9.34; P=0.048), severity of right ventricular dysfunction (OR=2.51 (light, moderate or severe dysfunction), 95% CI=1.22-5.19, P=0.013) and plasma concentration of Willebrand factor (1.74 quartiles, 95% CI=1.07-2.83, P=0.026) were identified as risk factors [22].

M.T. Schuijt et al. investigated 92 PAH-CHD patients and demonstrated that the deterioration to WHO FC IV (HR 18.34 for onset class IV), 50 m reduction of the distance in the 6-minute walk distance (HR 0.65 per 50 m), reduced saturation of oxygen at peak exercise by 5% (SaO2, HR 0.74 per 5%), NT-proBNP increase up to 1000 ng/l (HR, 2.25 per 1000 ng/l) and reduction the excursion of the tricuspid valve by 0.5 cm (TAPSE, HR 0,80 per 0,5 cm) significantly predicted mortality. Moreover, the deterioration of these parameters on serial measurements was more potent predictors compared to single result [23].

PAH-CHD has not only clear pathophysiological and hemodynamic features but also a better survival in comparison to other forms of PAH. The course of the disease is characterized by a slow progression. An expert approach to diagnosis, differential diagnosis, treatment tactics contributes to a better survival. The 20-year survival rate calculated using the Kaplan-Meyer curves is now 87% (77-93%) for the Eisenmenger syndrome group, 86% (60-96%) for the group with prevalence of systemic-to-pulmonary shunts, 66% (16-91%) in 15 years for small defects (p=0.015); the worst prognosis is in patients with residual PAH (36% [12-72%], p=0.0001) [24].

CONCLUSION

PAH-CHD patients comprise a heterogeneous population, and therefore the determining of optimal treatment tactics requires a thorough and expert approach. In recent years, significant progress has been made in the field of PAH-specific therapy. The study of clinical features, risk stratification and assessment of the effect of genetic background will help determine the best therapeutic and tactical approaches, which in turn is associated with improved quality of life and survival in PAH-CHD patients.

BIBLIOGRAPHY

1. *Lowe B.S., Therrien J., Ionescu-Ittu R. et al. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J. Am. Coll. Cardiol.2011;58:538–546. doi: 10.1016/j.jacc.2011.03.033.*
2. *Marelli A.J., Mackie A.S., Ionescu-Ittu R. et al. Congenital heart disease in the general population: Changing prevalence and age distribution. Circulation. 2007; 115: 163–172. doi: 10.1161/CIRCULATIONAHA.106.627224.*
3. *Eisenmenger V. Die angeboren defects des kammerscheidewand des herzen. Klin Med. 1897; 32:1-28.*
4. *Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J. 1958; 2: 701-709.*
5. *Galie N., Hoeper M.M., Humbert M. et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J, 2009; 30:2493-2537.*
6. *Galie N., Humbert M., Vachiery J.L. et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) Eur. Heart J. 2016; 37:67–119.*
7. *Morse J.H., Barst R.J., Fotino M. Familial pulmonary hypertension: immunogenetic findings in four Caucasian kindreds. Am Rev Respir Dis. 1992; 145:787–792.*
8. *Dimopoulos K., Wort S.J., Gatzoulis M.A. Pulmonary hypertension related to congenital heart disease: A call for action. Eur. Heart J. 2014;35:691–700. doi: 10.1093/eurheartj/eht437.*
9. *Van de Bruaene A., Delcroix M., Pasquet A., et al. The Belgian Eisenmenger syndrome registry: Implications for treatment strategies? Acta Cardiol. 2009; 64: 447-453. doi: 10.2143/AC.64.4.204160.*
10. *Olbinskaya L.I., Privalova E.V. Residual pulmonary hypertension. Cardiovascular therapy and prevention. 2003; 6:4-9 [in Russian].*
11. *Roberts K.E., McElroy J.J., Wong W.P. et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur. Respir. J. 2004; 24:371-374. doi: 10.1183/09031936.04.00018604.*
12. *Arkhipova O.A., Martynyuk T.V., Nakonechnikov S.N., Chazova I.Ye. Comparative assessment of demographic characteristics and functional abilities of patients with PAH in the Russian register and the major foreign registers. Book: abstracts of the III Russian Congress of Pulmonary hypertension. 2015. P. 35-36 [in Russian].*

13. Dimopoulos K., Wort S.J., Gatzoulis M.A. Pulmonary hypertension related to congenital heart disease: A call for action. Eur. Heart J. 2014; 35:691–700. doi: 10.1093/eurheartj/eht437.
14. Korten M.A., Helm P.C., Abdul-Khaliq H. et al. Competence Network for Congenital Heart Defects Investigators Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease. Heart. 2016; 102: 1552–1557. doi: 10.1136/heartjnl-2016-309437.
15. Chazova I.Ye., Martynyuk T.V. Pulmonary hypertension. M: Practice, 2015 [in Russian].
16. Broberg C.S., Ujita M., Prasad S. et al. Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 2007; 50:634-642.
17. Van Dissel A.C., Mulder B.J.M., Bouma B.J. The Changing Landscape of Pulmonary Arterial Hypertension in the Adult with Congenital Heart Disease. Journal of Clinical Medicine, 2017; 6(4), 40. http://doi.org/10.3390/jcm6040040.
18. Blok I.M., van Riel A.C., Schuuring M.J. et al. The role of cystatin C as a biomarker for prognosis in pulmonary arterial hypertension due to congenital heart disease. Int. J. Cardiol. 2016; 209:242–247. doi: 10.1016/j.ijcard.2016.02.003
19. Talwar S., Choudhary S.K., Saxena A. et al. Unidirectional valved patches for closure of septal defects in patients with severe pulmonary hypertension. Ann. Pediatr. Cardiol. 2008; 1: 114–119. doi: 10.4103/0974-2069.43876.
20. D'Alto M., Romeo E., Argiento P. et al. Hemodynamics of patients developing pulmonary arterial hypertension after shunt closure. Int. J. Cardiol.2013; 168:3797–3801. doi: 10.1016/j.ijcard.2013.06.036.
21. Gatzoulis M.A., Beghetti M., Landzberg M.J., Galie N. Pulmonary arterial hypertension associated with congenital heart disease: Recent advances and future directions. Int. J. Cardiol. 2014; 177: 340–347. doi: 10.1016/j.ijcard.2014.09.024.
22. Clavé M.M., Maeda N.Y., Castro C.R. et al. Factors influencing outcomes in patients with Eisenmenger syndrome: a nine-year follow-up study. Pulm Circ. 2017; 7 (3): 635-642. doi: 10.1177/2045893217721928.
23. Schuijt M.T.U., Blok I.M., Zwinderman A.H. et al. Mortality in pulmonary arterial hypertension due to congenital heart disease: Serial changes improve prognostication. Int J Cardiol. 2017; 243:449-453. doi: 10.1016/j.ijcard.2017.05.101.
24. Manes A., Palazzini M., Leci E. et al. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: A comparison between clinical subgroups. Eur. Heart J. 2014; 35: 716–724. doi: 10.1093/eurheartj/eht072.