



Principles of pharmacological correction of pulmonary arterial hypertension

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Abstract

Definition and classification: Pulmonary hypertension (PH) is a group of life-threatening progressive diseases of various genesis, characterized by a progressive increase in arterial pressure (AP) in the pulmonary artery (PA), the remodeling of pulmonary vessels, which leads to an increase in pulmonary vascular resistance and pulmonary arterial pressure and more often leads to right ventricular heart failure and premature death. Pulmonary hypertension is clinically divided into five groups: patients in the first group have idiopathic pulmonary arterial hypertension (IPAH), whereas in patients of other groups secondary PH associated with cardiopulmonary or other systemic diseases is observed. The development of secondary LH is caused by congenital heart defects, collagenoses, presence of thrombus in the pulmonary artery, prolonged high pressure in the left atrium, hypoxemia, chronic obstructive pulmonary diseases (COPDs). In case of secondary PH, thrombosis and other changes in the pulmonary veins occur.

Ways of pharmacological correction of pulmonary hypertension: Over the last decade pharmacotherapy of PH has been developing rapidly, and the introduction of modern methods of treatment, especially for primary PAH, has led to positive results. However, despite the progress in treatment, the functional limitations and survival of patients remain unsatisfactory. Currently, there are two levels of treatment for pulmonary hypertension: primary and specific pathogenetic therapies. Primary therapy is aimed at the main cause of PH. It also includes supportive therapy. Pathogenetic therapy includes prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Tactics of therapy can be established on the basis of either clinical classification, or functional class. Prostanoids are a promising group of drugs for the treatment of pulmonary arterial hypertension (PAH), since they possess not only vasodilating, but also antiplatelet and antiproliferative actions. Therefore, it seems logical to use prostacyclin and its analogs to treat patients with various forms of PAH.

Keywords

classification, pulmonary hypertension, pathogenetic therapy, primary therapy, prostanoids, pharmacological correction.

Definition and classification

Pulmonary arterial hypertension (PAH) is defined as a chronic increase in mean and systolic blood pressure in the pulmonary artery (it exceeds 25 mmHg at rest and more than 30 mmHg under physical exertion). The di-

sease is characterized by a progressive increase in pulmonary vascular resistance and hypertrophy of the right ventricle of the heart.

Pulmonary hypertension is clinically divided into five groups (Table 1): patients in the first group have idiopathic pulmonary arterial hypertension (IPAH), whereas in other

Table 1. Classification of pulmonary hypertension

1. Pulmonary hypertension
1.1. Idiopathic
1.2. Hereditary
1.2.1 Mutation of the type 2 receptor gene to the bone morphogenesis protein (BMP2);
1.2.2 Mutation of the activin-like kinase-1 gene (ALK-1) with and without hereditary hemorrhagic telangiectasia;
1.2.3 Unknown mutations
1.3. Pulmonary hypertension caused by medicinal and toxic effects
1.4. Pulmonary hypertension associated with:
1.4.1 Connective tissue diseases;
1.4.2 HIV infection;
1.4.3 Portal hypertension;
1.4.4 Congenital heart disease;
1.4.5 Schistosomiasis;
1.4.6 Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of newborns
2. Pulmonary hypertension due to lesion of the left chambers of the heart
2.1. Systolic dysfunction of the left ventricle
2.2. Diastolic dysfunction of the left ventricle
2.3. Defects of the valves of the left heart
3. Pulmonary hypertension due to the pathology of the respiratory system and/or hypoxia
3.1. Chronic obstructive pulmonary disease (COPD)
3.2. Interstitial lung diseases
3.3. Other pulmonary diseases with mixed restrictive and obstructive components
3.4. Respiratory disturbances during sleep
3.5. Alveolar hyperventilation
3.6. High-altitude pulmonary hypertension
3.7. Malformations of the respiratory system
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension due to unclear multifactorial mechanisms
5.1. Diseases of the blood: myeloproliferative diseases, splenectomy
5.2. Systemic diseases: sarcoidosis, Langerhans histiocytosis, histiocytosis X, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic diseases: glycogen accumulation disease, Gaucher's disease, thyroid disease
5.4. Others: tumor obstruction, pulmonary lymphangiomatosis, as a result of pulmonary artery compression, adenopathy, fibrosing mediastinitis, chronic renal failure in patients on hemodialysis.

patients, secondary PH is associated with cardiopulmonary or other systemic diseases (Simonneau et al. 2009).

Idiopathic PAH occurs in the absence of known risk factors and is the most common form of the disease (Galie et al. 2009d, Badesch et al. 2010).

Figures 1 and 2 show the distribution of additional sub-categories of PAH that include the family form (now called hereditary), the form induced by drugs and toxins, and forms associated with connective tissue diseases, congenital heart diseases, HIV infection, portal hypertension and other conditions (Badesch et al. 2010).

Based on hemodynamic parameters, pulmonary hypertension is classified into two groups.

Pre-capillary form of pulmonary hypertension is characterized by increased pressure (and hence resistance) in small arterial vessels of the pulmonary trunk system. The causes of precapillary hypertension are spasm of arterioles and embolism of the branches of the pulmonary artery.

The postcapillary form of pulmonary hypertension is caused by a decrease in the outflow of blood through the pulmonary vein system. It is characterized by congestion in the lungs, arising and intensifying along with compression of the pulmonary veins with a tumor, connective tissue scars, as well as with various diseases accompanied

by left ventricular heart failure (mitral stenosis, hypertension, myocardial infarction, cardiosclerosis, etc.). It should be noted that the postcapillary form may complicate the precapillary form, and the precapillary form may complicate the postcapillary form.

Ways of pharmacological correction of pulmonary hypertension

Over the last decade, pharmacological correction of pulmonary hypertension has been developing rapidly, and the introduction of new treatments, especially for idiopathic pulmonary arterial hypertension, has improved the results of treatment of patients with this disease.

Growing interest of researchers in the world to the problem of pulmonary arterial hypertension and its pharmacological correction is clearly shown in Figure 3. An analysis of the publication activity of authors in a retrieval system, PubMed, on the problem of pharmacological correction of pulmonary hypertension made it possible to establish a two-time increase in the number of publications for the period from 2007 to 2017.

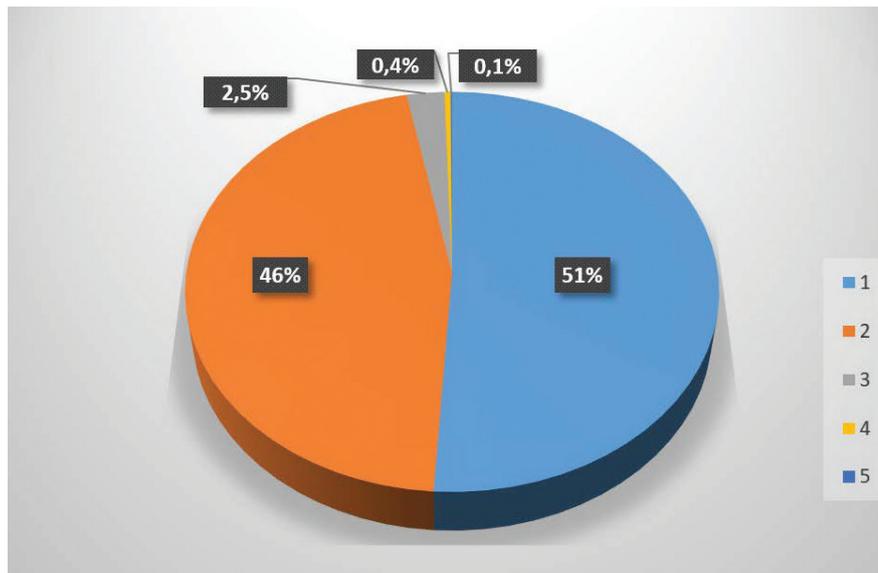


Figure 1. Classification of the first group of LAS in accordance with the data of the World Health Organization
 1 – Idiopathic pulmonary arterial hypertension (IPAH); 2 – associated pulmonary arterial hypertension (APAH); 3 – familial pulmonary arterial hypertension (FPAH); 4 – pulmonary veno-occlusive disease (PVOD); 5 – pulmonary capillary hemangiomatosis (PCHA)

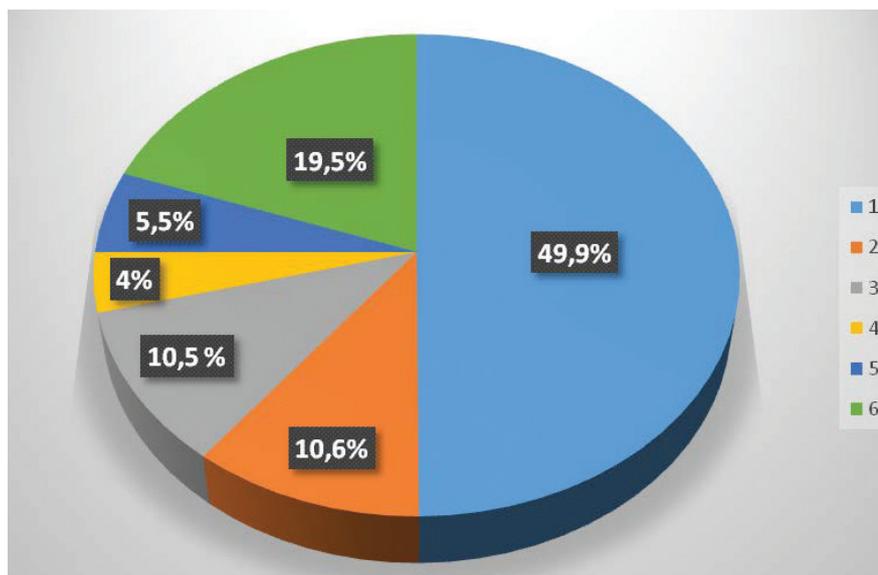


Figure 2. Classification of associated PAH in accordance with the data of the World Health Organization
 1 – collagen vascular diseases/connective tissue diseases; 2 – portal hypertension; 3 – drug-induced/toxin-induced; 4 – HIV-induced; 5 – other reasons; 6 – congenital heart diseases

A meta-analysis of 23 randomized controlled trials showed a 43% reduction in mortality and 61% reduction in admission rates for patients with idiopathic pulmonary arterial hypertension who received specific therapy compared with placebo (Galiè et al. 2009b).

Nevertheless, for a sufficiently large sample of patients, a very poor prognosis and a rapid deterioration of their condition are still characteristic, in connection with the development of heart failure leading to a fatal outcome.

For these reasons, early detection and treatment of pulmonary hypertension is crucial. Treatment begins with a

baseline assessment of the severity of the disease, which is important, since the response to therapy will be evaluated as a change from baseline indicators prior to pharmacological correction. Table 2 shows the functional classification of pulmonary hypertension according to WHO.

Functional disorder and hemodynamic disorder are the key determinants of the severity of the disease.

Echocardiography (EchoCG) is the most informative noninvasive method for diagnosing pulmonary hypertension (PH). It allows not only to calculate the pressure in the pulmonary artery (PLA) and determine a degree of

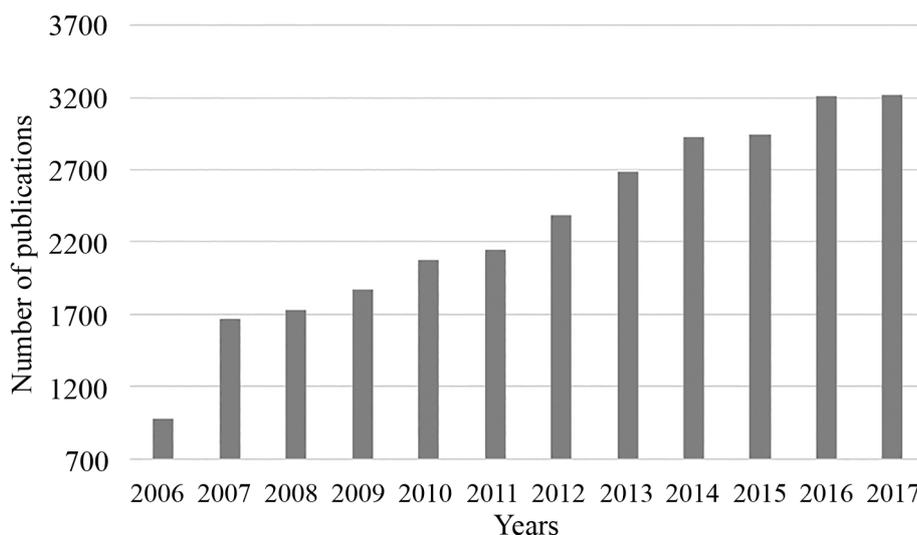


Figure 3. Indicators of the authors' publication activity in the PubMed information retrieval system on the problem of pharmacological correction of pulmonary hypertension from 2000 to 2017

Table 2. Functional classification of pulmonary hypertension in accordance with the World Health Organization (WHO)

I functional class

Patients with LH without restriction of physical activity. Normal physical activity does not lead to dyspnoea, fatigue, chest pain and syncope

II functional class

Patients with LH and a slight restriction in the physical activity. At rest there are no symptoms. Normal physical activity causes shortness of breath, fatigue, chest pain or syncope

III functional class

Patients with LH and a significant restriction of physical activity. At rest they feel comfortable. Physical activity is lower than usual, causing significant shortness of breath or fatigue, chest pain or syncope in patients

IV functional class

Patients with LH who can not perform any physical activity without the appearance of symptoms. Patients have symptoms of right-sided heart failure. Shortness of breath and weakness are noted at rest. Discomfort increases with any physical activity

its increase, but also to carry out a differential-diagnostic search. In addition, the complex EchoCG makes it possible to evaluate the structural and functional state of the heart and the prognostic parameters of PH, including: the presence of effusion in the pericardial cavity, the indexed area of the right atrium (RA), the degree of displacement of the interventricular septum into the cavity of the left ventricle (LV) in the diastole diastolic eccentricity index), tricuspid annular plane systolic excursion (TAPSE), pulmonary vascular resistance (PVR) and myocardial function index (Tei index)

To date, the pathogenesis of pulmonary hypertension is poorly understood, but includes pathological changes in the intima, media, and adventitial layers of the vascular wall. Both vascular endothelial and smooth muscle cells in the disease are characterized by abnormal growth, with excessive cell proliferation and resistance to apoptosis. These anomalies in resident vascular cells, combined with inflammation, excessive vasoconstriction and thrombosis in situ, contribute to a physical narrowing of the distal pulmonary arterioles. This narrowing causes a sharp increase in the resistance of the vessels of the lungs, which leads to a chronic and progressive increase in arterial pressure in the pulmonary artery.

The therapeutic targets for the treatment of pulmonary hypertension are goals aimed at correcting the metabolic pathways of prostacyclin, endothelin, or nitric oxide (NO). Reversion or reduction of vasoconstriction, proliferation of vascular endothelial cells, proliferation of smooth muscle cells and reduction in the degree of endothelial dysfunction are considered effective (Boutet et al. 2009). For example, as is known, prostacyclins are powerful vasodilators that can also inhibit the growth of smooth muscle vessels. PAH is associated with reduced levels of prostacyclin in the pulmonary region as a result of insufficient expression of endothelial prostacyclin synthase. Endothelin receptor antagonists (ERAs) block the action of endothelin, a potent endogenous vasoconstrictor and mitogen, on the receptors of smooth muscle cells. Phosphodiesterase type 5 inhibitors (PDE-5) facilitate vasodilation by stimulating the activity of the nitric oxide pathway by inhibiting the degradation of cGMP, a second messenger that causes relaxation of smooth muscle vessels. New developed treatment methods which are being currently developed are aimed at these and additional ways (Fig. 4).

Drugs currently used in the treatment of pulmonary hypertension in the United States or in the European Union

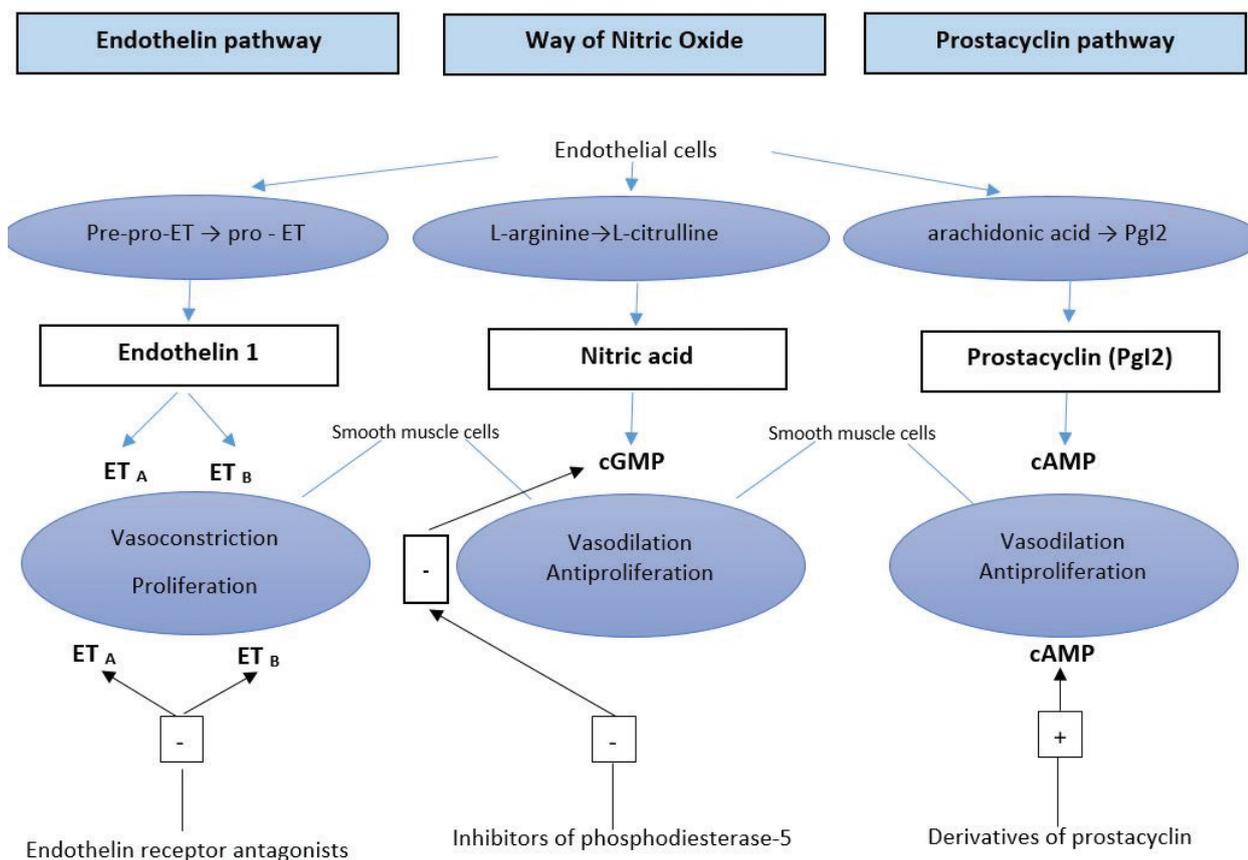


Figure 4. Mechanisms of the pathogenesis of pulmonary hypertension as targets for its pharmacological correction. *Note:* Pre-pro-ET is an endothelin precursor, ETA is an endothelin type A receptor, an ETB is an endothelin type B receptor, cGMP is a cyclic guanine monophosphate, cAMP is a cyclic adenosine phosphote, Pgl₂ is a prostaglandin I₂.

(EU) include PDE-5 inhibitors: sildenafil (Revatio) and tadalafil (Adcirca), and selective endothelin-1A antagonist ambrisentan [Leteris (United States)/Volibris (international)]. Patients with later stages of the disease are often treated with prostacyclin or prostacyclin analogs, such as iloprost or treprostinil, administered in the form of several daily inhalations, epoprostenol or treprostinil (Remodulin) as continuous intravenous infusions. Inhalation nitric oxide is permitted for the neonatal form of the PAH-resistant pulmonary hypertension of the newborn.

In general, there are 2 levels of pharmacological correction of pulmonary hypertension – primary therapy and specific therapy.

Primary pathogenetic therapy is aimed at correcting the underlying cause of pulmonary hypertension. It also includes supportive therapy, including adequate oxygen therapy, diuretics and anticoagulants, which should be included in the therapy of all patients with PAH. Pathogenetic therapy includes prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. These drugs are used in pharmacotherapy of all forms that affect several pathogenetic mechanisms of pulmonary arterial hypertension. Atrial septostomy and pulmonary transplantation are indicated for patients who are not amenable to drug treatment. Tactics of therapy can be established on the basis of both clinical classification and functional class.

Oxygen

Oxygen is the main element that participates in all energy processes of the body, providing it with normal vital activity. Oxygen is indicated for all forms of pulmonary hypertension. Under its action, hypoxia and, as a consequence, vasoconstriction (constriction) of vessels of a small circle decrease.

Oxygen therapy is one of the most important life-saving methods of treating pulmonary hypertension. It is based on breathing pure oxygen and allows to compensate for oxygen deficiency at the cellular level. Unlike most modern medical methods, oxygen therapy is completely safe, since oxygen has practically no contraindications and does not cause allergic reactions. It should be noted that patients with pulmonary hypertension need a long, sometimes lifelong, oxygen therapy. Oxygen is administered to patients by inhalation.

Indications for oxygen therapy are usually established with the value of arterial oxygen pressure (PaO₂) less than 60 mm Hg. Continuous administration of oxygen is the cornerstone of therapy for patients with group 3 pulmonary hypertension, but it should also be considered in all patients with pulmonary hypertension combined with hypoxemia at rest, during exercise and/or at night. Indeed, oxygen therapy is the only treatment with a

proven reduction in mortality in some patients with PAH, as demonstrated by two large randomized clinical trials in which patients with chronic obstructive pulmonary disease (COPD), the most common cause of development of PAH, were studied (NOTT 1980, MRC 1981). In contrast, there is no randomized data to suggest that long-term oxygen therapy is useful for patients with idiopathic pulmonary hypertension, although it has been demonstrated that pulmonary vascular resistance was reduced in patients when oxygen was administered (Galiè et al. 2009a)

Oxygen is usually administered through the nasal cannula, facial mask or Venturi mask.

Diuretics

Diuretics are used in case of decompensated heart failure for pharmacological correction of fluid retention, reduction of hepatic overload and peripheral edema in pulmonary hypertension (Cohn 2001).

The hemodynamic effects of diuretics include a reduction in right ventricular preload and the tension of its walls; a decrease in central venous pressure; a decrease in the degree of tricuspid regurgitation and an increase in the stroke volume of the right ventricle ejected into the pulmonary circuit; reduction in the deflection of the interventricular septum toward the left ventricle and improvement in filling of the left ventricle; and an increased cardiac output (Hosenpud and Greenberg 2007).

Diuretics are especially indicated in patients with groups 2 and 3 pulmonary hypertension. There is currently no information on randomized controlled clinical studies on the use of diuretics in pulmonary arterial hypertension; however, clinical experience also shows the symptomatic benefits from using diuretics when decompensated right heart failure occurs. It should be borne in mind that diuretics should be used with caution in order to avoid a reduction in cardiac output, arrhythmias caused by hypokalemia, and metabolic alkalosis. The most commonly used loop diuretic is furosemide, usually used in an initial dose of 20-40 mg per day.

Anticoagulants

Patients with pulmonary hypertension are at increased risk of intrapulmonary thrombosis and thromboembolism due to decreased pulmonary blood flow, enlarged right heart, venous stasis and sedentary lifestyles. These risk factors and the understanding that even a small blood clot can cause hemodynamic deterioration in a patient with compromised pulmonary vessels is the rationale for prescribing oral anticoagulant therapy for pulmonary hypertension. It is generally recognized that anticoagulants are indicated in patients with idiopathic pulmonary hypertension, hereditary PAH and drug-induced PAH (Barst et al. 2009, Galiè et al. 2009a, McLaughlin et al. 2009)

Most of the data was obtained in the study of patients with idiopathic pulmonary hypertension (Kawut et al. 2005, Barst et al. 2009). In a systematic analysis of seven studies evaluating the effect of warfarin in patients with group 1 pulmonary hypertension, five studies showed a reduction in the risk of intrapulmonary thrombosis and thromboembolism (Johnson et al. 2006).

In patients with hereditary PAH and drug-induced LAH, the benefits of anticoagulant therapy were evaluated taking into account the risk of bleeding. The drug of choice for oral anticoagulant therapy for pulmonary hypertension is warfarin.

Physical exercise

Physical exercise is indicated in patients with pulmonary hypertension. (Mereles et al. 2006, de Man et al. 2009). In randomized controlled clinical trials, improvement in physical performance was demonstrated in patients with PAH who performed a set of physical exercises (Mereles et al., 2006). Exercise improves the functional parameters of the bronchopulmonary system and peak oxygen consumption, not appreciably affecting hemodynamic parameters (Mereles et al. 2006). Moreover, patients with severe PAH have skeletal muscle hypertrophy, which can be corrected by a physical rehabilitation program (Galiè et al. 2009a). Thus, skeletal muscle training can play a role in the treatment of patients with PAH.

Pathogenetic therapy

Tactics of therapy can be established on the basis of both clinical classification and functional class. Specific pathogenetic therapy is performed in patients with functional class II, III or IV PAH, despite adequate primary therapy (Badesch et al. 2007, Barst et al. 2009). These drugs are used in pharmacotherapy of all forms and affect several pathogenetic mechanisms of pulmonary arterial hypertension.

The characteristics of drugs used to treat pulmonary hypertension is presented in Table 3.

Before starting therapy, it is necessary to assess hemodynamic parameters in patients with PAH. Patients with PAH 1 group should undergo a test for vasoreactivity with intravenous administration of adenosine, epoprostenol or inhalation of nitric oxide NO (Barst et al. 2009). Patients with a positive test for vasoreactivity need the prescription for oral therapy with calcium channel blockers. In contrast, patients with a negative vasoreactivity test need therapy with a prostanoid endothelin receptor antagonist or a type 5 phosphodiesterase inhibitor. A combination therapy is indicated in cases of refractoriness to ongoing pharmacotherapy. In case of ineffective pharmacotherapy, the issue of lung transplantation or shunting in atrial septostomy is considered (Keogh et al. 2009).

Table 3. Characteristics of drugs used to treat pulmonary hypertension

Drug	Route of administration	Dose
Calcium channel blockers		
Nifedipine	Orally	120-240 mg/day
Diltiazem	Orally	240-720 mg/day
Amlodipine	Orally	20 mg/day
Prostanoids		
Epoprostenol	Intravenously	1-40 ng/kg/min
Treprostinil	Subcutaneously/intravenously	2-80 ng/kg/min
Iloprost	Inhalation	2.5-5 µg, 6-9 times/day
Endothelin receptor antagonists		
Bozentan	Orally	62,5-125 mcg, 2 times/day
Ambrisentan	Orally	5-10 mg/day
Inhibitors of phosphodiesterase-5		
Sildenafil	Orally	20 mg, 3 times/day
Tadalafil	Orally	5-40 mg/day

Calcium channel blockers

The rationale for using vasodilators is their influence on pathogenetic mechanisms of a progressive increase in pulmonary vascular resistance and hypertrophy of the right ventricle of the heart in PAH.

However, only a small proportion of patients on the background of ongoing vasodilator therapy demonstrate a positive response to the vasoreactivity test. In patients taking nifedipine or diltiazem, the functional state of the bronchopulmonary system and hemodynamic parameters improve, and life expectancy also increases (Rich et al. 1992, Humbert et al. 2004a, Sitbon et al. 2005). Effective doses of calcium channel blockers used in different forms of PAH are 120-240 mg for nifedipine, and 240-720 mg for diltiazem. The therapy should be started with a minimum therapeutic dose of long-acting nifedipine (30 mg/day) or diltiazem (120 mg/day), which should be brought up to the maximum therapeutic dose. It is recommended to prescribe sustained-release preparations of nifedipine and diltiazem, since they minimize the adverse effects of therapy, especially systemic hypotension and orthostatic states. Patients who receive CCB therapy should undergo a controlled pharmacotherapy and dose adjustment after 3-6 months of treatment.

Endothelin receptor antagonists

Endothelin-1 is a potent vasoconstrictor and mitogenic factor for vascular smooth muscle cells, fibroblasts and cardiomyocytes. High concentrations of endothelin-1 were detected in the lungs of patients with PAH (Channick et al. 2004). In smooth muscle cells of pulmonary vessels and in endothelial cells, there are two different types of receptors: endothelin-A and endothelin-B receptors. Despite the differences in their activity towards different receptors, the efficacy of double and selective endothelin receptor antagonists seems to be comparable.

Bozentan is the first oral non-selective preparation of the class of endothelin-A and -B receptor blockers. Bozentan therapy was studied in patients with PH in 5 randomized controlled trials that demonstrated increased exercise tolerance, reduced functional class of PLG, improved hemodynamic parameters, echocardiography and dopplerographic indices, and an increased time to clinical deterioration.

The drug was effective in patients with pulmonary hypertension I group with II, III and IV functional class of PAH.

The initial therapeutic dose was 62.5 mg twice daily and was increased to 125 mg twice daily for 4 weeks. Long-term observational studies have confirmed the long-term effect of bosentan therapy. In 10% of patients, a dose-dependent increase in hepatic transaminases develops, which is completely reversible with a decrease in the dose of bosentan or its withdrawal. Therefore, patients receiving bosentan therapy should at least once a month take a blood test that determines the function of the liver.

Sitaxentan is a selective oral endothelin-A receptor blocker. Its efficacy was studied in two randomized controlled trials in patients with LH II/III FC according to the WHO. Depending on the etiology of LH, the group included patients with ILH, PLH, associated with systemic connective tissue diseases or congenital heart diseases. These studies demonstrated an increase in physical activity tolerance and improvement in hemodynamic parameters against the background of sitaxentan treatment. In an open observational study, the stability of the effect of sitaxentan treatment throughout the year was noted. The frequency of changes in functional hepatic tests was 3-5% for the approved dosage of sitaxentan of 100 mg/day; it was completely reversible. However, this side effect of sitaxentan requires monthly monitoring of liver samples.

Ambrisentan is a non-sulfonamide selective endothelin-A receptor antagonist, referring to preparations of propanoic acid. Ambrisentan therapy was studied in one pilot and two large randomized controlled trials that demonstrated a reduction in the clinical symptoms of PLH, increased exercise tolerance, improved hemodynamics, and an increased time to clinical deterioration. In an open obser-

vational study, the stability of the effect of ambrisental treatment throughout the year was noted (Galiè et al. 2008b, Oudiz et al. 2009). Ambrisentan is also approved for the treatment of patients of FC-II according to the WHO. The dose of 5 mg/day can be increased to 10 mg/day with the initial good tolerability profile of the drug. The frequency of changes in functional hepatic tests is 0.8-3% of cases. Nevertheless, all patients taking ambrisentine should have their liver tests monitored on a monthly basis.

Phosphodiesterase type 5 (PDE-5) inhibitors

The mechanism of action of PDE-5 inhibitors is associated with an effect of nitric oxide/NO-cyclic guanosine monophosphate on the system. The oppression of destruction of the latter leads to a sharp increase in its concentration in cells in which the main form of phosphodiesterases is precisely PDE-5. In smooth muscle cells of blood vessels, including pulmonary tissue, this causes relaxation and vasodilation.

Sildenafil is an oral potent selective phosphodiesterase-5 inhibitor that realizes its pharmacological effect by increasing the concentration of cGMP in the cell. A number of uncontrolled studies have described the beneficial effect of sildenafil therapy in patients with ILH, PLH associated with systemic connective tissue diseases and congenital heart diseases, and chronic thromboembolic PH (Galiè et al. 2005, Pepke-Zaba et al. 2008). The most significant was a randomized controlled trial with 278 patients with PLH who received sildenafil therapy at dosages of 20, 40 and 80 mg 3 times a day. It was used to confirm the positive effect of sildenafil on exercise tolerance, symptom severity and hemodynamics. Despite the approved dose of sildenafil of 20 mg 3 times a day, prolonged maintenance of the effect of therapy during the year was observed only with the use of sildenafil in a dose of 80 mg 3 times a day (Galiè et al. 2005). Typically, in clinical practice, titration of the dosage of sildenafil over 20 mg 3 times a day (usually 40-80 mg 3 times a day) is necessary. Most undesirable effects of sildenafil are mild or moderate and are most often due to vasodilation.

Tadalafil is an oral single-dose preparation, a selective phosphodiesterase-5 inhibitor, currently approved for the treatment of erectile dysfunction. The most important randomized controlled clinical trial included 406 patients with PGH who received 5, 10, 20 or 40 mg of tadalafil per day. It showed a beneficial effect on exercise tolerance, symptom severity, hemodynamics, as well as time to deterioration of LH course when using the highest dosage (Galiè et al. 2009c).

Combination therapy

It is suggested that a combination of pharmacological agents with different mechanisms of action may have an

additive effect or may cause the same effect at lower doses of each component. Currently, a comprehensive evaluation of the efficacy of combination therapy is conducted in clinical trials.

In a series of clinical studies, the efficacy and safety of various combinations were demonstrated. In the STEP-1 study, 12-week therapy with inhaling iloprost in combination with bosentan resulted in a pronounced increase in the distance in T6MX. After inhalation of iloprost, its increase was +26 m ($p=0.051$). When carrying out T6MX prior to inhalation, an increase in distance compared with placebo was +19m, which was unreliable. After 12 weeks of therapy with iloprost, no significant changes in hemodynamic parameters were noted, but the time to clinical deterioration was improved compared to that in the placebo group (0 events versus 5 in the placebo group) (Hoepfer et al. 2003). In contrast, a COMBI study evaluating the potential of the combination therapy with iloprost and bosentan was terminated prematurely due to a lack of effect on exercise tolerance and time to clinical deterioration. It is important to note the peculiarities in the joint use of drugs of specific PAH therapy. Thus, in the EARLY study, pharmacokinetic interactions between bosentan and sildenafil, which are respectively an inhibitor and inducer of cytochrome P450 isoenzymes, were studied. When combined, the concentration of sildenafil decreases, and that of bosentan increases. But this does not affect the efficacy of therapy (Mathai et al. 2007).

The indication for combination therapy in patients with PAH is lack of a stable clinical effect. Bosentan is an inducer of the cytochrome P450 isoenzymes CYP3A4, CYP2C9. Plasma concentrations of drugs metabolized by these isoenzymes decrease when used together with bosentan. The concentration of bosentan increases when combined with CYP3A4 inhibitors (ketonazole, ritonavir) and/or CYP2C9 inhibitors (amiodarone, fluconazole). Therefore, bosentan is potentially contraindicated when administering these drugs. Bosentan is considered contra-indicated when taking the following drugs: itraconazole, tacrolimus, sirolimus, carbamazepine, phenobarbital, and dapsone. The main pathway of sildenafil metabolism is CYP3A4 and, to a lesser extent, CYP2C9. CYP3A4 inducers (carbamazepines, phenytoin, phenobarbital, rifampicin) reduce the concentration of sildenafil. The concentration of the drug increases slightly when grapefruit juice is used - a weak inhibitor of CYP3A4/5. Because of the risk of systemic hypotension, special precaution is required when using a specific therapy of PAH with antihypertensive drugs, such as β -adrenoblockers and ACE inhibitors.

There are many unresolved issues regarding combination therapy, including the choice of the optimal combination of drugs, the optimal time and method of administration. Combination therapy of different groups of PAH is recommended for patients who do not respond adequately to monotherapy (Galiè et al. 2009a)

Surgical intervention

In extreme cases, when drug therapy does not have the desired effect, surgery is usually resorted to:

Atrial septostomy

Atrial septostomy involves the formation of a defect between the atria with the shunting of blood from right to left. Percutaneous step-by-step balloon septostomy is the preferred technique. The basis for this intervention is an increase in life expectancy in patients with PAH and patients with an open foramen ovale. The creation of a shunt reduces the preload on the right ventricle, which facilitates its work and can increase cardiac output and improve the tolerance of physical exertion. Such an increase in cardiac output occurs at the cost of reducing the systemic saturation of arterial blood; however, as a rule, the systemic transport of oxygen improves (Reichenberger et al. 2003). This intervention is usually performed on patients who have not responded to the maximum possible drug treatment, or as a palliative measure while waiting for transplantation (Doyle et al. 2004).

Lung transplantation

In recent years, significant progress has been made in the drug therapy of pulmonary vascular diseases, primarily idiopathic pulmonary hypertension, which has made it possible to exclude most such patients from waiting lists for transplantation of lung and the cardiopulmonary complex, thus significantly improving their prognosis for survival (Keogh et al. 2009). Studies show that up to 25% of patients with idiopathic PAH do not show any significant improvement in status against the background of specific pharmacotherapy and have a poor prognosis for survival (McLaughlin et al. 2002, Sitbon et al. 2002).

Lung transplantation (TL) is the only radical treatment for patients with irreversible pulmonary parenchyma and/or pulmonary vascular diseases. If multicomponent therapy, including the use of selective pulmonary vasodilators, is ineffective, bilateral TH is indicated for primary pulmonary arterial hypertension.

Bilateral lung or heart-lung transplantation is the procedure of choice (Keogh et al. 2009). The 3-year survival rate of patients who underwent transplantation of lung or heart and lung for idiopathic PAH is approximately 50% (Doyle et al. 2004, Trulock et al. 2007).

The recommendations for sending the patient for transplantation evaluation are as follows:

- functional class 3-4 according to NYHA, despite the ongoing PAH-specific therapy;
- rapid progression of the disease;
- use of intravenous PAH-specific drugs regardless of the symptoms or the size of the functional class;
- confirmed or suspected diagnosis of veno-occlusive disease of the lungs and/or pulmonary capillary hemangiomatosis.

Ethical aspects of such transplantation, as well as the condition of living-related donors, remain the topics of ongoing scientific discussions. In general, the living-related (lobar) lung transplantation is considered as an alternative to cadaveric transplantation only for those recipients who, in connection with their clinical status and anthropometric parameters, are unlikely to wait for cadaveric transplantation. The “golden standard” of lung transplantation and the only opportunity for transplantation of the cardiovascular system is cadaveric transplantation from donors with brain death. The criteria that determine mortality in such patients have not yet been determined by the moment and include a large number of indicators, which makes it difficult to accurately determine the time of transplanting lung to such patients (Davis and Garrity 2007).

Thromboendarterectomy of the lungs

Chronic thromboembolic pulmonary hypertension (CTERH) is an important cause of severe pulmonary hypertension and, as such, is associated with significant morbidity and mortality. The prognosis for this condition reflects the degree of concomitant right ventricular dysfunction with a predicted mortality rate associated with the severity of pulmonary hypertension.

In recent years, the epidemiology of this condition has been significantly revised. In the past it was considered a rare disease; recently it has been registered as chronic thromboembolic pulmonary hypertension (CTEPH), complicating 3.8% of acute pulmonary embolic events (Galiè et al. 2009a).

Chronic thromboembolic pulmonary hypertension is the only cause of severe pulmonary hypertension, which is potentially curable without resorting to lung transplantation. Pulmonary endarterectomy (PEA) is a surgical procedure that removes the obstructing thromboembolic material, which leads to a significant improvement (and in many cases, normalization) in hemodynamics and function of the right ventricle. This procedure requires a high degree of anesthesia and surgical skill combined with a diligent preoperative assessment of potential patients. Surgery is usually considered only in patients with proximal chronic thromboembolic disease, which are assessed using radiological studies (Rubin et al. 2006).

During the preoperative assessment of patients, subjective and objective data are used to decide whether to perform pulmonary thromboendarterectomy in patients suffering from chronic thromboembolic pulmonary hypertension (Dunning and McNeil 1999).

Indications for thromboendarterectomy are: FC III-IV, $PVR \geq 300$ dynes/sec/cm⁵, the central thrombi (up to the segmental level) ($\geq 50\%$ obstruction in the proximal arteries according to angiopulmonography), having thrombosis against adequate 3-months' anticoagulant therapy.

About 4,000 light thromboendarterectomy operations have been performed around the world, and good results have been received to improve the survival of patients,

to improve exercise tolerance, to improve hemodynamic parameters and to increase the time to clinical deterioration in patients (Keogh et al. 2009). In recent decades, perioperative mortality of patients who underwent thromboendarterectomy has decreased. According to statistics, of 500 patients operated on for chronic thromboembolic pulmonary hypertension, the mortality rate was 16% prior to 1990, 7% in the period between 1990 and 1999 and 4% in the period from 1998 to 2002 (Jamieson et al. 2003).

Algorithms of treatment

Scientists define new goals that should be pursued in the treatment of pulmonary hypertension, along with a reduction in pulmonary artery pressure (which is the focus of almost all drugs used to treat pulmonary hypertension at the present time). A problematic issue remains the algorithm for managing patients with pulmonary hypertension, belonging to groups II-V according to the WHO classification. Obviously, for many categories of patients from other groups, it is impossible to automatically extrapolate the results of clinical trials conducted on patients with pulmonary arterial hypertension, since a different pathogenesis of pulmonary hypertension and a significant effect of the underlying diseases causing cause this syndrome gives grounds to talk about significant differences in the necessary therapy in groups II-V and overall management strategy compared with group I. The experts can only state that the evidence base for patients with pulmonary hypertension belonging to groups II-V remains meager and in most cases makes it impossible to give evidence-based practical recommendations. At present, the number of real and potential therapeutic options for the treatment of this pathology has significantly increased, which has even reduced the need for lung transplantation in the developed countries of the world. It should be noted that a widespread use of modern drugs and methods of treatment is limited not only by a scanty evidence base,

but, above all, by the high cost of appropriate drugs, surgeries, and diagnostic procedures. The topical therapeutic strategies are indicated in Table 4.

Group 1

Treatment in patients in this group is based mainly on specific therapy, because there are no effective primary treatments, especially for patients with idiopathic PAH. Primary therapy is possible only with PAH associated with other diseases. If necessary, oxygen inhalations can be used as symptomatic therapy for severe dyspnoea and hypoxia. Diuretics are administered with pulmonary hypertension complicated by right ventricular failure. Disaggregants and anticoagulants of indirect effect that reduce blood viscosity are indicated in patients with idiopathic PAH (Barst et al. 2009, Galiè et al. 2009a, McLaughlin et al. 2009).

Group 2

Primary therapy is aimed at the main cause of PH. It also includes maintenance therapy, including adequate oxygen therapy, diuretics and anticoagulants, which should be included in the therapy of all patients with PAH. Pathogenetic therapy includes prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Although the optimization by means of neurohormonal antagonists remains the main one in the treatment of patients with systolic heart failure, attempts have been made to treat PAH according to the principles used in the treatment of idiopathic PAH. The FIRST (Floran International Randomized Survival Trial) study recorded 471 patients with advanced heart failure to receive continuous infusion of epoprostenol plus standard therapy or only standard therapy. Although hemodynamic improvement was recorded in patients receiving epoprostenol, the study was completed earlier due to a strong trend towards increased mortality in patients receiving epoprostenol (McLaugh-

Table 4. Therapeutic strategy according to clinical classification of PAH

Group (clinical classification)	Therapeutic strategy
1 Pulmonary arterial hypertension	Specific therapy (idiopathic and hereditary forms) Primary therapy (forms associated with other diseases) Maintenance therapy (oxygen, oral anticoagulants, diuretics) Surgical treatment (pulmonary and atrial transplantation, septostomy)
2 Pulmonary hypertension due to left heart disease	Primary therapy Supportive therapy (diuretics, oxygen)
3 Pulmonary hypertension due to lung diseases and/or hypoxemia	Primary therapy Supportive therapy (diuretics, oxygen) Specific therapy (in some patients) Surgical treatment (lung transplantation) Supportive therapy (oral anticoagulant)
4 Chronic thromboembolic pulmonary hypertension	Surgical treatment Specific therapy (in some patients)
5 Pulmonary hypertension with unclear and/or multifactorial mechanisms	Primary therapy Maintenance therapy (oxygen)

lin et al. 2009). Some explanations included long-term adverse effects of systemic vasodilation on systolic heart failure and possible dangerous effects of epoprostenol on patients with ischemia. Basing on the results of this study, the chronic use of epoprostenol in patients with systolic heart failure is contraindicated (Badesch et al. 2010).

Group 3

Primary therapy is the main treatment for patients in this group. Diuretics are prescribed in the case of heart failure, with careful monitoring the concentration of electrolytes in the blood, the state of kidney function, as well as the volume of circulating blood and systemic blood pressure. Oxygenotherapy (12–15 hours per day) is indicated for pulmonary hypertension in patients with COPD, the level of supported saturation should be kept at least at 90% (Ashutosh and Dunsky 1987).

Cardiac glycosides are used for symptoms of heart failure and attacks of atrial fibrillation. Anticoagulant therapy is performed at the INR target level of 1.5–2.5 in the case of idiopathic pulmonary hypertension; in the case of associated pulmonary hypertension, the size of the indicator is variable and depends on the underlying disease.

With a positive result of an acute vasoreactivity test, calcium channel blockers (CCBs) are prescribed, whose efficacy in pulmonary hypertension is proven in clinical trials with FC I–III.

Specific therapy for patients of group 3 should be administered cautiously, because of disruption of gas exchange resulted from inhibition of hypoxic pulmonary vasoconstriction due to insufficient efficacy of long-term administration (Ghofrani et al. 2002b, Blanco et al. 2010)

Group 4

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease associated with the remodeling of LA as a result of thromboembolism of the main vessel. The cumulative frequency (CTEPH) is 0.1 to 9.1% in the first 2 years after the symptomatic episode of pulmonary embolism.

Optimal drug therapy (CTEPH) includes the use of anticoagulants and diuretics, with adequate oxygenation. Lifetime administration of anticoagulants is recommended even after surgery, although there is no data on the efficacy and safety of new oral anticoagulants. Some nonrandomized studies have shown an improvement in exercise tolerance and hemodynamics. Drug treatment (CTEPH) with targeted therapy may be justified in technically inoperable patients, or when there is an unacceptable ratio of surgical risk and benefit.

The standard treatment of CTEPH is pulmonary thromboendarterectomy (Keogh et al. 2009). When residual LH develops and surgery is impossible, drug treatment is required by means of drugs used to treat pulmonary arterial hypertension (PAH).

Prostanoids, phosphodiesterase type 5 inhibitors, endothelin receptor antagonists have been studied in a number of open studies in patients with inoperable forms of CTEPH. In the BENEFIT study, by the 16th week bozentan would contribute to a significant decrease in PVR, an increased cardiac output, but compared to the placebo, would not improve exercise tolerance according to a 6-minute walk test. In a randomized, placebo-controlled CHEST-1,2 study, the efficacy and safety of riociguat was demonstrated, the first representative of a new class of stimulants for soluble guanylate cyclase. In September 2014, this drug was approved in Russia, including for the treatment of patients with inoperable CTEPH; persistent or recurrent CTEPH after surgery.

Group 5

Primary therapy is aimed at the main cause of PH. It also includes maintenance therapy, involving adequate oxygen therapy, diuretics and anticoagulants, which should be included in the therapy of all patients with PAH. Pathogenetic therapy includes prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. These drugs are used simultaneously for several pathogenetic mechanisms of LH and are specific for PAH. Atrial septostomy and pulmonary transplantation are indicated for patients who are not amenable to drug treatment. Prostanoids are a promising group of drugs for the treatment of pulmonary arterial hypertension, since they have not only vasodilating, but also antiplatelet and antiproliferative effects. Therefore, it seems logical to use prostacyclin and its analogs to treat patients with various forms of PAH (Fisher et al. 2006).

Therapy according to the functional class

A therapeutic approach to pharmacotherapy of patients with PAH is based on the severity of the disease (Galie et al. 2009a).

The functional class is a powerful predictor of outcomes for patients suffering from PAH. Even in case of administering a pathogenetic therapy, patients with WHO FC IV have an extremely poor prognosis compared to patients with lower functional classes. According to a recent study conducted in France, a lower functional class (I/II) was positively and significantly associated with better survival; while US REVEAL registry data suggest that functional class IV was not directly correlated with increased mortality in patients with PAH.

After making a diagnosis, the initial measures are connected with following the general recommendations and assigning a maintenance therapy. Patients with PAH need to be referred to an expert center.

All patients with PAH are indicated for having acute pharmacological tests (APT) to assess vasoreactivity. The

likelihood of a positive APT is especially high with IPAH, inherited PAH, PAH on the background of receiving anorectics. In this category of patients, success is most likely when assigning anticoagulants (AC) in high doses. It is necessary to confirm the stability of the therapy effect in 3-4 months.

When obtaining a negative APT, PAH patients with FC I-II must be assigned specific therapy with inhaling nitric oxide (course therapy in case of a stable disease), prostaglandin E1 (course therapy in case of a stable disease), ERA (bosentan or ambrisentan) or sildenafil type 5 (PDEI-5).

With a negative APT, patients with PAH FC III are to be treated by ERA or PDEI-5, or by prostanoids. There are no direct comparative studies of the effectiveness of different types of specific therapy of PAH. Selecting a drug depends on a PAH form, FC, contraindications, availability of the drug, a route of administration, a side-effect profile, experience of the physician and a patient's preferences.

Patients with FC IV are indicated for an initial combination specific PAH-therapy, including two drugs: a combination of ERA (bosentan or ambrisentan) and iloprost or sildenafil. If the dual specific therapy is ineffective, it is recommended to assign three drugs – ERA+iloprost+sildenafil.

Atrial septostomy and/or transplantation are indicated for patients with PAH in case of an inadequate clinical effect of drug therapy and must be carried out only at expert centers.

Targeted therapy

For many decades, very slow progress has been observed in the treatment of patients with PH. The situation has changed significantly in recent years, due to a considerable increase in the number of controlled studies. Calcium antagonists, anticoagulants, cardiac glycosides, oxygen therapy, despite the absence of appropriate clinical randomized trials, currently make up a standard therapy widely used in patients with PH. At the same time, new groups of drugs have appeared, the efficacy and safety of which have been proved by the results of controlled studies.

This is the therapy whose goal is to reduce functional disorders and to prolong life (Sitbon and Galiè 2010). Targeted therapy uses known prognostic indicators to assess the state of patients with PAH, which allows beginning a timely pharmacotherapy, preventing deterioration in the patients' condition. A key role in this strategy is played by the identification of the parameters that correlate with the risk of deterioration and mortality. The diagnostic strategy for PH involves conducting a comprehensive examination to establish a diagnosis, to evaluate a clinical class and type of PH, and to assess functional and hemodynamic statuses of patients. It is expedient to distinguish the following stages of the diagnostic and differential diagnostic process (Sitbon and Galiè 2010).

An objective evaluation of the functional capacity of PH patients is necessary to assess the severity of PH and the dynamics of the clinical state in connection with the ongoing therapy. In the study of tolerance to physical exertion, the most commonly used test is a 6-minute walk and a cardiopulmonary exercise test with an assessment of gas exchange.

In the past, the average life expectancy with idiopathic PH was 3 years, in patients in FC IV <6 months; now with a "targeted" therapy it has improved ($\approx 90\%$ and $\approx 80\%$ of patients who have been treated for arterial PH live for more than a year and two years, respectively). With the preserved reactivity of pulmonary vessels, 95% of patients live for more than 5 years.

New classes of drugs in the pharmacological correction of pulmonary hypertension

Despite the severity of the ailment, not all forms of pulmonary hypertension are included today in the list of life-threatening and chronic progressive rare (orphanic) diseases, leading to a reduction in the life expectancy of citizens or their disability. According to this list, patients are provided with medications. So, in the list of rare life-threatening diseases, there is "pulmonary arterial hypertension", but patients with a diagnosis of "chronic thromboembolic pulmonary hypertension" (CTEPH) do not receive appropriate medication treatment in Russia.

Therefore, the search for an "ideal" treatment continues; targeted research is conducted to identify new medicinal molecules and approaches to pharmacotherapy of PAHs of different groups.

Below is a brief description of new classes of drugs for pharmacotherapy of idiopathic PAH in the future, which require further study.

Rho-kinase inhibitors

Rho kinase plays an important role in damaging the vascular endothelium. To date, two of its isoforms are known: Rho-kinase1 and Rho-kinase2. The latter is expressed in cells of smooth muscle vessels and endothelial cells. Activation of Rho-kinase 2 is by active GTP-bound.

RhoA leads to calcium sensitization in smooth muscle cells via phosphorylation-mediated inhibition of myosin light chain phosphatase activity and, thereby, promotes an increase in the activity of the myosin regulatory light chain (Fukumoto et al. 2007).

It is known that Rho-kinase is involved in a variety of pathophysiological processes, among which the following can be distinguished: the narrowing of blood vessels, including the development of myogenic tone and excessive contractility of the smooth muscles, contraction of the smooth muscles of the bronchi, COPD, PAH, ED, CVD

(Do et al. 2009). These data are confirmed by a number of studies. Activation of RhoA/Rh-kinase plays an important role in the development of ED in patients with PAH. A significant decrease in endothelium-dependent relaxation and NO levels was found, while RhoA / Rho-kinase activity increased in the pulmonary arteries of patients with PAH compared with those in the control group. Thus, researchers linked the development of ED in PAH patients with inhibition of endothelial NO-synthase activity and activation of RhoA/Rho-kinase (Do et al., 2009).

In animal models, treatment with Rho-kinase inhibitors appears to improve endothelial dysfunction, enhancing the expression of eNOS, suppressing hypercontract and proliferation of smooth muscle cells (Fukumoto et al. 2007).

Fasudil is a selective inhibitor of Rho-kinase, a signaling molecule involved in the implementation of the mechanism of contraction of smooth muscle cells in response to such stimulants as acetylcholine, angiotensin II, endothelin, noradrenaline, and serotonin. In a study in rats with a monocrotolin model of pulmonary hypertension, monotherapy with the drug fasudil and in combination with sildenafil or bosentan was studied in a comparative aspect.

Fasudil reduced vasoconstriction and obstructive remodeling of the walls of pulmonary blood vessels and hypertrophy of the right heart. The combination of bosentan or sildenafil with fasudil was not accompanied by synergistic effects. These results suggest that Rho-kinase inhibitors may be a new therapeutic approach for treating PAH.

Stimulant and activator of soluble guanylate cyclase

The disruption of the production of nitric oxide plays an important role in the pathogenesis of PAH, which is due to the powerful vasodilating action, cytoprotective, antiproliferative, anti-inflammatory and antiaggregational effects. Riociguat is the first representative of a new class of drug-stimulants of soluble guanylate cyclase. Riociguat proved effective in phase II of clinical trials. In a randomized, double-blind, placebo-controlled, Phase III PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylatecyclase-Stimulator Trial) trial, 443 patients with PAH symptoms were randomized to receive placebo, riociguat in a single dose of up to 2.5 mg (with titration according to tolerability up to 2.5 mg 3 times a day) or in a dose of up to 1.5 mg (with titration of the dose depending on the tolerance to 1.5 mg 3 times a day). The study included patients who had not previously received PAH-specific therapy or who have been already taking endothelin receptor antagonists or prostanoids (except for parenteral). By the 12th week of riociguat treatment, the distance of the 6-minute walk test increased on average by 30 m in the group of patients receiving the maximum single dose of 2.5 mg and decreased by an average of 6 m in the placebo group (the difference between the groups was 36 m, 95 % confidence interval 20-52 m, $p < 0.001$).

Riociguat improved D6MX in both patients who had not previously received PAH-specific therapy (+38 m), and in patients who had been taking endothelin receptor antagonists or prostanoids (+36 m). In contrast to the placebo group, there was noted the reduction in pulmonary vascular resistance and mean pulmonary pressure ($p < 0.0001$), an increase in the cardiac index ($p < 0.0001$), a reduction in the level of NT-proBNP ($p < 0.0001$), functional class ($p = 0.003$), and Borg index ($p = 0.002$); the time to clinical deterioration increased ($p = 0.005$) (Dumitrascu et al. 2006). Therapy with riociguat was characterized by good tolerability. The effectiveness of the treatment persisted with prolonged follow-up in the PATENT-2 study. After a year of follow-up, the average value of DT6MX changed by 51 ± 74 m, WHO functional class increased in 33% of patients, stabilization of PC was observed in 61% and deterioration - in 6% of patients compared to the initial point of PATENT-1 study.

Riociguat is an oral stimulator of the NO s-receptor receptor, which demonstrated vasodilating and anti-remodeling properties in preclinical studies.

Further research is needed, but riociguat can be considered a new option for LH therapy included in patients with CTEPH (Kim 2010).

Serotonin antagonists

Serotonin can affect the smooth muscles of the vessels in two opposite directions. It causes the release of vasodilator mediators (NO, prostacyclin) in intact endothelial cells, and with direct action on the smooth muscles of the vessels causes a vasoconstrictor effect (MacLean and Dempsie 2010).

Serotonin is one of the most active BASs affecting various functions of bronchi and pulmonary parenchyma. When released in the aggregation of platelets, serotonin at threshold and subthreshold doses increases the vasoconstrictor effect of other mediators (norepinephrine, thromboxane A₂, prostaglandin F_{2a}, angiotensin), and also increases blood viscosity, affecting red blood cells and leukocytes. The pressure reaction is mediated by 5-hydroxytryptamine 2 (5-OT₂) receptors of blood vessels, especially with damage to the endothelium, and stimulation of 5-O₂ receptors on platelet membranes leads to their activation and aggregation. These changes, mediated by serotonin, occur throughout the body, but the role of serotonin in lung pathology is particularly great: 90% of unmetabolized serotonin is contained in electron-dense granules of platelets, whose task is the vascular bed of the lungs, and pulmonary endothelium is the main site of active metabolism of serotonin. In patients with PAH, an increased serotonin level, a decreased excretion of 5-hydroxyindoleacetic acid in the urine and a decreased activity of serotonin monoamine oxidase were found, indicating a disturbance in the metabolism of serotonin, while a decrease in its inactivation is considered one of the earliest criteria for damage to the pulmonary endothelium.

Currently, both serotonin receptor antagonists and serotonin-transporter inhibitors are considered to test the relevance of this new therapeutic strategy, specifically directed against the proliferation of pulmonary vessels.

Inhibitors of phosphodiesterase-1

Phosphodiesterases (PDEs) are important enzymes that hydrolyse the cyclic nucleotide 3'5'-cyclic monosilicate alanosine (cAMP) and 3'5'-cyclic guanosine monophosphate (cGMP) to their inactive 5'-monophosphates. Because of their key role in intracellular signaling, they are currently of considerable interest as therapeutic targets for a wide range of diseases, including PAH. An increased level of intracellular cAMP inhibits the activity of immune and inflammatory cells, and an increase in both cAMP and cGMP results in relaxation of smooth muscles. cAMP may play an additional role in modulating hypertrophy of smooth muscle and hyperplasia, as it has cytostatic effects in many types of cells and has an inhibitory effect on the proliferation of smooth airway muscles.

PDE1 makes up more than 35% of the cyclic nucleotide hydrolytic activity in the smooth muscle of human respiratory tract, and it is involved in the proliferation of human smooth muscle (Murray et al. 2007). It is not known whether it participates in the proliferation of smooth muscles of the airways, but if so, PDE1 inhibitors may be useful in the treatment of respiratory remodeling in PAHs of different genesis.

VIP (vasoactive intestinal peptide), a neurotransmitter of the non-adrenergic nervous system, is described as a neuroendocrine mediator, which plays an important role in the metabolism of water and electrolytes in the intestine. In addition, the vasoactive intestinal peptide acts as a potent systemic vasodilator and reduces pulmonary artery pressure and pulmonary vascular resistance in monocrotalin-induced pulmonary hypertension in rabbits; it inhibits platelet activation and smooth muscle cell proliferation. Recently, it has been shown that the vasoactive intestinal peptide prevents experimentally induced arthritis in mice. These biological effects are mediated by specific VIP receptors – VPAC-1 and VPAC-2, localized on the surface of the cell membrane. The VPAC receptors are found on the breathable epithelium, on the macrophages surrounding the capillaries, and in the subintima of the pulmonary arteries and veins. Stimulation of the VPAC receptors leads to the activation of cAMP and cGMP systems, which, as it has been shown, mediate the action of prostacyclins, NO, phosphodiesterase inhibitors in the treatment of pulmonary hypertension (Petkov et al. 2003). The use of vasoactive intestinal peptide as a therapeutic agent in primary pulmonary hypertension led to a significant improvement in hemodynamic and prognostic parameters of the disease without side effects. The vasoactive intestinal peptide takes part in the innervation of the respiratory tract. The

significance of the dysfunction of VIPergic innervation in the pathogenesis of obstructive pathology is currently being debated. However, there is a hypothesis about the role of the decreased biological activity of the vasoactive intestinal peptide in the mechanisms of development of bronchial asthma.

It is likely that the dysfunction in the system of this peptide may occur again due to the inflammatory process in the airways, accompanied by an increase in the level and activity of inflammatory cells – neutrophils, eosinophils, mast cells that are capable of producing various peptidases (eg, tryptase) that destroy the vasoactive intestinal peptide. Its increased degradation promotes the formation of hyperreactivity of the airways and causes reflex bronchospasm in patients with obstructive pathology.

Prostanoids are analogues of prostacyclin. Prostacycline is produced by endothelial cells, induces vasodilation and is a potent inhibitor of platelet aggregation. Its synthesis is reduced in patients with PAH. For the treatment, drugs with a short half-life, such as epoprostenol, treprostinil and iloprost, are used.

Prostanoids are a promising group of drugs for the treatment of pulmonary arterial hypertension, since they have not only vasodilating, but also antiplatelet and antiproliferative effects. Therefore, it seems logical to use prostacyclin and its analogs to treat patients with various forms of PAH. Prostacyclin has a very short-term effect. Its half-life in the blood plasma is about 1-2 minutes. Inactivation of the drug occurs in the liver. With intravenous administration, prostacyclin expands not only pulmonary, but also systemic arteries, so systemic hypotension is possible

Intravenous use of epoprostenol improves hemodynamic parameters and functional performance in patients with PAH (Barst et al. 1996, Higenbottam et al. 1998). This is the only treatment that improves survival in idiopathic PAH, according to randomized controlled clinical trials (Barst et al. 1996). The main limitation to its use is that it has a short half-life (3-5 min), and its metabolites are stable only for 8 hours. Therefore, it must be administered by continuous infusion through an implanted central venous catheter. Infusion begins at a dose of 2-4 ng/kg/min and increases by 1-2 ng/kg/min every 1-2 days. The optimal dose for pharmacotherapy varies from 20 to 40 ng/kg/min. Due to a large number of side effects arising from the perfusion of epoprostenol, the drug is used as the first line of therapy only in patients with severe disease, i.e. FC IV functional class.

Treprostinil is an analogue of epoprostenol with a longer half-life (58-80 min); the drug is suitable for intravenous, subcutaneous and aerosol administration. The inhalation route is suitable for patients with PAH of group 1. Treprostinil improves hemodynamic parameters, reduces the symptoms of the disease and increases exercise capacity (Benza et al. 2008). Subcutaneous administration of treprostinil begins at a dose of 1-2 ng/kg/min, with a gradual increase in the dose to avoid side effects. The optimal dose varies from 20 to 80 ng/kg/min. Intravenous use of

treprostinil was approved by the FDA in patients with II, III and IV functional class of PAH.

Iloprost is an inhaled synthetic analogue of prostacyclin. Iloprost has a short half-life and requires frequent administration (six to nine times per day) according to the individual patient's need and tolerance of the drug. According to randomized controlled clinical trials involving PAH patients from groups 1 and 4 and the placebo group, Iloprost was inhaled (at an average dose of 30 µg per day) for 12 weeks (Olschewski et al. 2002). A clinical endpoint was achieved in 16.8% of those who had inhaled iloprost compared to 4.9% of those who had received placebo ($p=0.007$). Tolerance to physical exertion (functional class, a 6-minute walk test) was quantitatively assessed. Inhaled iloprost is approved by the FDA for patients with PAH of III and IV functional classes.

Possibilities for evaluating pharmacological correction of pulmonary hypertension with new compounds in the experiment

An increase in the number of publications on the problem of pulmonary hypertension occurred due to a significant increase in reports on studying the pharmacological activity of compounds of new classes and groups as means of pharmacological correction of pulmonary hypertension in the experiments on models in laboratory animals.

One of the most common and easily reproducible models of the pathology under study is a model of monocrotalin-induced pulmonary hypertension.

Monocrotalin (MCT) is a macrocyclic pyrrolizidine alkaloid extracted from *Crotalaria spectabilis*. A lot of pyrrolizidine alkaloids, products of tropical plants of several genera, are toxic to mammals.

MCT, administered in large doses (more than 100 mg/kg, subcutaneously), like many other toxins, causes necrosis of liver cells. However, in low doses (40–60 mg/kg, subcutaneously), MCT acts selectively on the endothelium of the lung vessels. An increase in the total dose of MCT leads to damage to the vessels of the kidneys and small intestine. Now it is generally accepted that not MCT itself, but its derivative formed in the liver has a pneumotoxic action; it may be a dehydrogenated product – monocrotaline-pyrrole. When administered to animals, MCT-pyrrole has a stronger toxic effect on the lung vessels than MCT; its effective dose is 12–15 times lower than that of its predecessor. The metabolite reaches the pulmonary vessels, accumulating in the red blood cells. First of all, the MCT metabolite acts on the endothelial cells of the pulmonary vessels, causing their inflammation followed by remodeling of the vascular wall. Monocrotaline pulmonary hypertension (MCT-PH) is characterized by the formation of thrombi, especially in the postcapillary bed and inflammation of the pulmonary veins, which brings

the model closer to pulmonary veno-occlusive syndrome – one of the pathoanatomical manifestations of primary PH (Zakharov and Gerasimenya 2013).

For the first time MCT was applied in 1965 to create a model of “pulmonary heart”. Before the development of hypertrophy and failure of the right heart in rats treated with MCT, thrombocytopenia, the clumping of macrophages in the adventitia of pulmonary vessels and edema due to increased permeability of endothelial cells are observed. Treatment with MCT suppresses the activity of enzyme systems located on the surface of endothelial cells of the lung vessels – angiotensin-converting enzyme, plasminogen activator, reuptake systems and serotonin metabolism. After 3–4 weeks, depending on the dose of MCT – 40 or 60 mg/kg, pulmonary hypertension develops and hypertrophy of the right ventricle of the heart is observed (Zakharov and Gerasimenya 2013).

By this time, the inflammatory response is reduced, which is a consequence of the toxic effect of MCT. Thus, for example, the content of Substance P in the lung tissue decreases, which sharply (about 3 times) increases in the lungs after a monocrotalin injection.

According to the international medical information database PubMed, the monocrotalin model is used in more than 400 publications for modeling PH. In its etiology and pathophysiological manifestations, pulmonary hypertension caused by MCT is close to primary pulmonary hypertension in humans.

Conclusion

The average life expectancy of patients with pulmonary arterial hypertension between 1981 and 1985 was 2.8 years. The use of modern approaches to treatment has significantly improved the survival of such patients. So, among those taking epoprostenol, 5-year survival is 47–55%, and according to some data it reaches 70%. Patients with signs of right ventricular failure have a much shorter life expectancy than those with an isolated increase in systolic pressure in the pulmonary artery. About 15% of these patients, even those receiving modern therapy, die within a year.

Predictors of the unfavorable prognosis are: increased right atrial pressure (above 10 mm Hg), low cardiac index (below 2.1 L/min-m²), low mixed venous oxygen saturation (SaO₂ less than 63%), 6-minute walking distance less than 400 m, the preservation of symptoms of cardiac failure of FC III–IV, poor physical tolerance, pericardial effusion and an increased level of the brain natriuretic peptide.

The existing available drugs improve physical performance and functional class in patients with PAH. Randomized clinical trials have also showed the improved hemodynamic parameters and increased time to clinical deterioration. Although the impact on mortality was less pronounced, progress in therapeutic strategies has allowed better predictions, especially for patients with

PAH. It is likely that combination therapy will become the cornerstone of the treatment of idiopathic PAH in the future, and the study and introduction of new pharmacological preparations will become part of the therapeutic arsenal to improve the quality of life, to slow down the progression of the disease and to improve the survival of patients. Future directions are aimed at better description of the PAH pathogenesis, which remains incomplete. Indeed, the pathophysiology and genetics of this disease

can be a link to new therapies. Although it is clear that platelets, fibroblasts and circulating cells are involved in the progression of PAH, changes in smooth muscle cells of the pulmonary artery and in pulmonary arterial endothelial cells resulting from multiple genetic and acquired defects are probably the main cause of the occurrence. Accordingly, efforts to develop effective therapeutic strategies should target genes, molecular mechanisms and pathogenetic pathways involved in the disease.

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