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OPPORTUNITIES FOR OPTIMIZATION OF DRUG THERAPY BY ENDOTHELIN RECEPTOR ANTAGONISTS FOR THE PATIENT WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION AND ATRIAL SEPTOSTOMY

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ABSTRACT

The initiation of PAH-specific therapy in this case of IPAH was preceded by atrial septostomy. The chosen treatment plan put the patient at an unacceptable risk and did not contribute to the improvement of her clinical condition. The clinical case described in the paper demonstrates the importance of a reasonable approach to the implementation of palliative surgical interventions in patients with pulmonary hypertension in accordance with modern guidelines, as well as the possibility of optimizing drug therapy with endothelin receptor antagonists.

Keywords: *pulmonary arterial hypertension, idiopathic pulmonary arterial hypertension, atrial septostomy, endothelin receptor antagonists, macitentan.*

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Pulmonary arterial hypertension (PAH) is a severe progressive disease in which pronounced remodeling of the small pulmonary arteries and arterioles leads to an increase of pulmonary resistance, overload of the right ventricle, development of right ventricular heart failure and leads to fatal outcome [1].

The diagnostic criteria for PAH are a triad of the following hemodynamic parameters: an increase of the mean pulmonary artery pressure (PAPm) ≥25 mm Hg, pulmonary vascular resistance (PVR) of more than 3 Wood units with pulmonary artery wedge pressure (PAWP) ≤15 mm Hg by right heart catheterization (RHC) at rest [2].

According to the data of various registries, about half of patients with PAH have idiopathic pulmonary arterial hypertension (IPAH) [3].

IPAH is a rare disease of unknown etiology characterized by a pronounced increase in pulmonary vascular resistance and pressure in the pulmonary artery, often progressive course with the development of right ventricular failure, which causes premature death of patients [4].

Prior to the era of pathogenetic therapy of PAH, the prognosis of IPAH patients was dramatically poor. According to the first registry of IPAH, executed in the United States in 80-90s of the XXth century, the survival rate of 187 patients for 1, 3 and 5 years was 68, 48 and 34%, respectively [5]. Due to the implementation of PAH-specific therapy into clinical practice, the life expectancy of such patients has improved.

Currently, the following 4 drug classes are recommended for the treatment of patients with PAH: PDE-5 inhibitors, endothelin receptor antagonists (ERA), prostacyclin analogues (prostanoids), as well as the soluble guanylate cyclase stimulator riociguat. However, not all patients can achieve a significant improvement and/ or stabilization of the clinical condition even on the basis of

combination therapy affecting such pathogenetic targets, involved in the development and progression of PAH, as activation of endothelin-1 system, deficiency of endogenous prostacyclin and nitric oxide. In accordance with modern concepts of PAH management, only in the lack of the efficacy of triple PAH-specific therapy, when all possibilities of drug treatment have been depleted, an atrial septostomy can be considered as a palliative intervention to bridge the patient for lung transplantation.

The following clinical case is presented as an example, underlining the importance of a reasonable approach to the implementation of palliative surgical interventions in patients with pulmonary hypertension, as well as the possibility of optimizing drug therapy by endothelin receptor antagonists for the patients with IPAH.

Patient P., female, 39 years old with the diagnosis of IPAH has been followed in the Department of Pulmonary hypertension and Heart disease of the Institute of Clinical Cardiology named after Myasnikov A.L. since 2013. From the medical history: first signs of the disease appeared at the age of 7 years (1984). At that time pulmonary hypertension was firstly diagnosed with PAPs of 82 mm Hg assessed by RHC. At the same time, there was an assumption of congenital heart disease (open arterial ductus) which was not confirmed.

4 years later (1988), at the age of 11 years, patient had an increase of PAPs to 104 mm Hg, calculated by echocardiography. The patient was recommended to be followed every year; however, but at that time there was no possibility to prescribe PAH-specific therapy.

In July 2012, in one of the federal centers, the patient underwent atrial septostomy with interatrial septum stenting, and in August 2012, PAH-specific therapy with bosentan at a daily dose of 125 mg was initiated with further dose titration to 250 mg per day. However, despite performed therapy, there was no improvement in the patient's condition: the severity of dyspnea increased, and physical tolerance impaired.

In 2013, the patient was firstly admitted to the Federal State Budget Institution "National Medical Research Center of Cardiology". According to the examination results, the diagnosis of IPAH was confirmed. It should be noted that the right heart catheterization showed the following results: systolic PAP 63 mm Hg, PAPm 49 mm Hg, PVR 782 dyne*sec/cm^5, the ratio of pulmonary to systemic blood flow (Qp:Qs) 1.6 indicated a significant arteriovenous blood bypass from left to right through septostoma in the interatrial septum.

Subsequently, it was recommended to continue the treatment with bosentan at a dose of 250 mg per day, the correction of cardiac rhythm therapy was carried out (diltiazem was later replaced with ivabradine). The patient was hospitalized at the National Medical Research Center of Cardiology annually.

During hospitalization in 2017 due to complaints of breath shortness with minimal physical activity, the patient's condition was considered as moderate at the time of admission. The skin was clean, the lymph nodes were not palpated, no visible pathology of the osteoarticular and muscular system was found. The form of the chest was normosthenic, both halves of the chest participated in the breathing evenly, palpation of the chest was painless, clear pulmonary sound was determined by percussion. Vesicular breathing was heard above the lungs without wheezing. Examination of the circulatory system did not reveal an expansion of the relative dullness of the heart. At the heart auscultation the accent of the second tone over pulmonary artery (P2) paid attention; murmurs were not heard over the heart area. Heart rhythm was regular with heart rate of 70 beats per minute, BP 120/85 mm Hg. Digestive and urinary systems were normal.

According to laboratory data, no significant deviations from normal values were noted. In the six-minute walking test, the distance was 410 m, while the Borg scale dyspnea was 3 points.

On ECG: sinus rhythm with heart rate 73 per minute, deviation of the heart electrical axis to the right, signs of right ventricular hypertrophy (Fig. 1).

According to the results of echocardiography, a small increase size of the right ventricle (relative to the left) was detected (Fig. 4), as well as an increase in the size of the pulmonary trunk to 2.9 cm. In addition, tricuspid regurgitation of grades 1–2 was found with PAPs of 68 mm Hg (Fig. 2). In the area of the interatrial septum, a stent with arteriovenous (from left to right) shunting of blood was visualized (Fig. 3)

Chest radiography revealed changes in favor of significant pulmonary arterial hypertension (Moore's ratio increased to 40% (N = 22–30%), height of the pulmonary segment increased to 4.5 mm (N = 0–1 mm); Lyupi coefficient 33% (N = up to 33%), the right ventricle dilation.

The clinical diagnosis was made as "Idiopathic pulmonary arterial hypertension. Functional class III (WHO). Tricuspid valve insufficiency 1-2. State after atrial septostomy with interatrial septum stenting from September 2012".

Considering the appearance of complaints of nausea, nonspecific abdominal pain in the absence of gastrointestinal pathology and laboratory signs of hepatotoxicity (normal transaminases activity in the blood), as well as taking into account not achieving clinical improvement with bosentan therapy, it was decided to replace bosentan (250 mg / day) with macitentan (10 mg / day).

In the future. A result of the the above-mentioned treatment correction, the patient did not experienced dyspeptic symptoms, there was achieved the improvement in the patient's well-being, exercise tolerance, and therefore it was recommended to continue macitentan at the previously recommended dose of 10 mg per day. Re-hospitalization is being planned for the objective assessment of the patient's condition dynamics.

DISCUSSION

PAH-specific therapy, affecting the key pathogenesis mechanisms, is an important achievement of modern treatment of PAH. The effects of PAH-specific drugs are aimed at stabilizing and

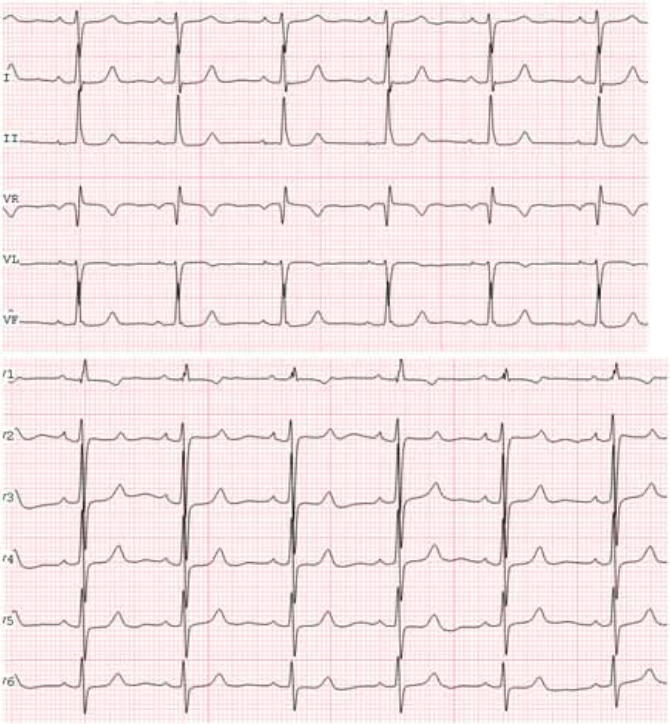

Figure 1. ECG of the patient P.

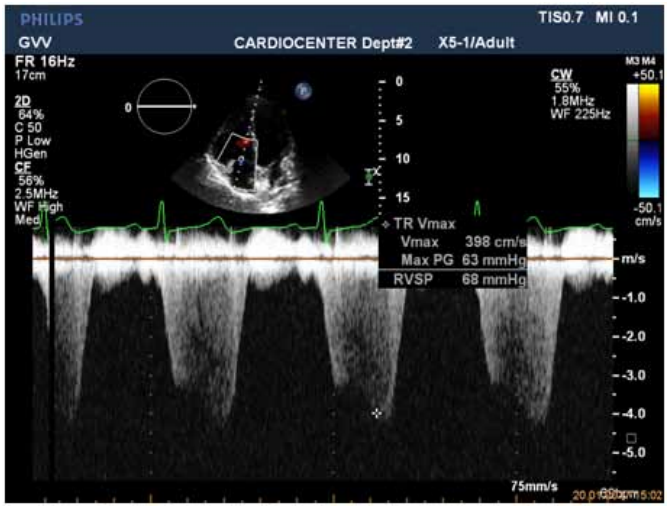

Figure 2. Continuous wave Doppler study of the tricuspid regurgitation for evaluating of systolic PAP (68 mm Hg).

improving the clinical condition, increasing of exercise tolerance, achieving positive dynamics of hemodynamic parameters and quality of life, slowing the rate of disease progression, and improving the prognosis of patients [6].

The prescription of drug therapy is indicated for patients with IPAH based on the algorithm for PAH patients in accordance with the Russian national guidelines for the diagnosis and treatment of pulmonary hypertension, based on the algorithm for PAH patients (Fig. 5), the prescription of drug therapy is indicated for patients with IPAH. In case of a positive testing for vasoreactivity, calcium channel blockers will be a choice, in all other cases – PAH-specific drugs. The drug choice depends on the form of PAH, the functional status of the patient, the presence of contraindications, the availability of the drug, the route of administration and profile of side effects.

However, it is not always possible to achieve an improvement or even stabilization of the condition of the patient when using monotherapy with pathogenetic drug for the treatment of PAH. In this case, there is a need to recommend a combination therapy with two or even three drugs which affect the main pathogenetic targets. The ineffective triple PAH-specific drugs combination points to the possible lung transplantation. As a "bridge" to lung

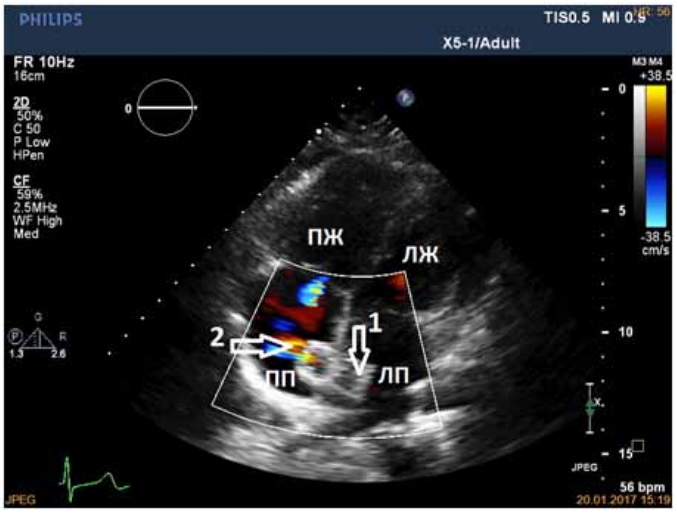

Figure 3. Modified apical 4-chamber view with color Doppler demonstrating L→R flow across the stent in the interatrial fenestration. 1 – butterfly stent, 2 – note the left-to-right shunt through the stent.

transplantation for the purpose of decompression of the right ventricle and stabilization of hemodynamics, it is possible to consider such palliative intervention as atrial septostomy.

Atrial septostomy is a palliative endovascular interventional procedure with creating a fenestration in the interatrial septum for shunting blood from right to left in order to decompress the right heart and increase systemic blood flow. However, an increase in cardiac output is accompanied by desaturation of arterial blood due to a right-left shunt, while achieving a balance between these parameters is not an easy task.

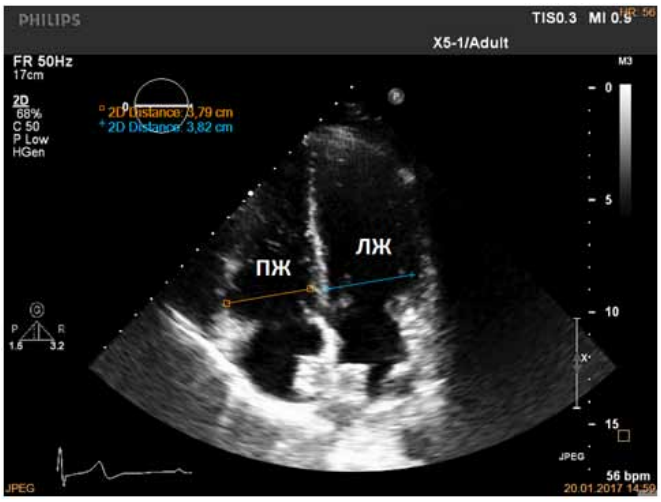

Figure 4. Apical four-chamber echocardiogram demonstrating basal diameters of the ventricles. RV / LV = 3.8 cm / 3.8 cm = 1 (N <1)

According to the indications, an atrial septostomy leads to an increase of cardiac index, a decrease in right atrium pressure and an increase of the distance in the six minute walking test, while not significantly affecting pulmonary artery pressure.

However, in the case of our patient, the performed atrial septostomy does not influence intracardiac hemodynamics, on the contrary, due to a significant left-right shunting through the interatrial fenestration only it creates an additional volume overload of the right ventricle.

It should be noted that there is currently no evidence based on the effect of atrial septostomy on the life expectancy of patients with pulmonary hypertension. In addition, mortality after the procedure, depending on the risk category of the patient, can vary widely – from 0 to 42% [7].

Management IPAH patients based on the PAH specific therapy in accordance with the Russian national guidelines for the diagnosis and treatment of pulmonary hypertension.

Each of PAH-specific drugs has its own side effects profile; therefore, in a certain number of patients there is a need to replace the drug. Even agents from the same class may have a different safety and efficacy profile.

There are certain categories of patients and clinical situations in which it is reasonable to optimize the treatment of ERA. Currently, clinical data are intensively accumulated in favor of the strategy of switching the ERA – replacing bosentan with macitentan for patients with PAH.

These clinical situations include the following:

1) patients taking a combination of bosentan and sildenafil, in which the efficacy may be reduced, as a result of drug-drug interactions;

2) patients at risk of drug-to-drug interactions with various drugs (bosentan is a moderate inducer of CYP3A4, CYP2C9 and,

possibly, CYP2C19) [8];

3) patients who take hormonal contraceptives (co-administration with bosentan reduces their efficacy);

4) patients with PAH associated with systemic sclerosis; macitentan can be considered as a drug of choice;

5) patients with newly diagnosed PAH, macitentan can be considered as a drug for starting therapy due to efficacy;

6) patients with impaired liver function on bosentan therapy;

7) non-complient patients possibility o.d. taking of macitentan [9].

Thus, the optimization of ERA therapy, namely, the transition from therapy with bosentan to macitentan, seems to be effective and can be considered in patients with PAH.

CONCLUSION

The described clinical case clearly confirms need for an informed approach to the treatment of patients with PAH in accordance with current clinical guidelines. Treatment of such patients should always begin with drug therapy in order to achieve the treatment goals, there are currently opportunities for both escalation (joining the 2d and even the 3d PAH-specific drugs) and optimization (replacement with the safest and most effective) of the drug therapy. Non-drug treatment for patients with PAH (atrial septostomy, lung transplantation) should be considered only when the combined PAH-specific therapy is inefficient.

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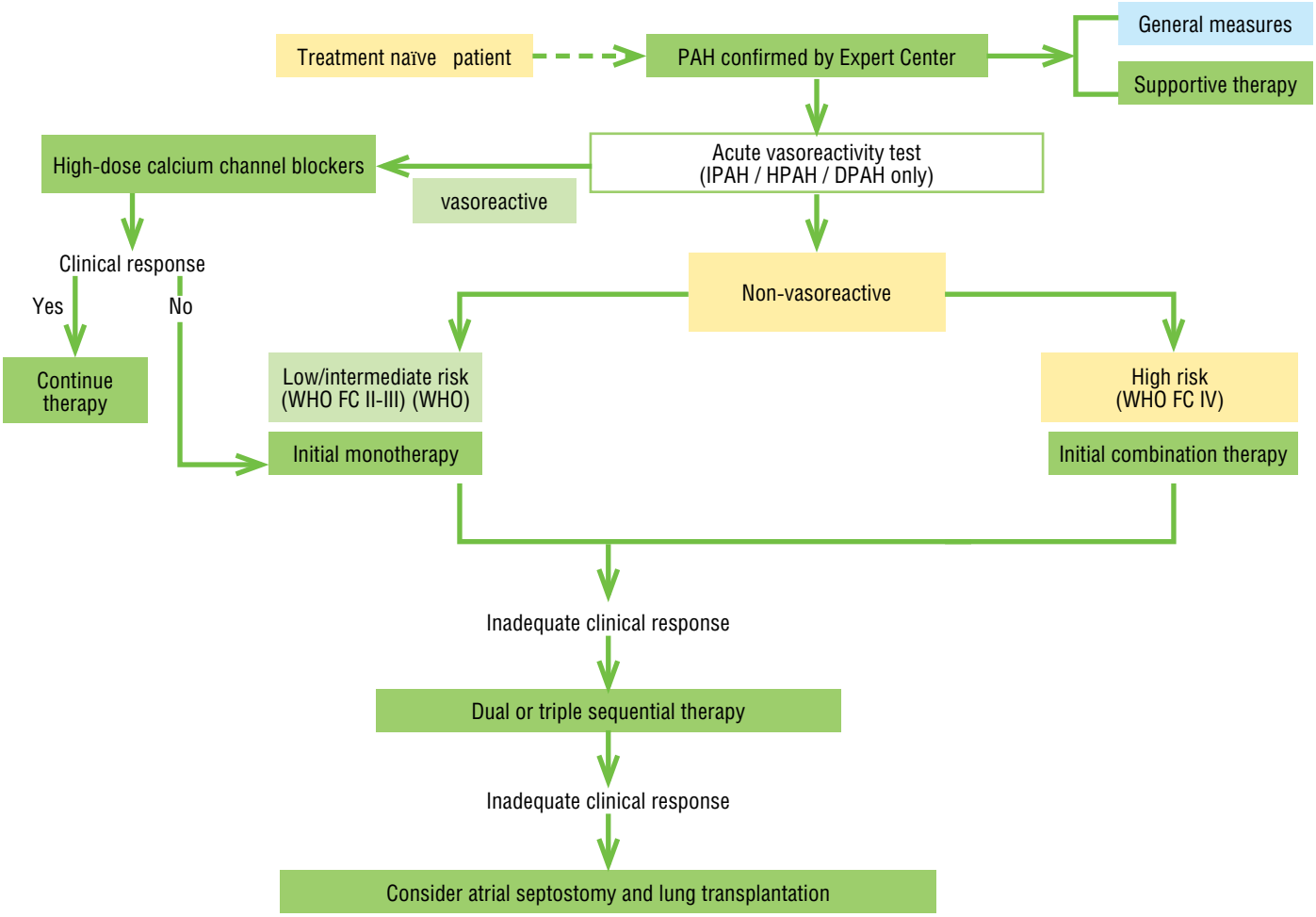

Figure 5. Treatment algorithm for patients with PAH (group 1)