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LIST OF ABBREVIATIONS

ABS - acid- base status;
ACE inhibitors - angiotensin converting enzyme;
ACS - acute coronary syndrome
AHD- acquired heart defects;
AHP - antihypertensives;
AMI - acute myocardial infarction;
ANF - atrial natriuretic factor;
APTT - activated partial thromboplastin time;
ARBs - angiotensine receptor blockers;
ARF - acute rheumatic fever;
ATPh - adenosine triphosphate;
BMI - body mass index;
BP - blood pressure;
BV - blood volume;
CA - calcium antagonists;
CHD - coronary heart disease;
CMP – cardiomyopathy;
CNS - central nervous system;
CO - cardiac output;
Cr - creatinine;
CV - cardioversion;
CVA - cerebrovascular accident;
CVD - cardio - vascular diseases;
CVI - cardio - vascular insufficiency;
CVP - central venous pressure;
CVS - cardio - vascular system;
DBP - diastolic blood pressure;
DIC - disseminated intravascular coagulation;
DM - daily monitoring;
DM – diabetes mellitus;
ECG - electrocardiogram;
ECHO - echocardiography;
EF - ejection fraction;
EFI - electrophysiological study;
ESR - erythrocyte sedimentation rate;
FAT - focal atrial tachycardia;
GIT - gastrointestinal tract;
HF - heart failure;
HIT - heparin-induced thrombocytopenia;
HR - heart rate;
ICVD - implantation of cardioverter - defibrillator;

LA - the left atrium;
LV - left ventricle;
LVH - left ventricular hypertrophy;
LVMI - left ventricular massindex;
MI - myocardial infarction;
OD - organ damage;
PAOP – pulmonary artery occlusion pressure
PAP – pulmonary artery pressure
PE - pre-eclampsia;
PH-pulmonary hypertension;
PM - pacemaker;
PVR – pulmonary vascular resistance;
RF - a risk factor;
RHC- right heart catheterization;
RLV - increased residual lung volume;
RV – right ventricle;
SBP - systolic blood pressure;
SLE - systemic lupus erythematosus;
SN- sinoatrial node;
SSS - sick sinus syndrome;
SV - stroke volume;
SVPT - supraventricular paroxysmal tachycardia;
TE - thromboembolism;
TPPG- transpulmonary pressure gradient;
TPVR - total peripheral vascular resistance;
UFH - unfractionated heparin;
VT - ventricular tachycardia;

Abstract

The tutorial possible fully and systematically reflected contemporary information about the etiology, pathogenesis, classification, clinic and diagnosis of PAH, the correct interpretation of which is the key not only accurate clinical diagnosis, but also adequate for individual selection of optimal therapies. Advances in modern medicine, the introduction in clinical practice of medicine principles of evidence, a significant expansion of the arsenal of medicinal drugs require treatment from a doctor a good knowledge of the pharmacodynamics and pharmacokinetics of the main groups of drugs used in diseases of the cardiovascular and bronchi pulmonary system.

1. Introduction

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death [1]. The average life expectancy in the mid-80s.the last century from the time of diagnosis in patients with idiopathic PAH (IPAH), formerly known as primary pulmonary hypertension (PPH), before the advent of specific targeted therapy was 2.8 years [2]. PAH includes IPAH [3], and pulmonary hypertension (PH) with various other conditions, such as broncho-pulmonary system, connective tissuedisease (CTD) in the pathology of the left ventricle, chronic thromboembolic disease, presence of congenital shunts between the systemic and pulmonary vessels, portal hypertension,HIV infection [4]. In all these states are developing similar obstructive changes in the pulmonary microcirculation [5, 6], which implies equivalent pathogenic processes in all diseases accompanied by PAH [7]. In the last decade, great progress in the study of the pathogenesis, diagnosis and treatment of PAH.

Great achievement to clarify pathogenetic sequence of events in PAH was the discovery of mutations in bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases of familial PAH (Slug) [8, 9]. Described a variety of cellular changes in the pulmonary vessels of patients, which may play an important role in the development and progression of PAH [7]. These include pulmonary endothelial dysfunction [10], which is characterized by impaired synthesis of nitric oxide,

thromboxane A2, prostacyclin and endothelin, pathology of potassium channels and a violation of the serotonin transporter in the smooth muscle cells, and increased matrix production in the adventitia [7].

It has now developed a new clinical classification and consensus -based on algorithms of various diagnostic measures that prevent other reasons and provide an accurate diagnosis of PAH [11]. In addition, the proposed non-invasive markers of disease severity, biomarkers or physiological tests that can be used widely and reliably monitor the clinical course of the disease [11, 12].

Finally, numerous controlled clinical trials for PAH done recently, allowed to refuse treatment based on the clinical picture and adopt a strategy based on the evidence, which includes new classes of drugs, such as prostanoids, endothelin receptor antagonists (EIA) and the inhibitors of phosphodiesterase type 5 (PDE -5).

Medical and social significance of the problem of lung disease and / or hypoxia in the development of pulmonary hypertension in recent years has been steadily increasing. Chronic lung disease and other hypoxic disorders are favorable for the formation of cardiovascular disease. This reflects not only the combination of respiratory and cardiovascular disease, but also the existence of cardio-respiratory continuum in which lung disease is a direct participant in the development of pulmonary hypertension (PH) and the formation of chronic pulmonary heart (CPH). At the heart of their development is a complex of pathogenetic mechanisms that act directly on target organs or indirectly through the development of damage to the vascular wall and endothelial dysfunction. These factors include hypoxemia at rest or during exercise, smoking, oxidative stress, systemic inflammation with a low graduation.

Formation of pulmonary hypertension and chronic pulmonary heart disease is the most serious complication of lung diseases. Besides the sharp decline of the quality of life,PH and CPHpredetermines an unfavorable outcome of the disease [6,18].

According to a study conducted by the World Health Organization and the World Bank, in 2020. COPD will occupy 5th place on morbidity and third place in the structure of mortality among all diseases. In the U.S., there are nearly 14 million

people suffering from COPD. According to the European Respiratory Society, died from complications of COPD in Europe ranked third and ranges from 2.3 (Greece) to 41.1 (Hungary) cases per 100 thousand population.

The situation is more severe in Uzbekistan. It should be noted that a respiratory morbidityin Uzbekistan occupies the first place, and mortality from them - second, behind only cardiovascular disease.[22].

In recent decades, in Uzbekistan, there is steadily growing interest of researchers to the problem of estimating functions of the right and left ventricle of the heart, especially his dysfunction diagnosis (both systolic and diastolic) in chronic heart failure,PH and CPH [23,25].

For PH and CPH, curative and preventive program is largely dependent on the timely initiated effective management of patients. According to statistics, only 25% of CPH cases diagnoses in a time. Cause increases of the incidence and mortality from lung disease and CPH in Uzbekistan is underdiagnosis and late detection.To establish an early diagnosis, adequate prevention and treatment PH, CPH necessary to clarify the pathogenesis of the disease, the factors causing and aggravating for him. [22]

At the same time, leading scientists [24,26] agree that it still remains unclear mechanism of RV remodeling in patients with lung diseases. Not developed criteria for predicting the development of pulmonary heart disease in patients with lung diseases and / or hypoxia, and premature mortality. To answer these and other questions concerning the pathogenetic concept of cardiovascular remodeling in lung diseases, need further study.

In studies of Uzbek scientists proved that syndrome,PH and CPHhas a significant impact on the physical and mental condition of the patients, seriously violates their quality of life [22,23].

2. Some questions of anatomy.

For a more complete understanding of the mechanisms for the development and presentation of chronic pulmonary hypertension, and involvement in the process of

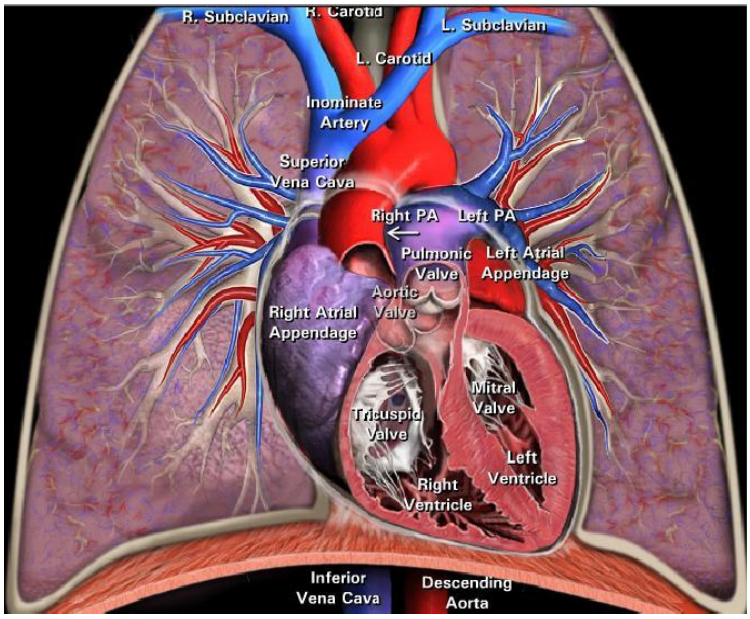
right ventricle, briefly on the anatomical structure of the data of the pulmonary circulation.

The entire circulatory system consists of a large and small circulation. The main function of a small circle - providing perfusion lung adequate pulmonary ventilation and arterial delivery of oxygenated blood to the left side of the heart and large circulation. The latter provides the inflow of arterial blood to all the internal organs and the outflow of venous blood from them,then flows into the right heart. Fig. 1 is a schematic representation of the heart chambers (atria and ventricles) and an aorta, pulmonary artery, the upper and lower hollow veins draining into the right atrium and pulmonary veins carry blood into the left atrium. The atriums and ventricles are separated by atrioventricular valves (mitral and tricuspid).In the output of the right and left ventricles there are arranged valves of aortic and pulmonary artery, each of which consists of three semilunar cusps.The work of heart delivers all the peripheral organs and tissues of oxygen. The supply of oxygen in the blood is carried by gas exchange in the vessels of the lungs during the act of breathing [43,49].

Breathing in humans includes external respiration and tissue respiration. Respiratory function is provided as the respiratory system and circulatory system. Ambient air through the tracheobronchial tree (trachea, main bronchuses, lobar bronchuses, segmental bronchuses, lobular bronchuses, bronchioles and alveolar ducts) misses the pulmonary alveoluses.

Fig. 1

Schematic representation of the chambers of the heart (the atriums and ventricles), and the aorta, pulmonary artery, upper and lower hollow veins, flowing into the right atrium, and pulmonary veins that supply blood into the left atrium.



Respiration is a unique feature of all living systems is governed autonomously through the respiratory center, which is located in the medulla oblongata. Violation in the regulation of breathing, pulmonary ventilation, gas exchange function may underlie the emergence of apnea syndrome. Respiratory system operates to provide physiological metabolic rate. Respiratory motor neurons originate from a cluster of neurons located in the medulla. Efferent neurons discharge and send a signal to the receptors, which are located in the chest, lungs, and thus establish the necessary amount of ventilation. Breathing is regulated by oxygen and carbon dioxide, and hydrogen ion concentration in blood and tissues. Peripheral and central chemoreceptors, as well as mechanoreceptors localized in the airways, lungs, chest, are involved in the generation of autonomous respiratory rhythm and respiratory patterning. Changes in oxygen and carbon dioxide tension perceived by the central chemoreceptors in medulla, and peripheral chemoreceptors located in the carotid arteries and aorta. Transmission of the signal is returned again to the respiratory center, allowing thus the homeostasis of the acid-base equilibrium.

Chemoreceptors and mechanoreceptors as the lungs and chest, can be projected in high centers of the brain, providing a direct assessment of the chemical state of the blood and the level of ventilation. Inspiratory activity of the respiratory center

begins with a powerful starting early discharge of inspiratory neurons, which are located in the rostral ventral respiratory group of neurons of the medulla oblongata. There are the following types of mechanoreceptorsin the human respiratory tract: irritative mucous receptors of airway, smooth muscle stretch receptors and J-receptors located in the alveolar septa. Irritation of the mucous irritative airway receptors causes reflex bronchoconstriction, closing the glottis, bradycardia. Numerous nerve endings located between epithelial cells and tracheal mucosa of the large bronchus.In this department of airway cough receptors are concentrated. Myelinated receptors are found in the epithelia of distal airways, their activity results in bronchoconstriction, increased mucus production,hyperpnoea.

Reflexes from the J- receptors, which are located in the alveolar septa, activated when the pressure increased in the interstitial tissue that occurs during the development of acute and chronic heart failure. Voltage changes PO2 and PCO2, and the concentration of hydrogen ions have a direct effect on the respiratory center and cortical brain structures [57].

3. Mechanisms of pulmonary arterial hypertension

The basis of the development of PH is the gradual formation of pulmonary arterial hypertension due to multiple pathogenic mechanisms. Although the value of each of them is different depending on the etiology of pulmonary hypertension, yet the main point of its pathogenesis in most cases is alveolar hypoxia that occurs in an increasingly uneven alveolar ventilation:

3. 1. Hypoxic pulmonary vasoconstriction. In a normally functioning lung exists rather complicated mechanism of regulation of local blood flow, which depends primarily on the partial pressure of oxygen in the alveolarair. If under physiological conditions oxygen partial pressure of in the alveolar air is decreased, in the same spot portion occurs reflex vasoconstriction, which leads to adequate blood flow restriction. As a result, local pulmonary blood flow adapts to the intensity of pulmonary ventilation, and violations of ventilation-perfusion ratios do not occurs.

If alveolar hypoventilation is high expressed and covers vast areas of the lung tissue (eg, patients with severe pulmonary fibrosis or obstructive lung disease, etc.),the tone of pulmonary arteriolesincreases,leading to an increase in total pulmonary vascular resistance and pulmonary hypertension (Fig. 2).

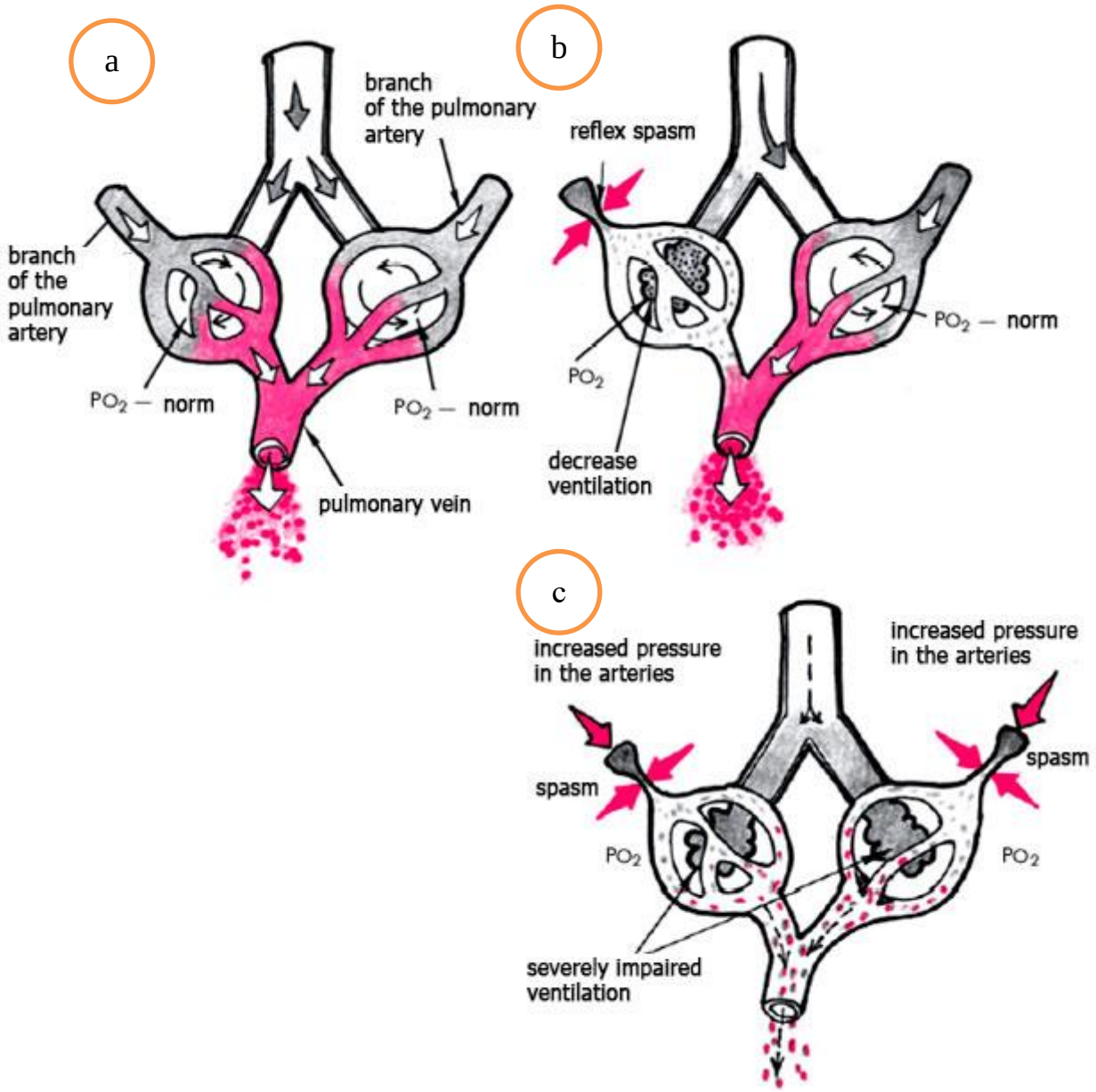


Diagram illustrating the mechanism of self-regulation of local pulmonary blood flow Euler- Liljestrand: a - pulmonary blood flow at normal oxygen partial pressure (PO_2); b - local decrease in alveolar ventilation and oxygen partial pressure, accompanied by local reflex spasm of the small branches of the pulmonary artery; c - expressed widespread reduction in alveolar

ventilation, leading to generalized vasoconstriction and increase of pulmonary artery pressure.

Hypoxic pulmonary vasoconstriction mechanism is not completely understood. Probably it realized with the participation of sympathoadrenal system (SAS), as well as endothelial vasoconstrictor factors. Endothelins and angiotensin II directly stimulates smooth muscle of the vascular wall, whereas decreased synthesis of prostaglandin PGI2, endothelial relaxing factor (NO) further enhances these vasoconstrictor influence.

3. 2. Effect of hypercapnia.

Hypercapnia (an increase of CO_2 concentration in the blood) also contributes to the development of pulmonary hypertension. However, the high concentration of CO_2 does not act directly on the pulmonary vascular tone and indirectly - caused primarily through its acidosis (pH < 7.2).

Furthermore, a delay of carbon dioxide (CO_2) promotes the reduction of sensitivity of the respiratory center to CO_2, which further reduces the ventilation and promotes obstructive pulmonary vasoconstriction.

3. 3. Anatomical changes in the pulmonary vascular bed. Great importance in the pathogenesis of pulmonary hypertension have structural changes in the bloodstream, which include: compression and emptying of arterioles and capillaries due to gradually progressive fibrosis of the lung tissue and emphysema, the development of the vascular wall thickening due to hypertrophy of muscle cells and the appearance of the media layer of longitudinal muscle cells in the intima that is accompanied by a decrease in lumen pulmonary arterioles and increases the severity and duration of vasoconstrictor responses, multiple micro-thrombosisarising in chronic impaired blood flow and increased platelet aggregation; recurrent thromboembolism of small branches of the pulmonary artery, the development of bronchopulmonary anastomoses, i.e. anastomoses between the branches of the bronchial arteries related to the systemic circulation, and the ramifications

of the pulmonary artery (small circle). Since the pressure in the bronchial arteries is higher than in the pulmonary circulation, bloodstream redistributes from bronchial arteries into the pulmonary artery branches system, which significantly increases pulmonary vascular resistance.

Vasculitis (for example, systemic connective tissue diseases)are also characterized by the proliferation of the intima, narrowing and obliteration of the lumen of blood vessels.

All these pathological changes of lung vascular bed naturally leads to a progressive increase in pulmonary vascular resistance and the development of pulmonary hypertension.

3. 4. Bronchial obstruction. Development of alveolar hypoxia and CPHexposed patients that suffer from chronic obstructive pulmonary disease (chronic obstructive bronchitis, bronchial asthma) with a predominance of signs of obstructive respiratory failure ("blue bloaters"). These patients are have expressed non-uniformity of pulmonary ventilation, resulting in significant violations of ventilation-perfusion ratios, exacerbates alveolar hypoxia and leads to generalized expression of hypoxic pulmonary vasoconstriction mechanism.

In patients with a predominance of restrictive disturbances and diffuse lesions in the lungs alveolar hypoxia expressed much less. For example, patients with severe diffuse emphysema ("pink puffers") are much less likely to develop chronic pulmonary hypertension and CPH.

Additional factors influencing the formation of pulmonary hypertension include:

• Increased blood viscosity and platelet aggregation;

• Increased cardiac output (CO);

• Tachycardia.

Pronounced polycythemia, which is typical formany of bronchopulmonary diseases, accompanied by increase in red blood cell aggregation and blood viscosity, which further obstructs blood flow to the

vascular bed of the lungs, increasing its resistance. In addition, an increase in viscosity and slowing blood flow contribute to the formation of mural thrombus of small pulmonary artery branches.

Increased cardiac output (CO) due to tachycardia and hypervolemia, which are very common in patients with chronic HP. One possible cause of hypervolemia, apparently, is a hypercapnia thatcontributing to increased concentrations of aldosterone in the blood and, therefore, delay the Na + and water.

Thus, the described mechanisms of increase pulmonary vascular resistance and the formation of pulmonary arterial hypertension is closely linked to the severity of changes in the airways and lung vasculature.Therefore, any aggravation of bronchopulmonary disease, usually accompanied by a worsening of pulmonary hypertension.Conversely, effective treatment of inflammatory changes in the lung parenchyma or airways in most cases accompanied by a decrease in pressure in the pulmonary system. This should be considered when selecting appropriate therapy aimed at reducing pulmonary vascular resistance, since any attempt such therapy may fail if simultaneously left untreated active inflammation in the bronchopulmonary system.

4. Definition

PH is defined as an increase in mean pulmonary arterial pressure results right heart catheterization (RHC) (Tables 1 and 2) [17]. Right heart catheterization is the primary method of direct measurement of pulmonary artery pressure. Research carried out in specialized clinics according to standard procedure using a "floating" catheter Swan- Ganz. The catheter is inserted through the internal jugular, external jugular, subclavian or femoral vein into the right atrium, then to the right ventricle and the pulmonary artery by measuring the pressure in these chambers of the heart. When the catheter is in one of the branches of the pulmonary artery, the balloon disposed at the end of the catheter is inflated. Short-term vascular occlusion allows measurement of pulmonary artery occlusion pressure (PAOP), which roughly

corresponds to the pressure in the pulmonary veins,LA and end-diastolic pressure in the left ventricle (LV).

Increased mean pulmonary arterial pressure (MPAP) > 25 mmHg at rest indicates pulmonary hypertension and is used for selecting patients in all RCTs and registries of PAH. The latest revision of the available data showed that the normal mean PAP at rest is 14 ± 3 mmHg the upper normal limit ≈ 20 mmHg [9, 10]. The mean PAP between 21 and 24 mmHg remains unclear. Patients with PAP in this range need further evaluation in epidemiological studies.

Table 1
Important Definitions

• Pulmonary hypertension (PH)– this is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP)> 25 mmHg at rest obtained by right heart catheterization (Table 2).PH can be detected by several clinical conditions (Table 3). • Mean PAP > 30 mmHg under a load of today is not the marker of PAH. Currently the load indicators of PH according to the KPS is not defined. • Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of pre-capillary PH (in the absence of other causes of pre-capillary PH: due to lung disease, chronic thromboembolic PH, or other rare diseases)(Table 2). PAH includes various forms that have similar clinical picture and have nearly identical pathological changes in the pulmonary microcirculation (Table 3).

According to various combinations of the pulmonary artery occlusion pressure, pulmonary vascular resistance (PVR) and cardiac output (CO) in Table 2 shows the various hemodynamic definition of PH: precapillary PH includes the clinical groups 1, 3, 4 and 5; post-capillary PH - clinical group 2 (Table 3).

5. CLASSIFICATION OF PH

5.1. Hemodynamic classification

PH is a hemodynamic and pathophysiological state, which can be observed in several clinical conditions. The latter were classified into six clinical groups with certain clinical features [32] (Table 3).

Table 2

***Hemodynamic definition* of pulmonary hypertension**[a]

Definition	**Features**	**Clinical groups**[b]
Pulmonary hypertension (PH)	Mean PAP ≥ 25 mmHg	All
Precapillary PH	Mean PAP ≥ 25 mmHg PAOP≤ 15 mmHg Cardiac Output (CO) normal or reduced[c]	1. Pulmonary arterial hypertension 2. PH, evolved as a result of lung disease 3. Chronic thromboembolic PH 4. PH with unclear and / or multifactorial mechanisms
Post - capillary PH	Mean PAP ≥ 25 mmHg PAOP≤ 15 mmHg Cardiac Output (CO) normal or reduced[c]	1. PH associated with left heart disease
Passive	TGP ≤ 12 mmHg	
Reactive (disproportionate)	TGP> 12 mmHg	

a. All values are measured at rest.

b. According to Table 2.

c. Increased CO can be in cases of hyperkinetic conditions such as systemic - pulmonary shunts (only in a small circle of blood), anemia, thyrotoxicosis, etc.
CO - cardiac output;PAP - pulmonary arterial pressure, PH - pulmonary hypertension;PAOP – pulmonary artery occlusion pressure; TGP–transpulmonal gradient pressure (Mean PAP – MeanPAOP).

5.2. The clinical classification of PH

Pulmonary hypertension was first identified by Dr. Ernst von Romberg in 1891, but despite a long historical period of the concept of chronic pulmonary hypertension, active learning and the development of mechanisms for the development of classification have been made only in the second half of the twentieth century. Understanding and clinical application of classification will help the following reasoning. Earlier PH was divided into two categories: Primary pulmonary hypertension (PPH) and secondary PH, depending on the presence or absence of the identified causes or risk factors [3, 17]. The diagnosis of PPH was a diagnosis of exclusion after exclusion of all other causes of PH. In 2018, during the II World Conference on PH held in Evian (France), was proposed classification of PH based on clinical manifestations. The purpose of " Evian classification " was to allocate variants ofPH having similar pathophysiological mechanisms, clinical manifestations and therapeutic approaches. Such clinical classification is necessary to discuss specific patients, standardization of diagnosis and treatment, research on homogeneous groups of patients, and finally, to analyze the pathophysiological changes in the well-matched patient populations. Obviously, the clinical classification does not exclude the existence of other classifications, such as pathological classification based on histological features, or functional classification based on the severity of symptoms. III-d World Symposium on PAH held in 2013 in Venice (Italy), to appreciate the value and usefulness of " Evian classification " and suggested some changes. It was decided to keep the main idea and structure of " Evian classification ", but at the same time proposed a number of changes, the main ones were the rejection of the term "primary pulmonary hypertension" and replacing it with the term "idiopathic pulmonary arterial hypertension," the revision of the place pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) in the classification, review of risk factors and conditions associated with PAH, as well as the improvement of the classification of congenital systemic- pulmonary shunts.

The clinical classification of PH has undergone several changes since the first version was proposed in 1973 at the first international conference on primary pulmonary hypertension and endorsed by the World Health Organization. The previous version of the practical guide ESC-PAH represented adopted in Evian - Venice classification proposed in the second and third meeting of the WHO PAH in 2018 and 2013, respectively [17]. In these classifications, clinical conditions with PH are divided into five groups according to pathological, pathophysiological and therapeutic characteristics. Despite the high values of comparable PAP and pulmonary vascular resistance (PVR) in different clinical groups, the underlying mechanisms, diagnostic approaches, prognostic and therapeutic aspects are quite different. During the fourth World Symposium on PH held in 2018 in Dana Point, California, consensus building experts throughout the world is to maintain the general philosophy and developed in Evian - Venice classification, as well as taking into account new information and to improve the clarity was amended some specific questions.

New clinical classification (adopted at the meeting in Dana Point) is shown in Table 3. To avoid possible confusion in terms of PH and PAH, the specific definitions are included in Table 1.

Table 3
Updated clinical classification of pulmonary hypertension (Dana Point, 2018)

1 group. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Hereditary
1.2.1 RKMB 2
1.2.2 AIC 1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Induced drugs or toxins
1.4 Associated with (APAH)
1.4.1 connective tissue disease

1.4.2 HIV - 1.4.3 portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.4.6 Chronic hemolytic anemia 1.4.7 persistent pulmonary hypertension of newborn
1. Endoflebitis of pulmonary veins and / or pulmonary capillary hemangiomatosis
Group 2. Pulmonary hypertension due to left heart disease 2.1 Systolic dysfunction 2.2 Diastolic dysfunction 2.3 Valve Disease
Group 3. Pulmonary hypertension due to lung diseases and / or hypoxia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive types 3.4 Violation of breathing during sleep 3.5 Violations of alveolar hypoventilation 3.6 Chronic exposure to high doses of 3.7 Malformations
Group 4. Chronic thromboembolic pulmonary hypertension
Group 5. PH with unknown and / or multifactorial mechanisms 5.1 Hematologic disorders: myeloproliferative disorders, splenectomy 5.2 Systemic diseases: sarcoidosis, pulmonary granulomatosis of Langerhans cells limphangioleuyomyomatosis, neurofibromatosis, vasculitis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disease 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ARK-1 - gene-activin receptor-like kinase-1 type; APAH - associated pulmonary arterial hypertension; BMPR 2 - bone morphogenetic protein receptor - type 2, HIV - human immunodeficiency virus; PAH - pulmonary arterial hypertension.

Changes clinical classification compared to the previous version are as follows:

• Group 1, PAH (Table 3): The term familial PAH has been replaced by heritable PAH because specific gene mutations have been identified in sporadic cases with no family history. Inherited forms of PAH include clinical sporadic idiopathic PAH (IPAH) with sexual mutations (mostly bone morphogenic protein receptor 2 gene and gene activin receptor- kinase type -1 or endoglin gene) and the familial cases without clinical or sex specific mutations [17]. This new category of heritable PAH does not require genetic testing in patients with IPAH or familial PAH cases because it does not lead to a change in clinical management. Classification of congenital heart disease (CHD) causing PAH updated and include clinical, anatomical and pathophysiological version in order to better define each individual patient. Associated PAH (APAH) include conditions that may have similar clinical presentations were observed in IPAH with identical histological findings, including the development of plexiform lesions. In specialized centers APAH share accounted for about half of all patients with PAH.

Schistosomiasis has been included in a number of shapes APAH as recent publications have shown that patients with schistosomiasis and PAH can have certain specific clinical and pathological characteristics. The mechanism of PAH in patients with schistosomiasis is probably multifactorial and includes portal hypertension, frequent complications of the disease, local vascular inflammation caused by schistosome eggs. Chronic hemolytic anemia, such as sickle cell anemia, thalassemia, hereditary spherocytosis, stomatocytosis and microangiopathic hemolytic anemia can lead to PAH and are included in the form APAH. Mechanism of PAH in chronic hemolysis associated with high consumption of nitric oxide (NO), leading to a state of resistance to the biological activity of NO.

In chronic hemolytic anemia cyclic guanosine - monophosphate smooth muscle - a powerful vasodilator / antiproliferative mediator and second messenger NO is not valid.

- Group 1 ' EPV and pulmonary capillary gemangiomatosic violations, still, it is difficult to classify because they share some characteristics with IPAH but also demonstrate a number of differences. Given evidence decided that the state should be separate categories, but not completely separated from PAH and identified as clinical group 1 '.
- Group 2, PH associated with left heart pathology, and group 3, PH due to lung diseases and hypoxia, have not changed significantly.
- Group 4, CTEPH: as clear criteria for separating the proximal obstructive lesions in distal CTEPH from does not exist, it was decided to keep only one category of CTEPH without attempting to distinguish between the proximal and distal forms.
- Group 5, PH with unclear and / or multifactorial mechanisms: this group includes a set of heterogeneous disease with uncertain pathogenetic mechanisms leading to PH including hematological, systemic, metabolic and other rare diseases.

6. Pathological anatomy of pulmonary hypertension

Various pathological features characterize different clinical groups of PH:

6.1. **Pulmonary arterial hypertension (Group 1)**: pathological lesions, particularly affect the distal pulmonary arteries (<500 micrometers in diameter). They are characterized by medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with moderate perivascular inflammatory infiltrates, complex (mesh, expanded damage) and thrombotic lesions. Pulmonary veins are classically unaffected.

- Group 1: mainly consists of EPV, which includes septal veins and venules prepartition (always involved) occluded with fibrotic lesions, venous muscle tissue development, frequent capillary proliferation (heterogeneity), pulmonary edema, occult alveolar haemorrhage, lymphatic dilatation and expansion lymph nodes

(vascular transformation of the sinus), and inflammatory infiltrates. Distal pulmonary arteries suffer from medial hypertrophy, intimal fibrosis and rare complex lesions.

6.2. PH associated with left heart disease (Group 2): pathological changes in this group are characterized by thickened and dilated pulmonary veins, pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, enlargement of the lymph vessels and lymph nodes. Distal pulmonary arteries may be affected by media hypertrophy and intimal fibrosis.

6.3. PH due to lung diseases and / or hypoxia (Group 3): pathological changes in these cases include medial hypertrophy and intimal obstructive proliferation of the distal pulmonary arteries. Can also be variable degree of destruction of the vascular bed in emphysematous or fibrotic areas.

6.4.Chronic Thromboembolic PH (Group 4): pathological lesions are characterized by organized thrombosis tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, instead of the normal intima. They can completely close the lumen or form different degree of stenosis, and network cords. Interestingly, in the non- occluded areas can develop indistinguishable from PAH pulmonary arteriopathy (including plexiform lesions). Collateral vessels from the systemic circulation (bronchial, costal, diaphragmatic and coronary arteries) can grow up to reperfusion, at least partially in the distal full of obstacles.

6.5. PH with unclear and / or multifactorial mechanisms (Group 5): this group includes heterogeneous condition with various pathological features, in which the etiology is unclear or multifactorial.

7. The pathophysiology of pulmonary hypertension

Various pathophysiological features [51] characterize different clinical groups of PH.

7.1. PAH (Group 1): the exact processes that initiate the pathological changes seen in PAH are still unknown even if it is generally accepted that the PAH has a multifactorial pathophysiology, which includes various biochemical pathways and cell types.IncreasePVR due to various mechanisms, including vasoconstriction,

proliferation and reconstruction obstructive pulmonary wall inflammation and thrombosis. The excessive vasoconstriction associated with impaired function or expression of the potassium channel in smooth muscle cells and endothelial dysfunction. Endothelial dysfunction leads to chronic producing vasodilatory and antiproliferative agents disorders, such as NO and prostacyclin, along with excessive vasoconstrictive and proliferative substances such as thromboxane A2 and endothelin - 1. Patients with PAH have a low levelof vasodilators antiproliferative substances such as vasoactive intestinal peptide. Many of these abnormalities increase the tone of blood vessels and contribute to vascular proliferative remodeling means which consist of multiple cell types, including endothelial and smooth muscle, and fibroblasts. Furthermore, there is increased production of extracellular matrixin adventitia, including collagen, elastin, fibronectin and tenascin. Inflammatory cells and platelets (through the serotonin pathway) may also play an important role in PAH. Prothrombotic changes and thrombosis are present in both arteries as small distal pulmonary arteries and proximal elastic pulmonary arteries.

7.2. PH due to left heart disease (Group 2): mechanisms responsible for the increase in PAP are numerous and include passive postback high pressure (post-capillary passive PH, Table 1). In these cases transpulmonary pressure gradient (TPPG = mean PAP - mean PAOP) and PVR is within the normal range. In other circumstances, there is an increase PAP more than PAOP (increased TPPG), as well as an increase in PVR (post-capillary reactive or "disproportionate " PH, Table 1).PVR increase due to increase of vasomotor tone of the pulmonary artery and / or fixed structural remodeling of resistance vessels of the pulmonary artery [33]. What factors do lead to reactive (disproportionate) PH and why some patients develop acute reversible obstructive vasoconstrictor or fixed component, or both, is not fully known. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from stretch receptors located in the left atrium and pulmonary veins, pulmonary artery endothelial dysfunction, which may contribute to vasoconstriction and proliferation of cells of the vessel wall.

7.3.PH due to lung diseases and / or hypoxia(Group 3): pathobiological and pathophysiological mechanisms involved in this condition are diverse and include hypoxic vasoconstriction, mechanical stress over extended (overstretched) of the lungs, loss of capillaries, inflammation, as well as toxic effects of cigarette smoke. There is also evidence of endothelium- dependent vasoconstrictor - vasodilator imbalance.

7.3.1. Chronic obstructive pulmonary disease.

Pathophysiological changes in COPD include the following abnormalities: mucus hypersecretion, ciliary dysfunction, airflow obstruction, parenchymal destruction and emphysema, gas exchange disorders, pulmonary hypertension, pulmonary heart, systemic manifestations. Hypersecretion of mucus -secreting glands caused by stimulation of goblet cells and leukotrienes, proteases and neuropeptides. Ciliated epithelium undergoes squamous metaplasia, resulting in impaired mucociliary clearance (violation of the evacuation of sputum from the lungs). These initial manifestations of COPD may persist for many years, not progressing.

An obstruction in COPD is mainly formed at the small and smallest bronches. Given the large number of small bronches, with about their constriction, the overall resistance of the lower respiratory tract increases twice.

Bronchial smooth muscle spasm, inflammation and mucus hypersecretion may form a small part of the obstruction, reversible under the influence of treatment. Exudation and inflammation are particularly important during exacerbation.

With the development of a long process of developing obstructive pulmonary hyperinflation (PHI) - increased air lung tissue formation and growth "air cushion" in the lungs.Depending on the cause of sub-divided into two types:

• Static PHI: due to incomplete emptying of the alveoles due to decreased expiratory elastic recoil of lung;

• Dynamic PHI: due to a decrease in expiratory time under severe limitations of expiratory airflow;

From the perspective of pathophysiology, PHI is an adaptive mechanism, since it leads to a decrease in airway resistance, improved air distribution and increase in minute ventilation alone. However, PHI leads to the following adverse effects:

1. The weakness of the respiratory muscles. And shorten the flattening of the diaphragm, making it ineffective contraction.
2. Limiting the rise in tidal volume during exercise. In healthy people, under load is increased respiratory minute volume by increasing the frequency and depth of breathing. COPD patients during exercise increases pulmonary hyperinflation, since the increase in respiratory rate in COPD leads to a shortening of expiration, and yet most of the air is retained in the alveoli. Increase in the "air cushion" does not allow to significantly increase the depth of breathing.
3. Hypercapnia during exercise. Due to the reduction ratio RLV to vital capacity (VC) by reducing the VC due PHI is an increase in arterial blood PaCO2.
4. Creation of an internal positive end-expiratory pressure (intrinsic positive end-expiratory pressure, PEEPi). Due to the growth of " air cushion " arises elastic recoil pressure of the lungs. Normally PEEPi zero in severe COPD exacerbation is - no more than 7-9 cmAq, and in acute respiratory failure reaches 20-22 cmAq. This leads to an increased load on the respiratory muscles, start reducing respiratory muscle does not coincide with the beginning of the tidal flow,it starts only when the pressure exerted by muscles exceeds PEEPi, when alveolar pressure becomes negative, which is necessary for inspiration.
5. Increased elastic load on the lungs.
6. Pulmonary hypertension. Ultimately PHI leads to pulmonary hypertension. Development of pulmonary hypertension associated with compression of the heart and intrathoracic vessels due PHI.

Emphysema. Parenchymal destruction leads to lower lung elastic recoil, and therefore has a direct relation to the restriction of airflow and increase the resistance to air in the lungs. Small bronches, losing touch with the alveoles, before be flat, fallen down and cease to be passable.

Gas exchange disorder. Airway obstruction, parenchymal destruction, and pulmonary blood flow disorders reduce the ability of the lung for gas exchange, leading to a first hypoxemiaand thento hypercapnia. Correlation between the level of lung function and arterial blood gases poorly defined, but more than 1 liter FEV1 rarely have significant changes of blood gas composition. In the initial stages of hypoxemia occurs only during exercise, but as the disease progresses - and at rest.

By the development of pulmonary hypertension are related vasoconstriction and pulmonary vascular wall thickening due to remodeling of the pulmonary arteries, pulmonary capillary destruction in emphysema, which further increases the pressure required to pass the blood through the lungs. Vasoconstriction may be due to hypoxia, which causes the smooth muscle of the pulmonary arteries, disorders of endothelium-dependent vasodilation mechanisms (decreased production of NO), pathological secretion of vasoconstrictor peptides (such as ET-1 - the product of inflammatory cells). Vascular remodeling - one of the main causes of pulmonary hypertension, is due to the release of growth factors or due to mechanical stress during hypoxic vasoconstriction.

As a result of the formation of PH and develop gradually progresses hemodynamic changes:
1) right ventricular hypertrophy (without affecting its function), which develops in response to the pronounced and prolonged increase in afterload;
2) a gradual decrease in systolic RV function, accompanied by increased end-diastolic pressure of RV dilation and its development stagnation of blood in the venous line of the systemic circulation;
3) the tendency to increase blood volume, delay Na + and water in the body.
4) in the later stages of the disease - a decrease in cardiac output and blood

pressure due to a decrease in blood flow in the pulmonary circulation and, consequently, LV filling (mainly due to the critical fall of systolic RV function and the formation of "second barrier" as expressed by the structural changes of the vascular bed of lungs);

7.3.2.Interstitial lung disease.

Main common feature of these diseases - alveolitis, and in most cases the immune nature. Main features - the degree and level of involvement in the pathological process of the basic structures of the lung, as well as the severity and nature of the progression of respiratory failure. So, in sarcoidosis, extrinsic allergic alveolitis (EAA), alveolar proteinosis affected primarily lung stroma and lobular structures. In pulmonary tuberculosis and pneumoconioses - lobular structure, in IFA (idiopathic fibrosing alveolitis) and rheumatic diseases - intralobular structures.

7.3.3. Pulmonary diseases with mixed restrictive and obstructive types.

There are three types of respiratory disorders:

• obstruktivy type;

• restrictive type;

• mixed type;

Obstructive type is associated with bronchial obstruction. In the pathogenes based on bronchoconstriction.

Causes bronchoconstriction:

• bronchospasm

• allergic edema,

• inflammatory edema,

• infiltration of the bronchial mucosa,

• obstruction of bronchial sputum,

• sclerosis bronchial walls,

• destruction of the bronchial walls of the frame.

Bronchoconstriction is responsible for higher resistance to air flow in the bronches.

Increase in resistance to air flow reduces its rate exponentially. Compensation reduce airflow occurs due to significant additional respiratory muscle effort.

Reducing bronchodilation complemented natural narrowing during expiration, so obstructive type exhale always difficult.

Because of the increase in airway resistance by exhalation occurs involuntary displacement of respiratory pauses in inspiratory phase. This shift occurs via a lower location of the diaphragm and inspiratory respiratory muscle tension. At the same breath starts when inspiratory alveolar tension and increases the volume of residual air.

In the initial stage of developing the disease offset respiratory pause has a functional character. Subsequently, atrophy occurs due to compression of the alveolar walls of capillaries high pressure breathing.As a result of atrophy of the alveolar walls develop secondary pulmonary emphysema and respiratory pause offset becoming irreversible.

Due to the increase in airway resistance is a significant increase in the load on the respiratory muscles and increase the duration of exhalation. Theduration of exhalation with respect to the duration of inhalation can be increased up to 3:1 or more. Thus, the 3/4 time respiratory muscles make the hard work to overcome airway resistance. In severe obstruction of the respiratory muscles can no longer fully compensate for the loss of airflow.

Also during the 3/4 time high intrathoracic pressure compresses the veins and capillaries of the lungs. Squeezing the capillaries and veins leads to a significant increase in resistance to blood flow in the lungs. Increase in resistance to blood flow causes secondary hypertension pulmonary circulation and develops chronic pulmonary hypertension.

7.3.4. Interruption of breathing during sleep.

Distinguish between obstructive and central sleep apnea, as well as mixed forms [32,58].Obstructive sleep apnea: narrowing of the upper airway during sleep predisposes to obstructive sleep apnea. Apnea lasting more than 10 seconds, there is a state of hypoxia and hypercapnia with metabolic acidosis, with increasing

severity of the changes with the growth duration of apnea. At a certain threshold of these changes comes the awakening or the transition to the surface stage of sleep in which the tone of the muscles of the pharynx and mouth with restoration of patency of the pharynx. This is accompanied by a series of breaths, typically with strong snoring. As the normalization of blood gas phase occurs deeper sleep.

Patients with obstructive sleep apnea there is no reduction in blood pressure during sleep, during an episode of sleep apnea it is, on the contrary, increases. In this connection, obstructive sleep apnea is a risk factor for diseases of the cardiovascular system - hypertension (at 40-90 % of patients), coronary heart disease, stroke.

Central sleep apnea: central sleep apnea occurs in normal, often falling asleep and in REM sleep. In healthy individuals, the central apnea are rare and are not accompanied by pathophysiological and clinical manifestations. If you violate the stability of the central (stem) develop mechanisms for the regulation of respiration respiratory disorders characteristic of obstructive sleep apnea. Often observed hypocapnia without hypoxemia, hypercapnia, and rarely formed hypoxemia accompanied by pulmonary hypertension and right ventricular failure.

7.3.5. Chronic exposure to high dosesof radiation

Chronic radiation sickness, is caused by long-term continuous or fractionated irradiation dose excreted in 0.1-0.5 Gy / day, with a total dose in excess of 0.7-1 Gy. Long-term consequences of irradiation point in the skin, connective tissue, blood vessels, kidney and lung in the form of seals and atrophy of the irradiated portions, the loss of elasticity and other morphological and functional disorders that lead to fibrosis and sclerosis, due to developing complex process involving reduction in the number of cells, and fibroblasts dysfunction. Blood vessel damage in the lung eventually leading to the inevitable changes in their structure with a loss of elasticity, which leads to high blood pressure or chronic pulmonary hypertension.

7.4. Chronic thromboembolic pulmonary hypertension (group 4).

Pulmonary embolism (PE) - acute occlusion by thrombus or embolus trunk of one or more branches of pulmonary artery. PE - part of the syndrome of thrombosis of the upper and lower vena cava (usually pelvic vein thrombosis and deep veins of the lower extremities), so in practice the two foreign diseases collectively called - "venous thromboembolism". [32]

The pathogenesis of venous thrombosis defined by the triad of Virchow: 1 - endothelial damage (more inflammation - phlebitis), 2 - slowing of venous flow, 3 - hypercoagulable syndrome. Determinants Virchow triad implementation, shown in Table 7.

Table7.Factors governing the exercise of Virchow triad

Risk factors for DVT and PE	Factors contributing to PE
Chronic heart failure Chronic lung disease Injuries to the lower extremities Thrombophlebitis of the lower limbs Inflammatory diseases of the genitourinary system Surgeriesmalignancies Blood disorders Antiphospholipid syndrome	Age over 60 years Obesity Oral contraceptives Pregnancy and childbirth

In the event of pulmonary embolism occur two mechanisms of pathological process : "mechanical" obstruction of the vascular bed and humoral disorders arising from the release of biologically active substances.

Extensive thromboembolic obstruction pulmonary arterial bed (reducing the total area of the lumen of the arterial bed by 40-50 %, which corresponds to the inclusion in the pathological process of pulmonary artery branches 2-3) increases the total PVR, preventing the release of blood from the right ventricle, reduces filling left ventricle, which leads to a reduction in total CO and blood pressure drop. PVR increases and due to vasoconstriction resulting in release of biologically

active substances from the platelets in the aggregates of the thrombus (thromboxane, histamine, serotonin), it is confirmed by the clinical and experimental observations. For diagnostic or monitoring registered probing central hemodynamics (CH) in patients with myocardial infarction (MI) after catheter insertion (Swan-Ganz), the diameter of which is comparable with the size of thromboembolism in the right heart and pulmonary artery system to the segmental vessels, clinics PE not observed. In the experiment with infusion of blood serum of animals undergoing pulmonary embolism, healthy animals registered hemodynamic and clinical signs for pulmonary embolism.

As a result of occlusion of the pulmonary artery branches appear no-perfused but ventilated areas of the lung tissue - the "dead space" manifestedby increase ventilation- perfusion ratio > 1 (normal V / Q = 1). Release of biologically active substances promotes local bronchial obstruction in the affected area, followed by decreased production of alveolar surfactant and atelectasis of the lung tissue, which appears on the 2nd day after the cessation of pulmonary blood flow.

Increase PVR accompanied by the development of pulmonary hypertension, bronchopulmonary shunt opening and increased shunt right - left. Emerging arterial hypoxemia may worsen shunt right - left atrial level through the oval window by increasing the pressure in the right ventricle and atrium. Unresolved acute embolic mass later fibrosing and lead to mechanical obstruction of the pulmonary arteries and are the most important pathobiological process in CTEPH. Pulmonary embolism or thrombosis in situ may be initiated or exacerbated by impaired blood clotting cascade, the function of platelets or endothelial cells which participate in the coagulation process. [28] In some patients, pathology and biochemical features of platelet procoagulant environment in support of the pulmonary vascular blood flow have the potential role of local thrombosis in initiating the disease. In most cases, it remains unclear thrombosis and platelet dysfunctions are a cause or consequence of the disease. Inflammatory infiltrates typically found in samples of pulmonary endarterectomy (PEA). Studies thrombophilia showed that lupus - anticoagulants can be found at ≈ 10 % of these

patients and 20 % are carriers of antiphospholipid antibodies, lupus anticoagulant or both substrates. It turned out that the plasma levels of factor VIII, a protein associated with both primary and repeated venous thromboembolism, is elevated in 39 % of patients with CTEPH. Violations of fibrinolysis were not identified.

7.5. PH with unclear and / or multifactorial mechanisms (group 5) in the pathophysiology of this group is unknown or multifactorial.

8. Epidemiology and risk factors of pulmonary hypertension

Comparative epidemiological data on the prevalence of different groups of PH does not exist. Surveys [29], the prevalence of PH (defined as PH systolic pressure > 40 mmHg)of 4579 patients was 10.5%. Among the 483 casesof PH, 78.7 % had left heart disease (group 2), 9.7% - lung diseases and hypoxia (group 3), 4.2 % - PAH (group 1), 0.6 % - CTEPH (group 4), and in 6.8 % of patients it was not possible to establish the diagnosis.

8.1. PAH (Group 1): recent registries have described Epidemiology PAH. The lowest prevalence rates of IPAH and PAH is 15 and 5.9 cases / million.adult population, respectively.

Low incidence estimate of PAH is 2.4 cases / million.adult population per year. Recent data from Scotland and other countries have confirmed that the prevalence of PAH in Europe is in the range of 15-50 subjects per million population. In the French registry 39.2% of patients who have IPAH and 3.9% - a family history of PAH. In the subgroup ALAG, 15.3 % have a connective tissue disease (CTD; mainly systemic sclerosis), 11.3 % - atelocardia, 10.4% - portal hypertension, 9.5% - PAH associated with anorexia, and 6, 2% of them - the human immunodeficiency virus (HIV)[17,32].

PAH may develop in different situations depending on the associated clinical conditions. IPAH correspond sporadic disease, without any - or a family history of PAH or known triggering factor. When PAH occurs in a family context, sexual mutations detected bone morphogenetic protein receptor 2 gene. Mutations in this gene can also be detected in 11-40 % of sporadic cases explicitly, thus representing a major genetic predisposing factor for PAH. Mutations of other

receptors for these substances, such as activin receptor- like kinase 1 and endoglin were found in the majority of patients with PAH with a personal or family history of hereditary hemorrhagic telangiectasia (Osler-Weber syndrome, Randy). A number of risk factors for the development of PAH, defined as any factor or condition that presumably plays a predisposing or mediating role in the development of the disease. Risk factors are classified into certain, probable, possible or unlikely depending on the strength of their relationship with PH and their probable causal role. Certain interrelation recognized when the epidemic, the likely - if a single-center study conducted by the method of case-control or multiple serial cases demonstrated interrelation. Possible relationship can be suspected, for example, drugs with the same mechanism of action, which are considered definite or probable category, but which have not yet been investigated, such as drugs for the treatment of attention deficit disorders. Finally, an unlikely relationship is defined by the presence of one of the suspect factor studied in epidemiological studies, and whose connection with PAH has not been established. Certain clinical correlation of the number of states APAH listed in Table 2, and the risk of various drugs and toxins are summarized in Table 4.

Table 4
Updated risk level of drugs and toxins that can cause PAH

Certain	**Possible**
• aminorex • fenfluramine • dexfenfluramine • toxic rapeseed oil • benfluorex	• Cocaine • Phenylpropanolamine • St. John's Wort • Chemotherapy drugs • Selective serotonin reuptake inhibitor • Pergolide
Probable	**Unlikely**
• Amphetamines • L - tryptophan • Methamphetamine	• Perralnye contraceptives • Estrogens • Smoking

8.2. PH due to left heart disease (Group 2): even if constitutional factors may play a role in the development of PH in this group, no specific genetic linkages have been identified. The prevalence of PH in patients with chronic heart failure increases with the progression of functional class violations. Up to 60 % of patients with severe systolic dysfunction of the left ventricle (LV) and up to 70 % of patients with isolated diastolic dysfunction may have PH. When the left-hand valve disease, the prevalence increases with increasing PH defect severity and symptoms. PH can be found in almost all patients with symptomatic acute mitral valve disease and 65 % of those with symptomatic aortic stenosis [49,51].

8.3. PH due to lung diseases and / or hypoxemia (Group 3):

8.3.1. Chronic obstructive pulmonary disease - a significant incidence of PH in patients with COPD, at least one previous hospitalization due to worsening respiratory failure is 20%. In severe COPD LH common (> 50 %), although in general it is only mild.In interstitial lung disease, the prevalence of PH is between 32 to 39% [37]. The combination of lung fibrosis with emphysema is associated with a high incidence of LH [38].

Until recently, the abbreviation "COPD " stands for " chronic obstructive pulmonary disease," and was treated as a collective term that includes environmentally mediated chronic respiratory disease with predominant involvement of the distal parts of the respiratory tract with partially reversible airflow obstruction, characterized by increasing progression and chronic respiratory failure.

In the group of chronic obstructive pulmonary disease, or, as it is called chronic nonspecific pulmonary diseases (COPD), include a number of different clinical manifestations and pathogenesis of disease are grouped together thanks in part reversible progressive airway obstruction. Fall under this definition chronic obstructive bronchitis, emphysema, severe asthma, chronic bronchiolitis obliterans, bronchiectasis, cystic fibrosis, byssinosis. This generalized approach considerably complicates epidemiological studies, the development of diagnostic criteria and

principles of therapy due to differences pathogenesis Diseases, part of the concept of COPD.

According to the definition of COPD (singular), this global strategy GOLD, this narrowed concepts eliminated primary emphysema, since it is caused by deficiency of α1- antitrypsin [en] (rather than the impact of harmful factors) . Outdated term chronic obstructive bronchitis (COB) , since this state was regarded as a process that develops mainly in the bronchi, and the development of COPD, starting in the bronchi, affects all, without exception, functional and structural elements of the lung tissue, including alveolar tissue, vascular bed, pleura, respiratory muscles) , which is reflected by the term "COPD ". Saetta M. et al. in 2018 it was shown that inflammation in the membranous bronchitis is one of the causes of panacinar emphysema. Existing research methods do not allow to fix the transition process with pathological bronchial respiratory zone : increased residual lung volume (RLV), pulmonary hypertension and cor pulmonale indicate an advanced stage of the disease may therefore GOLD mention the term "COB". Excluded from the concept of "COPD " pulmonary tuberculosis at the stage of residual phenomena may occur when partial bronchial obstruction, the later stages of histiocytosis X, lymphangioleuyomyomatosis at all logical to consider these conditions as bronchial obstruction syndrome. For this reason, the concept of excluded bronchiectasis, bronchial asthma, severe course, cystic fibrosis, chronic obliterans bronchiolitis.

8.3.2. Interstitial lung disease - a heterogeneous group of diseases (which includes about 200 diseases) combined radiological syndrome bilateral dissemination. All IBL by etiological basis divided into diseases with known etiology unknown nature, and secondary systemic diseases. Some authors propose to exclude from the notion of IBL tuberculosis, pneumoconiosis, lung tumor dissemination of nature and a number of other diseases with known etiologic factors and pathogenic mechanisms and treat them as part of the differential diagnosis with ILD of unknown etiology, which are united in the concept of " idiopathic pulmonary fibrosis."

The most common ILD of unknown etiology include regular interstitial pneumonia, desquamative interstitial pneumonia, acute interstitial pneumonia, nonspecific interstitial pneumonia, sarcoidosis, histiocytosis X, alveolar proteinosis, idiopathic pulmonary hemosiderosis, Wegener's granulomatosis, Churg -Strauss syndrome and Goodpasture.

Among the risk factors of pulmonary interstitial lesions type ELISA discusses the role of smoking, systemic diseases, medications, professional and related external environment pollutants. Particular attention is paid to the role of viral infections in the pathogenesis of inflammatory and Fibroplastic changes in the lungs. As possible types of toxins inhaled gases treated (ozone, nitrogen oxide, sulfur oxide, chloro) ; vapors, aerosols, smoke (cadmium oxide, acid aerosols) , inorganic (nickel complexes, asbestos filaments of silicon) , organic (cereals, food additives, softwood, refined fuel) particles, radioactive gases and particles (alpha - and beta - nuclides) , and their possible combinations, e.g. cigarette smoke, automobile and industrial emissions. Relationship of viral infection and IFA is not always possible to confirm, but observations show that patients infected with Epstein-Barr virus, hepatitis B and C, there is frequent development of morphological changes in the territory of the small airways, similar to bronchiolitis obliterans, and joining the clinical signs of bronchial obstruction. Medications can also be the cause of interstitial lung damage. In the pathogenesis of pulmonary iatrogenic matter direct and indirect damaging effects of free radicals on pulmonary structure and progression of fibrosis.Under the influence of drugs and their metabolites (calcium channel blockers, cytostatics, antibiotics, narcotic analgesics, etc.) in the lung may be a violation of the secretory function of the epithelium and alveolar macrophages, leading to morphological changes in the type of phospholipidosis. Tobacco is considered one of the main contenders for the role in the development of a trigger IFA and especially bronchiolitis obliterans. Occupational exposures (silica, asbestos, metal compounds, organic compounds, dust, plant and animal origin) cause pneumoconiosis and exogenous allergic alveolitis.

8.3.3. Malformations.

With the improvement of medicine, the emergence of modern survey techniques, development of thoracic surgery, related disciplines in the XX century and the beginning of the XXI professionals have increasingly faced with congenital anomalies and hereditary diseases caused by light [17]. It was found that congenital anomalies and hereditary lung disease occur much more frequently than expected, and some patients are the main cause of the inflammatory process, or respiratory failure respiratory system.

8.4. Chronic thromboembolic pulmonary hypertension (group 4) specific genetic mutations associated with the development of CTEPH does not exist. Even if the latest studies show that the prevalence of CTEPH reaches 3.8% in survivors acute pulmonary embolism, most experts believe that the true incidence of CTEPH after acute pulmonary embolism is 0.5-2%. CTEPH can be detected in patients without previous clinical episodes of acute thrombosis, pulmonary embolism or deep venous thrombosis (50%) .

8.5. Group 5, PH with unclear and / or multifactorial mechanisms: because of the heterogeneity of this group to date, no relevant descriptions of genetics, epidemiology and risk factors of this group LH.

9. Diagnosis of pulmonary hypertension

Process evaluation of a patient with suspected LH requires a series of studies designed to confirm the diagnosis, clarify the clinical group of LH and specific etiology within the groupof PH, the assessment of the functional and hemodynamic disorders. After the description of each survey shows a comprehensive diagnostic algorithm (Fig. 3). Because of the PAH and especially IPAH, is a diagnosis of exclusion, this algorithm can be useful as a starting point in any case likely PH.

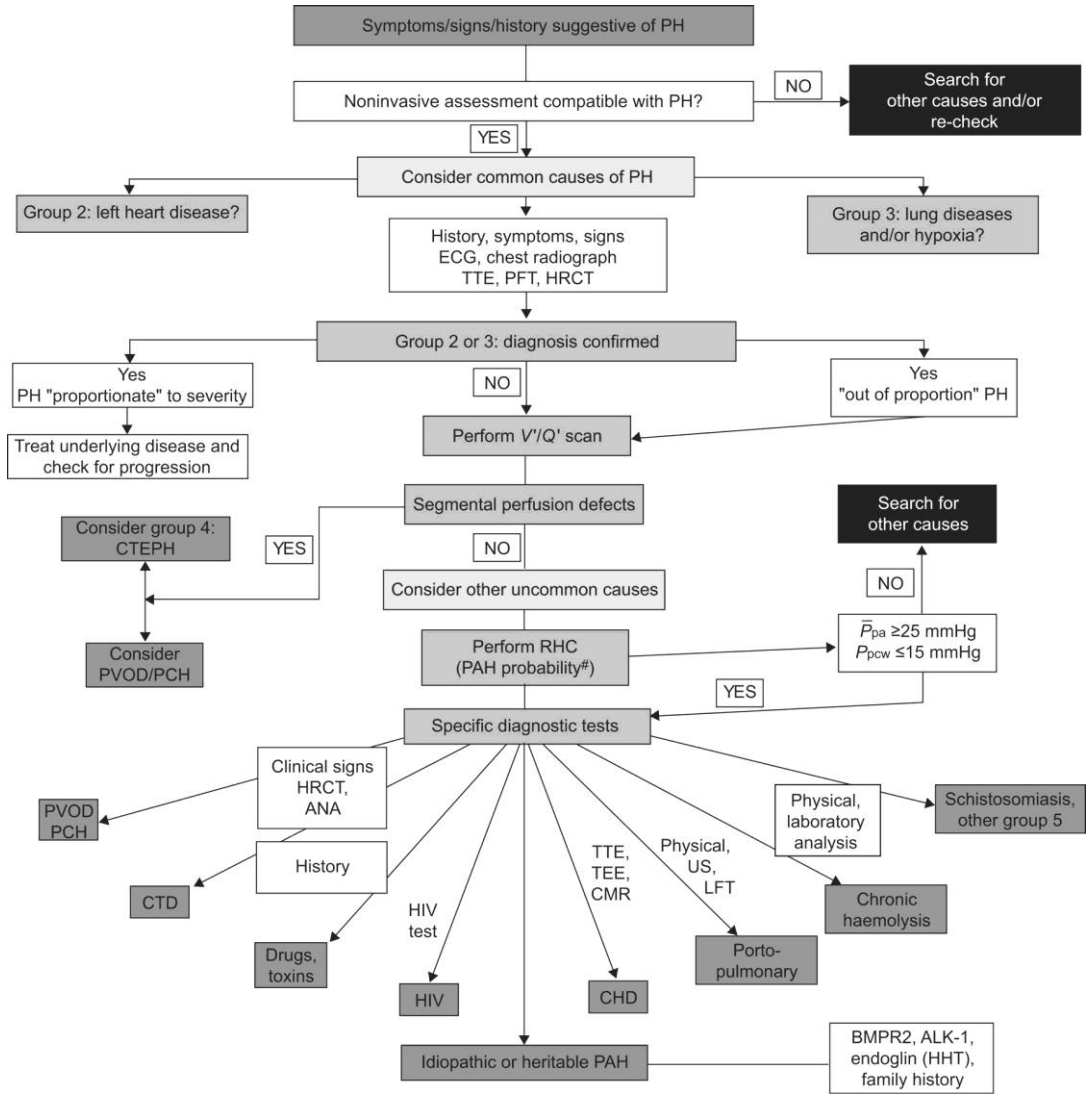
*Clinical manifestations.*The majority of patients with chronic PH for a long time dominated by characteristic clinical signs of inflammation in bronchopulmonar system, and respiratory failure. Clinical manifestations PH, eccentric hypertrophy of mud and, especially, - systolic dysfunction RV detected quite late, although some of them may be installed with the help of modern

instrumental methods of investigation. The problem of early diagnosis of chronic PH compounded by the fact that in the initial stages of the disease pulmonary artery pressure increases only during physical activity or in case of exacerbation of the inflammatory process in the lungs, while at rest, or in the period of remission of the disease remains almost normal.

Expanded clinical picture of PH is characterized by the increase in the average pressure in the pulmonary artery above 25 mmHg, presence of distinct hypertrophy RV, its regions, as well as signs of progressive isolated right heart failure.

Shortness of breath is the most subjective characteristic manifestation of PH. However, in the early stages of the disease it is difficult to distinguish from

Fig. 3 Diagnostic algorithm.



actually manifestations of respiratory failure characteristic of patients with chronic inflammatory processes in the lungs. In these cases should consider the lack of other objective evidence of the presence of pulmonary hypertension (hypertrophy of the RV, doppler echocardiographic signs of increased average pressure in the pulmonary artery, etc.), as well as clear communication of dyspnea with cough, sputum, fever and objective signs of bronchial obstruction or restrictive disturbances. Shortness of breath is the result of limited pulmonary blood flow caused by generalized arteriolar spasm, reduction of their lumen, microthrombosis and thromboembolism of small branches of the pulmonary artery and the pulmonary vascular bed empties. This leads to disruption of blood oxygenation in the lungs, arterial hypoxemia, and irritation of the respiratory center.

However, it should be borne in mind that the sensation of dyspnea is not always the severity of arterial hypoxemia, hypercapnia and the level of pressure in the pulmonary artery.Characteristically, dyspnea in pulmonary hypertension can be reduced mainly on the background of the effective application of bronchodilators, giving oxygen, the active anti-inflammatory therapy, whereas the use of cardiac glycosides or diuretics not only reduces breathlessness, but may worsen the patient's condition.

Unlike dyspnea associated with left ventricular failure and venous engorgement of blood in the lungs, shortness of breath when PH is not amplified in the horizontal position of the patient and does not decrease in a sitting position.

Tachycardia is a very characteristic, although not specific, sign PH. Often it can be a manifestation of respiratory failure and increase reflex activity SAS in patients with arterial hypoxemia.

Pain in the heart is found in over half of patients with chronic PH. Although pain in the heart and not in the nature of typical angina, it is assumed that the reason for their occurrence is relative coronary insufficiency due to a significant increase in muscle mass RV relative underdevelopment of the capillary network,

reflex spasm of the right SC, obstruction of coronary blood flow in the pancreas due to increase in its end-diastolic pressure. Probably also has value infectious toxic myocardial damage and pulmocardiac reflex.

In the study of respiratory system detect various changes, depending on the nature of the basic pathological process in the lungs, which caused the formation of PH. Inspection and palpation of the heart can detect RV hypertrophy and dilatation at the stage of compensated pulmonary heart disease, ie before the onset of clinical signs of right ventricular failure. The most typical appearance of cardiac impulse - pronounced ripple spilled left of the sternum, in the area of absolute dullness of heart, and in the epigastric region, due to the hypertrophied and dilated RV. This important clinical sign has long been the only indication of a patient with chronic lung disease of morphological changes in the pancreas caused by pulmonary hypertension.

The most characteristic feature of the auscultatory PH (Fig. 4) is the emphasis on tone II pulmonary artery. Splitting II tone in II intercostal space left of the sternum, as often seen in patients with PH usually indicates a slowing of blood expulsion hypertrophied RV later closing of the valve leaflets and pulmonary artery, respectively, later forming part II pulmonary tone.

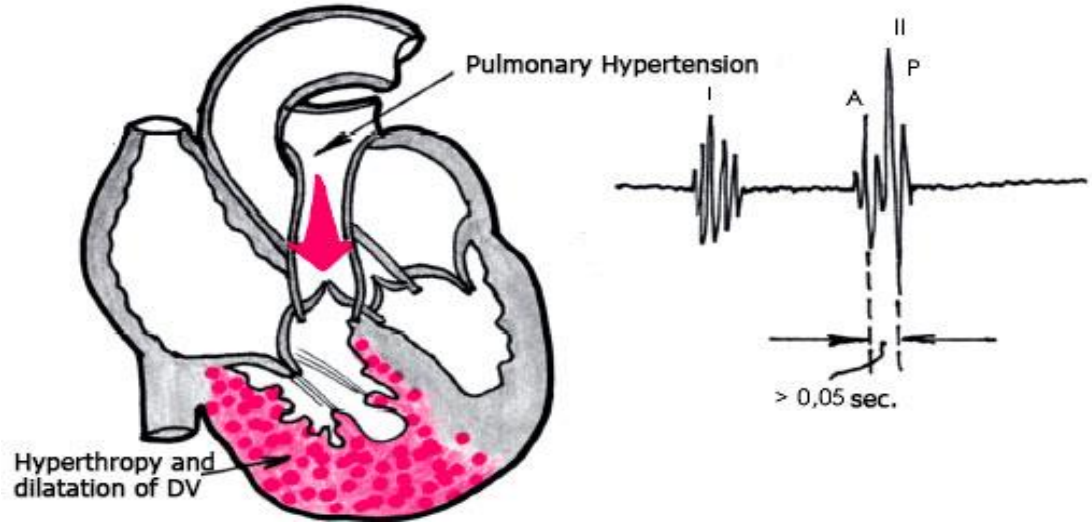


Fig. 4

The mechanism of formation of accent and splitting of II tone in chronic PH.

I heart sound may be somewhat weakened by a slower reduction of the hypertrophied and dilated RV. At the same time, half of the patients saved I tone or even somewhat enhanced, which is associated with the heart by turning around its longitudinal axis and approaching the hypertrophied and dilated RV to the surface of the thorax.

IV right ventricular heart sound is sometimes detected in severe hypertrophy of the RV. Its occurrence in patients with drug may indirectly indicate the presence of severe diastolic dysfunction of RV and increase the contribution of PP in its diastolic filling. When an RV systolic dysfunction and expressed its volume overload sometimes revealed right ventricular III pathological heart sound.

In severe pulmonary hypertension and reduction of RV systolic function is frequently observed reduced blood flow to the left side of the heart, which is accompanied by a distinct tendency to decrease in systemic blood pressure. In severe cases, the content decreases, the voltage and the magnitude of the arterial pulse. Sometimes it is possible to identify a paradoxical pulse as a reduction in systolic blood pressure during inspiration is more than 10 mmHg.

Peripheral edema may not be a sign of pancreatic insufficiency as they may develop from the effects of hypoxemia and hypercapnia on the renin- angiotensin-aldosterone system.

A blood test. In clinical analysis of blood in patients with chronic PH in most cases revealed polycythemia, increased hematocrit and hemoglobin, which is a characteristic of chronic arterial hypoxemia. In severe cases, polycythemia with increasing content of red blood cells, platelets and leukocytes. Reducing the ESR is often associated with an increase in blood viscosity, which also regularly observed in many patients suffering from respiratory failure.

Described changes in blood tests, of course, are not direct evidence of the drugs, but they tend to indicate the severity of pulmonary arterial hypoxemia - the main component of the pathogenesis of PH.

*Electrocardiography.*When electrocardiographic study in patients with severe chronic PH revealed signs of hypertrophy of the RV and PP. The earliest changes in the ECG - is the emergence in leads II, III, aVF (sometimes V1) high amplitude, with a pointed apex, teeth, P, and their duration is not more than 0.10 s.

Somewhat later will detect ECG signs of RV hypertrophy. In moderate hypertrophy of the RV, when its mass approaches the mass of the left ventricular myocardium or slightly less than its observed: the appearance in V1 QRS complex type rSR;

- increase in wave amplitude R'V1 and SV5, 6, the amplitude R'V1> 7 mm or R'V1 + SV5, 6 > 10.5 mm;
- signs of rotation around the longitudinal axis of the heart in a clockwise direction (the displacement of the transition zone to the left, to leads V5, V6, and the appearance in leads V5, V6 QRS complex type RS);
- increase in the duration of the interval of internal abnormalities in the right precordial leads (V1) with more than 0.03;
- segment RS-T down and the appearance of negative T waves in leads III, aVF, V1 and V2;
- offset the electrical axis of the heart to the right (angle a> +100 °) (changeable sign).

When expressed RV hypertrophy its mass slightly larger LV mass. For this type of ECG changes typical:

- appearance in V1 QRS complex type QR or qR;
- increase in wave amplitude RV1 and SV5, 6. The amplitude of the RV1> 7 mm or RV1 + SV5, 6 > 10.5 mm;
- signs of rotation around the longitudinal axis of the heart in a clockwise direction (the displacement of the transition zone to the left, to leads V5, V6, and the appearance in leads V5, V6 QRS complex type RS);
- increase in the duration of the interval of internal abnormalities in the right precordial leads (V1) with more than 0.03;

- -segment RS-T down and the appearance of negative T waves in leads III, aVF, V1 and V2;
- offset the electrical axis of the heart to the right (angle a> +100 °) (changeable sign).

S- type ECG changes are often observed in patients with severe emphysema, when hypertrophied heart abruptly shifted posteriorly, mainly due to emphysema. The vector of ventricular depolarization is projected on the negative parts of axles chest leads and limb leads (signs of turning around a transverse axis of the heart apex posteriorly). This explains the essential features of the QRS complex changes in these patients:

- in all precordial leads V1 to V6 QRS complex has the form rS or RS c pronounced tooth S;
- in the limb leads frequently registered syndrome SISIISIII (sign of rotation around the transverse axis of the heart apex posteriorly);
- on an electrocardiogram revealed signs of rotation around the longitudinal axis of the heart in a clockwise direction (displacement of the transition zone to the left, to leads V5, V6, and the appearance in leads V5, V6 QRS complex type RS);
- determined by the vertical position of the electrical axis of the heart.

It should be noted that for all three types of ECG diagnosis of hypertrophy of the RV changes indirectly confirmed by the presence of signs of hypertrophy PP detected in leads II, III, and aVF.

X-ray study helps to clarify the nature of lung disease, as well as identify several important radiological signs pointing to an increase in the size of the RV and the presence of pulmonary hypertension:

1. Bulging of the pulmonary artery trunk, front right oblique and less in direct projection (II expansion arc left contour of the heart).

2. Extension roots of the lungs.

3. Increasing the size of the RV in the right and left anterior and left lateral projections and a decrease of the retrosternal space.

4. Significant bulging rear contour shadow hearts until retrocardial space narrowing that occurs with severe RV hypertrophy and dilatation, which shifts the LV posterior.

5. Reaming and central branches of the pulmonary artery, which is combined with the depletion of the vascular pattern at the periphery of the lung fields, by reducing the small pulmonary arteries.

Echocardiography in patients with chronic PH is conducted to: objective evidence of the presence of hypertrophy of the RV and the RA evaluation of RV systolic function, the indirect determination of pulmonary artery pressure.

Echocardiographic diagnosis (Fig.5) of RV hypertrophy is a rather complicated problem. This is due primarily to the difficulty involved in manual contouring of endocardial ventricular trabecular characterized expressed, as well as lack of visualization of the heart, most of which is normally located behind the breastbone. Myocardial hypertrophy of the pancreas can be diagnosed with M - modal (one-dimensional) study with a high degree of probability when the thickness of the front wall of the RV exceeding 5 mm. However, this is true only in cases where ultrasound achieved good visualization of endocardial anterior wall of the RV. A preliminary study of two-dimensional access parasternal short axis of the heart or from the apical four-chamber position often allows for better visualization of the pancreas and select the optimal direction of the ultrasonic beam traversing the wall of the RV with M - modal study. There is no doubt that a more thorough search for signs of myocardial hypertrophy RV shows in those cases when the two-dimensional study determined that dilatation of the heart, in most cases, indicating the presence of systolic volume overload or RV.

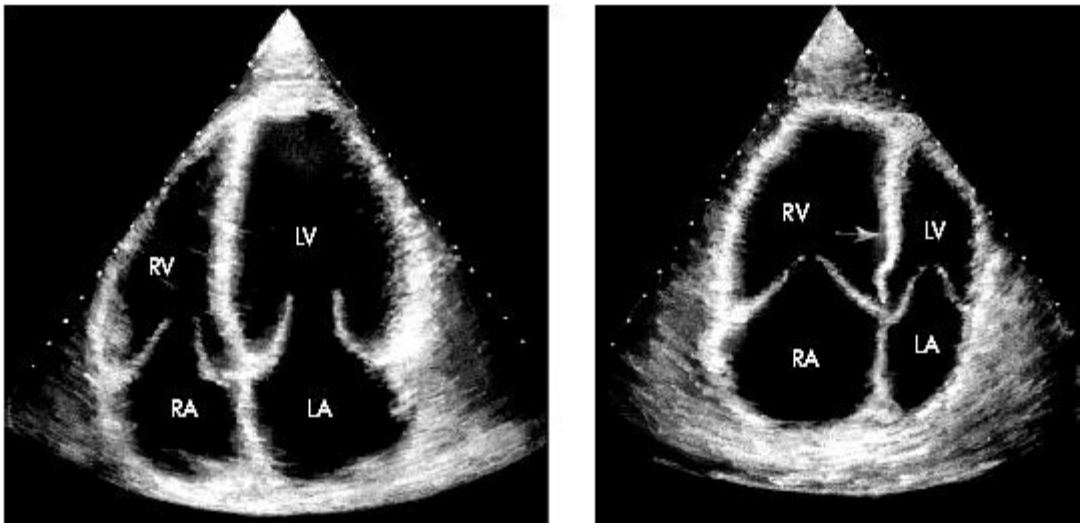


Fig.5

Two-dimensional echocardiogram, apical four-chamber registered in normal position (a) and in patients with severe dilatation of the right ventricle (b). In the latter case, the tip of the heart is formed by the pancreas, which substantially exceeds the volume of the left ventricle volume, there is a paradoxical movement of the interventricular septum toward the left ventricle (marked by arrow)

Diagnosis of pulmonary arterial hypertension is necessary to assess the severity and prognosis. For this purpose a form of Doppler blood flow in the RV outflow tract and the mouth of the pulmonary valve. At normal pressure in the pulmonary artery blood flow pattern is close to the dome and symmetrical with pulmonary hypertension and becomes a two-peak, or triangular.

Quantitative determination of systolic pulmonary artery pressure is possible using permanent -wave Doppler tricuspid regurgitation, and diastolic blood pressure - the maximum speed in the evaluation of diastolic regurgitation of blood from the pulmonary artery in the pancreas.

For a quantitative confirmation of PH used right heart catheterization (RHC).

Pulmonary function tests and arterial blood gases.Pulmonary function tests and arterial blood gases will determine the type of injury - either the main airway or parenchymal lung disease. Can also be detected peripheral airway obstruction.

Arterial oxygen tension is normal or slightly below normal at rest and arterial carbon dioxide tension is reduced due to alveolar hyperventilation.

Scanning ventilation / perfusion lung.Scanning ventilation / perfusion lung should be performed in patients with PH to search for potentially treatable CTEPH. Normal or low scan ventilation / perfusion effectively excludes CTEPH with a sensitivity of 90-100 % and specificity of 94-100 Contrast CT can be used as an additional study, but does not replace the scan.

High resolution computed tomography, contrast computed tomography and pulmonary angiography. High-resolution CT provides a detailed picture of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema.

Cardiac magnetic resonance imaging.Cardiac magnetic resonance imaging provides a direct estimate of RV size, morphology and function, and also allows for noninvasive assessment of blood flow, including stroke volume, cardiac output, increased RV mass and pulmonary artery [32]. Reduced stroke volume, increased course - RV diastolic volume and reduced course - LV diastolic volume, measured at baseline, associated with poor prognosis. Among the triad of prognostic signs, increased end-diastolic volume of the RV may be the most appropriate marker followed gradually developing pancreatic insufficiency.

Right heart catheterization and vasoreactivity.To confirm the diagnosis of PH, assessing the severity of hemodynamic and pulmonary circulation vasoreactivity test requires RHC. During the RHC should be identified following parameters: PAP (systolic, diastolic and mean) , right atrial pressure, PAOP,RV pressure, CO. Adequate record PAOP necessary for the differential diagnosis of PH associated with left heart disease. PAOP> 15 mmHg exclude the diagnosis of pre- capillary PAH.

*Biochemical markers.*Atrial natriuretic peptide and brain natriuretic peptide (BNP) share similar physiological properties. Both cause vasodilation and natriuresis are exempt from the myocardium in response to parietal stress. Determination of plasma levels of BNP / NT- proBNP levels are recommended for

initial risk stratification and may be considered for monitoring the effects of treatment, due to their predictive value. Low and stable or reduced rate BNP / NT-proBNP may be a useful indicator of successful disease control in PAH.

9.1.Diagnosisof pulmonary arterial hypertension(group 1)

PAH is a type of PH, in which over the last decade has seen the most important advances in the understanding and treatment. Furthermore, it is a group, in which PH is the "core" of clinical problems and can be treated by certain drugs.

PAH practically represents heterogeneous states, which share comparable clinical and hemodynamic manifestations and virtually identical pathological changes of pulmonary microcirculation.

Even if many of the pathophysiological mechanisms installed in the cells and tissues of patients with PAH, the exact interactions between them in the initiation and progression of pathological processes not fully understood. Consistent increase in PVR leads to an overload of the right ventricle (RV) hypertrophy and dilatation, and eventually to RV failure and death. The importance of progression of RV failure as an outcome in patients with IPAH confirmed prognostic value right atrial pressure, cardiac index (CI),PAP [28] and the three main parameters of the pumping function of the pancreas. Inadequate adaptation of myocardial contractility, is supposed to be one of the main events in the progression of heart failure in chronically overloaded RV. Afterload mismatch remains the leading determinant of heart failure in patients with PAH and CTEPH. Hemodynamic changes and prognosis in patients with PAH associated with the complex pathophysiological interactions between the rate of progression (or regression) obstructive changes in the pulmonary microcirculation and the response of the overloaded RV, which may also be due to genetic determinants.

*Clinical data.*PAH symptoms and involvement in the right ventricle, nonspecific and include shortness of breath, fatigue, weakness, angina, syncope, and bloating. Development of pulmonary hypertension can be identified by There punctuated pulmonary component of the second heart sound. The physical manifestations of involvement in the right ventricle: left parasternal cardiac

impulse, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and third tone pancreas. Jugular veins, hepatomegaly, peripheral edema, ascites, and cool extremities characterize patients more serious condition. The survey also contains data on the cause of PH. Telangiectasia, ulceration of the fingers and acroscleroderma observed in scleroderma, while inspiratory crackles may indicate interstitial lung disease. Should be considered the stigmata of liver disease such as spider nevi, testicular atrophy, and palmar erythema confirming signs of portal hypertension according to PSM research abdomen. If the symptom occurs drumsticks in IPAH, you should look for an alternative diagnosis such as CHD or EPV.

In schistosomiasis - intestinal lesions clinic and genitourinary system (pulmonary hypertension develops in contact with eggs in the vessels of the lungs), chronic hemolytic anemia is often accompanied by shortness of breath, weakness, appearance of acrocyanosis, changes of the spleen, which requires a thorough investigation of peripheral blood (PH develops in chronic intravascular hemolysis, including the vessels of the lungs).

PAH to be considered in the differential diagnosis of severe dyspnea, syncope, angina pectoris and / or progressive limitation of physical activity, especially in patients with no obvious risk factors common signs and symptoms of cardiovascular and respiratory disorders.

Electrocardiography

ECG may provide suggestive evidence confirming or PH, showing hypertrophy and dilatation of the RV and stretching of the right atrium. RV hypertrophy on ECG is present in 87 % and right axis deviation - in 79% of patients with IPAH. The absence of these data do not exclude the presence of PH and severe hemodynamic disturbances. ECG has insufficient sensitivity (55%) and specificity (70%) for a screening method to identify significant PH. Ventricular arrhythmias are rare. Supraventricular arrhythmias may be determined in the severe stage, such as atrial flutter and atrial fibrillation, which almost always leads to further clinical deterioration [28,33].

The chest radiograph

In 90 % of patients with IPAH at diagnosis chest radiograph is pathological. The survey results include the extension of the central pulmonary arteries, which contrasts with the "Cutting "(loss) of the peripheral blood vessels. In more severe cases, there may be an extension of the right atrium and the RV. Chest radiography eliminates lung disease from moderate to severe (group 3, Table 2) or pulmonary venous hypertension (group 2, Table 2) associated with left heart disease. In general, the degree of PH in any patient does not correlate with the degree of X-ray changes.

Echocardiography

Transthoracic echocardiography provides several data that correlate with right heart hemodynamics including PAP, and should always be carried out in case of suspicion of PH.

Evaluation is based on PAP maximum flow rate of tricuspid regurgitation.. Ideally, there should be taken into account the influence of age, sex and body weight [30].

Other echocardiographic indices that can cause or exacerbate suspicion of PH conclude an increase in the rate of pulmonary valve regurgitation and shortening acceleration time of RV ejection fraction in PA. Increasing the size of the right heart chambers, a violation of the form and function of the interventricular septum, increased RV wall thickness and reaming PA also suggest PH, but tend to occur later in the disease. Their sensitivity is questionable.

Scanning ventilation / perfusion lung

Scanning ventilation / perfusion lung should be performed in patients with PH to search for potentially treatable CTEPH. Normal or low scan ventilation / perfusion effectively excludes CTEPH with a sensitivity of 90-100 % and specificity of 94-100 Contrast CT can be used as an additional study, but does not replace the scan.

High resolution computed tomography, contrast computed tomography and pulmonary angiography

High-resolution CT provides a detailed picture of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema. High-resolution CT can be very useful when there is a clinically probable EPV. Characteristic changes of interstitial edema with diffuse central subpleural foci seal type "frosted glass" and thickened interlobular septa suggest PVOD [27], additional survey results may include lymphadenopathy and pleural effusion. Pulmonary capillary angiomatosis expected due to bilateral diffuse thickening of the interlobular septa and the presence of small, centrilobular, poorly limited nodal seals.

Angiography may be useful in assessing the possible vasculitis or pulmonary arteriovenous malformations.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging provides a direct estimate of RV size, morphology and function, and also allows for noninvasive assessment of blood flow, including stroke volume, cardiac output, increased RV mass and LA [32]. Reduced stroke volume, increased course - RV diastolic volume and reduced course - LV diastolic volume, measured at baseline, associated with poor prognosis. Among the triad of prognostic signs, increased end-diastolic volume of the RV may be the most appropriate marker followed gradually developing pancreatic insufficiency.

Blood tests and immunology

HIV testing is mandatory.To 2% in patients with liver disease is detected PAH, so if there are clinical manifestations, it is necessary to determine the functional state of the liver and serological markers of hepatitis. Thyroid disorders are often found in PAH and should always be considered, especially when there are abrupt changes in the clinical course of PAH.

Serologic assays are important to detect underlying CTD, HIV and hepatitis. Up to 40 % of patients with IPAH have elevated levels of anti - antibodies Nuclei usually in low titer (1:80)[37]. Most important for the exclusion of the FTA is

systemic sclerosis, because this condition has a high rate of PAH. In patients with systemic lupus erythematosus can be found antibodies anti-cardiolipin.

9.1.1. Pulmonary arterial hypertension associated with congenital cardiac shunts

According to the clinical classification of PAH associated with CHD is included in group 1. Signs and symptoms of Eisenmenger's syndrome are the result of PH, low blood O2 saturation, and secondary erythrocytosis. These include shortness of breath, fatigue and fainting. In patients with PAH associated with CHD without closing reverse shunt, degree of cyanosis and erythrocytes can be mild to moderate. Patients with Eisenmenger's syndrome suffer from hemoptysis, strokes, brain abscesses, coagulation disorders and sudden death. Improved survival may possibly be due to preservation of RV function as the RV does not undergo remodeling at birth and remains hypertrophied. In addition, the pancreas is released through the shunt from left to right, keeping the system NE by hypoxemia and cyanosis.

Patients with CHD (especially without shunt) may develop due to PH Left calving heart disease (group 2, Table 2) or related lung diseases (group 3, Table 2). In these cases a complete diagnostic examination.

9.1.2. Pulmonary arterial hypertension associated with connective tissue diseases

PAH is a well- known complication of the FTA, such as systemic sclerosis, systemic lupus erythematosus, mixed CTD and, to a lesser extent, rheumatoid arthritis, Sjogren's syndrome and dermatomyositis. PAH associated with CTD, the registry is the second most common type of PAH after IPAH.

Systemic sclerosis, particularly in its limited variant (CREST syndrome), represents the main CTD associated with PAH. In these patients, PAH may occur in connection with the development of interstitial fibrosis or as a result of an isolated pulmonary arteriopathy. In addition, there may be a venous pulmonary hypertension due to left heart disease. It is imperative to determine which mechanism is operative, as it determines the treatment. As with other forms of

PAH, RHC is recommended in all cases likely PAH associated with CTD to confirm the diagnosis, determine the severity and exclude left heart disease. RHC is mandatory if targeted treatments are considered.

9.1.3. Pulmonary arterial hypertension associated with portal hypertension.

PAH is a well-recognized complication of chronic liver disease. Portal hypertension, but not the liver disorders were the major determinant of risk for developing PAH.

It is estimated that 1-2 % of patients with liver disease and portal hypertension develop PAH, but the proportion of PAH may reach 5 % in patients with severe liver disease. The pathogenesis is unclear and may be associated with toxic substances derived from the gastrointestinal tract, which are not eliminated by the liver due to portosystemic shunts, which may damage the endothelium of the lung. Another possibility is that the state with the highest CO includes PAH. Patients with portopulmonary hypertension have a significantly higher CO and significantly reduced systemic vascular resistance and PVR compared with patients with IPAH.

9.1.4. Pulmonary arterial hypertension associated with infection with the human immunodeficiency virus.

The pathogenesis of PAH associated with HIV infection remains unclear. The absence of viral particles in complex plexiform lesions observed in these patients demonstrates that the indirect effect of the viral infection on inflammation and growth factors can act as a trigger in susceptible patients. Among patients with PAH associated with HIV will increasingly men and i/v PINs

9.2. Endoflebitis of pulmonary veins and pulmonary capillary hemangiomatosis (group 1`)

Both EPV and pulmonary capillary hemangiomatosis, states are infrequent, but are increasingly recognized as causes of PAH [55]. They were classified in a specific subgroup of the clinical classification (Table 4, group 1`) for pathological, clinical and therapeutic differences with other forms of PAH included in group 1'. In the literature, reported less than 200 cases of PVOD and pulmonary capillary hemangiomatosis. Reported occurrence of EPV family, patients with this disease is

detected mutation bone morphogenetic protein receptor -2. Unlike IPAH EPV prevail in men and prognosis was worse in men too.

EPV diagnosis with high probability can be set by a combination of clinical suspicion, physical examination, bronchoscopy and radiological data. In this non-invasive approach can avoid lung biopsy ("gold standard" to confirm the diagnosis EPV) in most cases.

*Clinic data.*Most patients complain of shortness of breath on exertion and fatigue, clinical manifestations are not different from IPAH. Physical examination may reveal clubbing and bilateral finely wheezing on auscultation, which can be explained by the presence of typical chronic interstitial pulmonary edema EPV and / or low levels of NE and / or the presence of patent foramen ovale.

Chest X-ray in addition to other typical signs of PH may reveal Kerley B. lines and peripheral interstitial infiltrates.

High resolution computed tomography is the study of choice. Results suggesting EPV represent the presence of subpleural thickened septa, subpleural centrilobular foci seal type " frosted glass " (unlike panlobular distribution detected in IPAH) and mediastinal lymphadenopathy. The association of these three results was defined as 100% specific marker EPV in cases of PAH with 66 % sensitivity.

Pulmonary capillary hemangiomatosis.

This is a very rare condition that can be difficult to distinguish from EPV, and diagnostic and therapeutic aspects are very similar. Often, only pathological examination is able to distinguish between the two states [53].

9.3. Pulmonary hypertension due to left heart disease (group 2).

Traditionally, heart failure and its severity was associated with decreased cardiac contractility (systolic HF), which is often assessed by the magnitude of LVEF. However, a significant proportion of patients with heart failure have a normal or near-normal LVEF. In such cases it is advisable to talk about HF with preserved ejection fraction (HF - PEF) or with preserved systolic function (HF - PSF). More than 90 % of cases, particularly in older age groups, where a high proportion of patients with increased stiffness of the myocardium, with

hypertension and left ventricular hypertrophy, diabetes, CH -PSF may be due to the actual diastolic dysfunction, but in some patients may also be associated with increased rigidity arterial vascular bed. The presence of a patient with HF -PSF confirmed by objective methods diastolic disorders lets talk about him as a patient with diastolic heart failure (DHF), and with absolutely normal contractility indices - as patients with isolated DHF.

At the moment there is no clear distinction between " Intact " and " low" ejection fraction, as their value is largely determined by end-diastolic left ventricular size, moreover, the majority of patients suffering from heart failure, there are signs of both systolic and diastolic dysfunction at rest or during exercise. Correct to consider these two states in the prevalence of concentric or eccentric hypertrophy (dilation). Between these opposing manifestations of the disease there is a broad transition zone, which may affect various factors (female gender, hypertension, advanced age, etc.). The majority of patients with HF structure of the heart occupies an intermediate position between the eccentric and concentric.

Note that if SDS is isolated, the systolic heart failure usually occurs not only with the systolic, diastolic but also disorders, i.e. often is mixed.

From the pathophysiological point of view with myocardial injury violations diastolic relaxation is usually preceded by a breach of systole, which joined later, with the arrival (in addition to diastolic disorders) systolic dysfunction often manifests clinical HF.

Echocardiography allows to solve the main diagnostic task - to clarify the fact of dysfunction and its character and conduct dynamic assessment of the heart and hemodynamics. Determination of left ventricular ejection fraction allows us to differentiate patients with systolic dysfunction from those who have preserved systolic function. As an indicator, highly suggestive of preservation of systolic function, we can recommend the level of LVEF ≥ 50%, calculated by two-dimensional echocardiography by Simpson (or ≥ 55% by Teiccholz). The degree of reduction in LVEF associated with the severity of systolic dysfunction, is used to determine the risk of surgical treatment. Dynamics of left ventricular ejection

fraction is a measure of disease progression and treatment efficacy, low LVEF is a marker of adverse prognosis.

In the early post-MI or in the explicit value of mitral regurgitation LVEF did not accurately reflect the true extent of systolic dysfunction. It is important to remember that a normal LVEF not exclude the presence of HF.

To assess the presence and severity of diastolic dysfunction using a combined assessment of mitral diastolic flow (migrant domestic workers) and the speed of the mitral annulus. There are three types of LV filling: with delayed relaxation, pseudonormal and restrictive, which correspond to low, moderate and severe diastolic dysfunction.

Detection of violations of diastolic filling of the heart is important not only to determine the pathogenesis of heart failure: it is proved that the disorder is more closely diastole than systole disorders are associated with the severity of the clinical condition, the degree of reduced tolerance to stress, quality of life.

*Diagnostic approach to PH, which developed as a result of left heart disease is similar in PAH,*doppler echocardiography is the best tool for screening purposes. LV diastolic dysfunction should be suspected in the presence of enlarged left atrium, atrial fibrillation, characteristic changes in the profile of the mitral flow profile, pulmonary venous flow Doppler signals in tissue mitral annulus and left ventricular hypertrophy [32].

Tissue Doppler data estimates suggest that the ratio E / E ' flow rate early mitral valve (E) divided at an early diastolic (E') the elongation speed is closely related to the LV filling pressure when the ratio E / E ' exceeds 15, the filling pressure LV raise, and when this ratio is less than 8, LV filling pressure is reduced, and if 15 > E / E '> 8, it requires additional non-invasive studies [64]. Changing the basic echocardiographic indicators and their interpretation Table 5.

Characteristic clinical features and echocardiographic PH associated with diastolic dysfunction are shown in Table 6.

Although increased left ventricular filling pressure can be estimated Doppler echocardiography [64, 228], or invasive measurement PAOP course - LV diastolic

pressure may be necessary to confirm the diagnosis of PH due to left heart disease.PAOP and of course - the LV diastolic pressure may be "pseudonormal", especially when patients are treated diuretics. Under these conditions, it was suggested holding load volume hemodynamic tests to determine left ventricular dysfunction, but these diagnostic tools require further standardization. Increased transpulmonary gradient (mean PAP minus mean PAOP)> 12 mmHg is a predictor of internal changes in the pulmonary circulation with predominant passive increase in PAOP. Some patients may be difficult to distinguish PAH from PH associated with left ventricular dysfunction, especially in patients with borderline values of PAOP (15-18 mmHg). Benefit determination of plasma BNP levels for the diagnosis of left heart disease in the presence of PH is clearly established as the rise in BNP may be observed in both pathophysiological states.

9.4. Pulmonary hypertension associated with lung diseases and / or hypoxia (Group 3)

9.4.1. Chronic obstructive pulmonary disease (COPD) - a disease characterized by not fully reversible airflow limitation. This limitation is usually progressive and associated with abnormal reaction to light particles and harmful gases[21,58].

Pathological process begins in the bronchial mucosa: in response to external pathogenic factors, a change in the function of the secretory apparatus (mucus hypersecretion, changes of bronchial secretions), associated infection, a cascade of reactions leading to damage to the bronchi, bronchioles and adjacent alveoli.

Violation ratio of proteolytic enzymes and antiproteases defects antioxidant protection exacerbate lung damage.

The main clinical diagnostic criteria are(cough, phlegm and shortness of breath), history (presence of risk factors) and functional (decreased FEV1 less than 80% after inhalation of a bronchodilator predicted in conjunction with a reduced FEV1/FVC ratio less than 70 %) manifestations.

Stratification of severity (stage)

The basis of stratification two criteria: clinical, including cough, phlegm and wheezing education, and functional, taking into account the degree of

irreversibility of airway obstruction. Cited are post-bronchodilator FEV1, ie severity assessed by airflow obstruction after inhalation of a bronchodilator [2]:

Stage I. easy

• FEV1/FVC less than 70 % predicted

• FEV1 80 % of predicted

• With or without chronic symptoms (cough, phlegm)

FEV1 remained within normal ranges, and the ratio of FEV1 to FVC falls below 70% of the predicted value. This indicator reflects the early manifestation of bronchial obstruction, detectable by spirometry. He characterizes the change in the structure of the exhalation, that is, 1 second forced expiratory patient exhales indicator for the average norm, but in relation to the FVC this percentage reduced to 70 from the norm, that identifies an individual violation of respiratory function.

Stage II. Average

• FEV1/FVC less than 70 % predicted

• FEV1 less than 80 % predicted

• With or without chronic symptoms (cough, phlegm, shortness of breath)

Stage III. heavy

• FEV1/FVC less than 70 % predicted

• FEV1 less than 50 % predicted

• With or without chronic symptoms (cough, phlegm, shortness of breath)

Stage IV. Extremely heavy -

• FEV1/FVC less than 70 % predicted

• FEV1 less than 30 % predicted or less than 50 % in combination with chronic respiratory failure

Pulmonary hypertension develops in stage IV - extremely severe COPD, with hypoxemia (PaO2 less than 8 kPa or 60 mmHg)and often also hypercapnia.

Table 5.

Changing the basic echocardiographic indicators and their interpretation

Parameter	Deviations	Interpretation
LVEF	Decreased(<45-50 %)	Systolic dysfunction
General and Regional LV contractility	Akinesia, hypokinesia, dyskinesia	Necrosis, ischemia, cardiomyopathy, myocarditis
LVEDd	Increased (>55-60 mm)	Volume overload (probably CH)
LVESd	Increased (>45 mm)	Volume overload (probably systolic dysfunction)
Fractional shortening	Decreased(<25%)	Systolic dysfunction
LA size	Increased (>40 mm)	Increased filling pressure, mitral valve dysfunction, atrial fibrillation
LV wall thickness	Hypertrophy (>11-12 mm)	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
Valves condition	Stenosis or regurgitation (especially aortic stenosis and mitral insufficiency)	May be the primary cause of heart failure or a complication
Transmitral diastolic flow	Changes in the rates of early and late diastolic filling	Diastolic dysfunction
Tricuspidal regurgitation	Increasing the speed of more than 3 m / s	Increase in RV systolic pressure - the suspicion of pulmonary hypertension
Pericardium condition	Hydropericardium thickening of pericardial leaflets	Possible tamponade, uremia, malignancy, systemic disease, pericarditis
E/A	More than 1 Less than 1 1-2 More than 2	Normal filling pressure In the elderly, slow relaxation Pseudonormal level Restriction and young
E/Ea	More than 15 Less than 8 8-15	High filling pressure Low filling pressure Uninformative level
S/D	More than 1	Low pressure in the pulmonary veins
VP	Less than 45 см/с	Slow relaxation
E/Vp	More than 2,5 Less than 2	High filling pressure Low filling pressure

Table 6

Factors contributing to the diagnosis of left ventricular diastolic dysfunction in the presence of pulmonary hypertension, defined by Doppler echocardiography

Clinical signs	**Echocardiography**
Age> 65 years	Left atrium enlargement
Increased systolic blood pressure	LV concentric remodeling (relative wall thickness> 0.45)
Increased pulse pressure	LV hypertrophy
Obesity, metabolic syndrome	The presence of echocardiographic indicators of increased LV filling pressure
Hypertension	Symptomatic response to diuretics
Reassessment of chest radiography in accordance with heart failure	Excessive rise of systolic blood pressure in load

9.4.2. Interstitial lung disease (ILD)

The main clinical signs of ILD is very limited: dyspnea, cough, hemoptysis, pleural and extrapulmonary symptoms. Diagnostic importance is not only the presence or absence of a trait, but its expression, variability, and the combination with others, including extrapulmonary symptoms. At IFA dyspnea appears early, often before the emergence of radiological signs of disease, is the inspiration in nature. Dyspnea in sarcoidosis is a late sign, often a mismatch radiographic severity dissemination complete absence of dyspnea. Patients EAA dyspnea is mixed, its occurrence is associated with a causal factor (allergen) and is undulating character. Cough at IFA - a late sign and may be the result of infection (bacteria, fungi, viruses) or the formation of traction bronchiectasis. For EAA and sarcoidosis indicates the presence of cough bronchocentric process. Hemoptysis is a sign of destruction of lung tissue and is most characteristic of Wegener's granulomatosis, Goodpasture's syndrome, pulmonary hemosiderosis, fibrosing alveolitis in rheumatic diseases. At IFA cough is a late sign, manifested in 13% of

cases. Pleural effusion can be observed in rheumatic diseases, drug-induced lung disease, asbestosis, leuyomyomatosis. Pneumothorax characteristic of histiocytosis X and leuyomyomatosis. ILD diagnosis is based on clinical, radiographic studies (chest radiography and HRCT), pulmonary function tests and laboratory data. In case of doubt in the diagnosis performed bronchoscopy and / or lung biopsy.

The group of rare interstitial lung disease include: Langerhans cell histiocytosis, lymphangioleuyomyomatosis, alveolar proteinosis, lung, idiopathic pulmonary amyloidosis, idiopathic pulmonary hemosiderosis, osteoplastic pneumopathy.

9.4.3. Interruption of breathing during sleep.

Sleep apnea - a condition which is characterized by cessation of pulmonary ventilation during sleep for more than 10 seconds. Frequently observed in patients with duration of 20-30 seconds of apnea, although in severe cases can be up to 2-3 minutes and take up 60% of total sleep time sleep. With regular apnea (usually at least 10-15 per hour) occurs sleep apnea syndrome with impaired sleep patterns and daytime sleepiness, memory impairment and intelligence, complaints decreased performance and constant fatigue.There is frequent awakenings with daytime sleepiness.

Apnea occurs quite often in these cases:

• diseases of nasopharynx - increased polyps, flabby sky;

• curvature of the nasal septum;

• diseases of the endocrine system;

• hormonal disruptions;

• obesity;

• hereditary disorder apnea.

Lead to the development of sleep apnea are the following factors:

• alcohol intake - it narrows the nasal muscles;

• smoking;

• taking medicines that affect the course of sleep. This sedatives, sleeping pills.

Up to 10 % of cases of sleep apnea, pulmonary hypertension with right ventricular failure, chronic hypercapnia and hypoxia associated with the weakening of nervous impulses to the respiratory muscles or generalized bronchial obstruction. In conjunction with obesity (which is a risk factor for obstructive sleep apnea) and sleepiness, this picture is called "The Pickwick syndrome."

9.4.4. Chronic exposure to high doses of radiation.

CRS case of external irradiation is a complex clinical syndrome involving several organs and systems, the frequency is related to the flow dynamics of the formation of radiation exposure, ie the continuation or cessation of exposure [41,52]. CRS originality consists in the fact that in actively proliferating tissues through intensive processes of cell renewal, for a long time may be possible morphological tissue recovery organization. At the same time stable systems such as the nervous, cardiovascular, and endocrine, respond to chronic radiation exposure complex set of functional responses and extremely slow attack minor degenerative changes.

Long-term consequences of exposure - somatic and stochastic effects, manifested through a long period of time (months or years) after a single or as a result of chronic exposure include, in addition to the clinical manifestations of pulmonary hypertension with involvement in the process of the right ventricle, changes in the reproductive system, radiation cataracts, cancer genesis, genetic and teratogenic effects.

9.4.5. Malformations

The clinical significance of lung malformations due to the fact that only a small part of the lung malformations may be asymptomatic.In most cases, the infection evolves background blemish and gradually formed a picture of chronic pulmonary inflammation or pus. Gradually growing changes in lung function observed in malformations in adults more often, less often in adolescence. This is due to the late detection of defects in the lungs due to the difficulty of diagnosis. Lung disease hereditary diseases are complex and poorly understood problem of

modern pulmonology. Lung lesions not associated with hereditary diseases, and the latter, in some cases, do not diagnose.

Among the many reasons that lead to the development of severe acute or chronic bronchopulmonary disease, primary (genetically deterministic or congenital) defects of the immune system have a special place. For pulmonary syndromes with defects of the immune system characterized by increased susceptibility to infections that are difficult to treat, unusual pathogens, sudden or severe complications, lack of asymptomatic remissions.
Changes and diseases in which the affected bronchopulmonary system malformations in the lungs, hereditary diseases and primary immunodeficiency arise in them and second, as a rule, do not differ specificity. Such patients are long and unsuccessfully treated on an outpatient basis with a GP, pediatrician or tuberculosis institutions with pneumonia, chronic bronchitis, tuberculosis, etc. In many diseases of this group of death occurs in childhood and early childhood.

9.5. Chronic thromboembolic pulmonary hypertension (Group 4).

Fundamentally venous thrombosis of any location can be complicated by the development of pulmonary embolism. Most embolic localization pool is the inferior vena cava, which is associated with about 90 % of all PE. Most often the primary thrombus is iliocaval segments or proximal veins of the lower extremities (popliteal, femoral segment).Similar localization of venous thrombosis complicated by pulmonary embolism in 50 % of cases. Venous thrombosis with localization in the distal deep venous (shin) is complicated by pulmonary embolism from 1 up to 5%.

There have been recent reports of an increase in cases of pulmonary embolism from the pool of superior vena cava (w3,5 %) as a result of asking venous catheters in intensive care units and intensive care units.

Much less lead to pulmonary embolism with thrombus localization in the right atrium provided dilatation or atrial fibrillation.

Most dangerous for the development of pulmonary embolism are " floating thrombus ", having a point of fixation in the distal venous system, the rest of him is

free and all over is not associated with the walls of the veins, and their length can vary from 5 to 20 cm " floating thrombus " typically formed in veins of smaller caliber, and the process of thrombus formation extends proximally into larger: deep vein tibia of - in the popliteal vein, and then deep common femoral artery from inside - in the common iliac, common iliac from - the lower vena cava.

Dimensions thromboembolic determine their location in the blood vessels of the pulmonary artery, they are usually fixed to the ground dividing lung vessels. According to various authors, embolization of the trunk and main branches of the pulmonary artery occurs in 50%, and segmental equity - 22%, small branches - in 30% of cases (Fig. 1). Simultaneous arterial disease in both lungs reaches 65 % of all cases of pulmonary embolism, 20 % - affected only the right, 10 % - only the left lung, the lower lobes are affected 4 times more often than the upper lobe.

European Society of Cardiology classified pulmonary artery embolism by the vascular lesions (solid and nonmassive),by the severity of the pathological process (acute, subacute and chronic recurrent). PE is regarded as a massive, if patients develop cardiogenic shock phenomena or hypotension (not related to hypovolemia, sepsis, arrhythmias). Nonmassive PE in patients diagnosed with a relatively stable hemodynamics without overt signs of right ventricular failure.

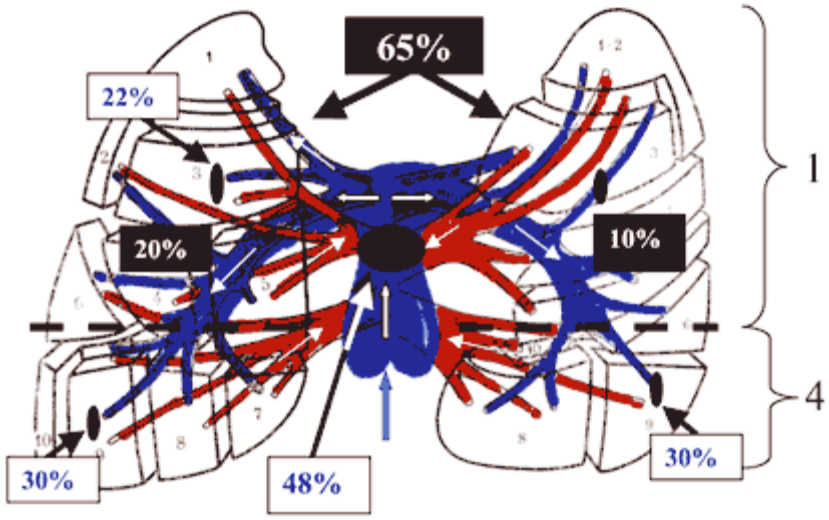


Fig.7 Frequency localization thromboembolic pulmonary artery

Clinical signs of thromboembolism. The clinical picture depends on the volume of pulmonary embolism pulmonary arterial lesions and cardio- pulmonary pre-embolicpatient status (CHF, COPD).

The sudden shortness of breath - the most common complaint with pulmonary embolism, aggravated by moving the patient in the sitting position or standing when reduced blood flow to the right heart. In the presence of block blood flow in the lung is reduced filling of the left ventricle, thereby reducing DoD and drop in blood pressure. Dyspnea in heart failure decreases with ortho position of the patient, as in pneumonia or COPD, it does not change when you change the position of the patient.

Peripheral pain in chest PATE most characteristic lesions of small pulmonary artery branches, due to the inclusion in the inflammatory process of the visceral pleura. Pain in the right upper quadrant shows the enlargement of the liver and acute tension Glisson capsule. Retrosternal anginal pain is common for large branches embolism pulmonary artery arises from the expansion of acute right heart, leading to compression of the coronary arteries between the pericardium and advanced right heart. Chest pain most often occurs in patients with CAD undergoing pulmonary embolism.

Hemoptysis in infarcted pneumonia as a result of pulmonary embolism in the form of strips of blood in the sputum differs from hemoptysis in mitral valve stenosis - blood phlegm.

Strengthening II tone of the pulmonary artery and the appearance of systolic gallop rhythm with PE indicate increased pressure in the pulmonary artery and right ventricle hyperfunction.

Basic principles of diagnosis of pulmonary embolism. For suspected pulmonary embolism on the basis of the patient's complaints and assessment of risk factors of venous thrombosis is necessary to conduct routine methods instrumental examination: ECG, X-ray, echocardiography, clinical and biochemical blood tests.

To verify the diagnosis of pulmonary embolism in the technical equipment of facility where the patient is necessary to conduct and angiopulmonography scintigraphy to assess the extent, location and severity of pulmonary embolism.

Clinical symptoms of pulmonary embolism are three variants:

1. " Infarct pneumonia" (corresponds thromboembolism small pulmonary artery branches) - manifests acute dyspnea occurred, which is exacerbated when moving the patient in an upright position, hemoptysis, tachycardia, peripheral pain in the chest (the place of the lung) as a result of involvement in the pathological process of the pleura.
2. " Acute pulmonary heart " (corresponding to major thromboembolism pulmonary artery branches) - the sudden dyspnea, cardiogenic shock or hypotension, retrosternal anginal pain.
3. " Unmotivated dyspnea " (corresponds to recurrent pulmonary embolism small branches) - episodes of sudden, quick passing dyspnea, which after some time can manifest chronic pulmonary heart clinic. Patients with a history of disease course is usually no chronic cardio Pulmonary disease, and the development of chronic pulmonary arterial hypertension is the result of accumulation of previous episodes of pulmonary embolism.

Hypoxemia with pulmonary embolism is caused by complex mechanisms, including - intrapulmonary shunting and impaired ventilation-perfusion relationships. Thromboembolism large branches of the pulmonary artery can cause a sharp increase in pulmonary artery pressure. If this is not the right ventricle hypertrophied, its functional reserves may not be sufficient to ensure the proper discharge sharply increased resistance against expulsion. In such cases, there is an acute pulmonary heart and right ventricular failure requiring immediate intervention. When the original right ventricular hypertrophy stroke volume does not fall despite the dramatic increase in pressure in the pulmonary artery. In this case, pulmonary embolism leads to severe pulmonary hypertension without right ventricular failure. Manifestations of pulmonary embolism depend on cardiac output (which, in turn, is determined by the degree of obstruction of the pulmonary

artery and right ventricular functional reserve) and on the related factors (lung disease, left ventricular dysfunction).Causes of morbidity and mortality - severe pulmonary hypertension and acute right ventricular failure.Chronic pulmonary hypertension develops more than 1% of cases.

While acute pulmonary embolism may be clinically silent, there is evidence that the accumulation of CTEPH may also develop in the absence of previous pulmonary embolism [40]. In these cases, the disease is probably triggered by inflammatory or thrombotic lesion in the pulmonary vascular system. When obliteration of the vessel is sufficient to cause an increase in PAP process starts pulmonary vascular remodeling, which is self-regulating and establishes the progression of PH, even in the absence of further thromboembolic events. Certain conditions are associated with an increased risk of CTEPH, including previous splenectomy, the presence of atrioventricular shunt to treat hydrocephalus, myeloproliferative disorders and chronic inflammatory bowel disease. The linkages of these states with CTEPH not fully understood, but chronic inflammation or chronic infection of the blood can play a decisive role.

Any patient with unexplained PH should be screened for CTEPH.Especially when the patient has a history of previous venous thromboembolism. Survivors of acute pulmonary embolism after acute episode should be observed carefully for signs or symptoms of CTEPH. Patients with acute pulmonary embolism showing signs of PH or RV dysfunction, during any time of their admission to hospital should undergo dynamic control echocardiography after discharge (usually after 3 - 6 months) to determine whether or not resolved PH.

Blood testsand immunology.In CTEPHshouldbe madethrombophiliascreening, includingthe definition ofantiphospholipid antibodies, lupus anticoagulantantibodiesandanti-cardiolipin.

The final diagnosis of CTEPH is based on the presence precapillary PH (mean PAP ≥ 25 mmHg,PAOP ≤ 15 mmHg, PVR > 2 Wood units) in patients with multiple chronic / organized occlusive thrombi / emboli in the elastic pulmonary arteries (basic share, segmental, subsegmental).

10. Therapy

Over the past few years, the treatment of PAH has undergone a significant evolution that led to the development and production of guidelines for the diagnosis and treatment of pulmonary arterial hypertension: in 2019.released updated recommendations of the European Society of Cardiology and the European Respiratory Society, which formed the basis of this manual.

General measures

Patients with PAH require sensible advice on the general activities of daily living and the need to adapt to the uncertainty associated with serious chronic life-threatening diseases. Physical activity and supervised rehabilitation

To the best of symptoms, patients should be encouraged to be active. Slight shortness of breath, but patients should avoid stress, which leads to severe shortness of breath, dizziness, or chest pain. Increases the amount of data confirming the loss of peripheral muscle mass in patients with advanced PAH, and this can be corrected through specific rehabilitation program.

Pregnancy, birth control and post-menopausal hormone therapy.

There is a WHO conclusion, practical guidelines and Expert Consensus Document ESC [27] that pregnancy is associated with 30-50% mortality in patients with PAH and as a result, PAH is a contraindication to pregnancy. Women should be advised of the high risk pregnancy, otherwise, should be discussed abortion. In those patients who choose to continue the pregnancy should use a specific disease-related therapy, planned mode of delivery and efficient work closely with obstetricians.

It is unclear whether appropriate use of hormone therapy in women postmenopausalperiod. It can be considered cases of severe symptoms of menopause in combination with oral anticoagulants.

Psychosocial support

Many PAH patients develop anxiety and depression, leading to a deterioration in quality of life. If necessary, should be done timely referral to a

psychologist. Information about the severity of the disease can be obtained from a large number of non-professional sources, and the important role of the physician is to provide patients with accurate and current information.

Infection prevention

PAH patients are susceptible to developing pneumonia, which is a cause of death in 7% of cases [44]. Currently there are no controlled trials, it is recommended to be vaccinated against influenza and pneumococcal pneumonia.

Standard methods of treatment of pulmonary arterial hypertension are:

- Supporting oxygen therapy (to maintain blood oxygen saturation of at least 91%)
- Diuretics (in patients with clinically significant edema and ascites)
- Anticoagulants (if not contraindicated)
- Cardiac glycosides (occasionally)

Oxygen

Although it has been demonstrated that the use of O2 reduces PVR in PAH patients randomized data suggesting that long-term O2 therapy is beneficial not. Most patients with PAH, except for persons with CHD and pulmonary - systemic shunts have minor degrees of arterial hypoxemia at rest, unless they have a patent foramen ovale. There are data showing that nocturnal O2 therapy does not alter the natural course of severe Eisenmenger's syndrome. Landmarks can be based on evidence in patients with COPD: the pressure of oxygen in arterial blood significantly below 8 kPa (60 mmHg) patients are advised to take to achieve O2 O2 arterial blood pressure > 8 kPa.

Diuretics

Decompensated right heart failure leads to fluid retention, increased central venous pressure,stagnation in the liver, ascites, and peripheral edema. Although RCTs in PAH no diuretics, clinical experience shows clear symptomatic benefit of this therapy in patients with fluid overload. Choice and dose of diuretic therapy may be left to the discretion of the physician. Possible addition of aldosterone antagonists. It is important to monitor renal function and blood biochemistry in patients with

hypokalemia and to avoid the influence of reduced intravascular blood volume, leading to pre-renal renal failure.

Oral Anticoagulants

IPAH patients at autopsy in a large percentage of cases detected intravascular thrombotic lesions. This, along with the possible presence of non-specific risk factors for venous thromboembolism, including heart failure and significant limitation of physical activity, is the rationale for the use of oral anticoagulation in PAH. The potential benefits of oral anticoagulants should be weighed against the risk for conditions such as Port Pulmonary hypertension with severe esophageal varices.

Digoxin

At / in the application of cardiac glycosides (digoxin) was shown to improve cardiac output in IPAH, although chronic use its effectiveness is unknown. Digoxin can be assigned to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias.

10.1. Specific drug therapy 1 patientsgroup.

A meta-analysis of RCTs are currently recommended eight drugs with different points of application, however, in the near future is expected to release additional drugs. Modern drug therapy leads to significant improvement in symptomatic status of patients and slows the rate of clinical worsening. In addition, a meta-analysis conducted in 23 RCTs in PAH patients (published before October 2018) reported a 43% reduction in mortality and 61% reduction of hospitalization in patients treated with a specific drug therapy versus patients randomized to placebo. These results were achieved after an average treatment period of 14.3 weeks, support the efficacy of currently approved drugs for the treatment of PAH. Despite this finding, PAH remains incurable chronic disease. In addition, medication and interventional therapies in more advanced cases are invasive and have significant side effects be confirmed.

Therapy in PAH patients can not be regarded as a simple prescription drugs, and characterized by a complex strategy, which includes an assessment of severity, and

general supportive measures vasoreactivity assessment, evaluation of the effectiveness, as well as a combination of different drugs with interventional procedures.

Calcium channel blockers

Long known that hypertrophy, hyperplasia and vasoconstriction smooth - muscle cells contributes to the pathogenesis of IPAH and this led to the use of traditional vasodilators since the mid -1980s.Mainly associated with the use of BPC.

However, to date, found that calcium channel blockers should be used only in the treatment of those patients with pulmonary hypertension, which during right heart catheterization was identified short- documented response to vasodilator. These patients account for about 6% of all patients with DEL, and only half of them vasodilator effect is persistent. Therefore, calcium antagonists should not be used without verification vasoreactivity. Found that among patients treated with calcium antagonists, 1 -, 3 - and 5 -year survival rate of 94, 94 and 94% versus 68, 47 and 38% in patients who have a reaction to this drug is absent. In these groups of patients should consider the appointment of endothelin receptor antagonists, phosphodiesterase inhibitors, 5 - or prostacyclin [34].

Positive response to acute vasodilator drug test schiat reduction in mean pulmonary artery pressure at least 10 mmHg to a value not exceeding 40 mm Hg provided that the lack of reduction in cardiac output. If yes, the recommended daily dose of CCBs that have shown efficacy in IPAH are relatively high, 120-240 mg of nifedipine, 240-720 mg for diltiazem and 20 mg for amlodipine. It is recommended to start with a low dose, e.g., slow release of 30 mg of nifedipine twice daily, 60 mg of diltiazem or three times a day (tid) or 2.5 mg of amlodipine once daily and gently gradually increase to the maximum tolerated dose. Limiting factors for increasing doses are usually systemic hypotension and peripheral edema of the lower extremities. Patients with IPAH who meet the criteria for a positive response to vasodilators, and treated with CCBs should be carefully monitored for safety and efficacy of treatment with reassessment after 3-4 months of treatment, including CPS.

Prostanoids

Prostacyclin advantageously produced by endothelial cells and stimulates a powerful vasodilation all vascular beds. This drug is the most potent endogenous inhibitor of platelet aggregation, as well as providing cytoprotective antiproliferative effects [50]. Prostacyclin metabolic dysregulation has been shown in patients with PAH, estimated to reduce prostacyclin synthase in the pulmonary artery and prostacyclin metabolites in the urine. Clinical study of prostacyclin in patients with PAH was continued synthesis of stable analogs that possess different pharmacokinetic properties but share qualitatively similar pharmacodynamic effects: Epoprostenol (synthetic prostacyclin) is available as a stable lyophilized formulation, the effectiveness of continuous / in the introduction it has been investigated in three blind RCTs have patients with IPAH and PAH associated with scleroderma; Iloprost - chemically stable prostacyclin analogue available for intravenous, oral and aerosol administration; Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability, suitable for use at room temperature. These characteristics allow to introduce the drug in / and n / a; beraprost is the first chemically stable and active form of the oral prostacyclin analogue.

Endothelin Receptor Antagonists

Activation of endothelin were found in both plasma and lung tissue in patients with PAH. [35] Although it is not known whether the increase in the endothelin -1 in plasma PH cause or consequence, these data suggest an important role of endothelin in the pathogenesis of PAH. Endothelin -1 has a vasoconstrictive and mitogenic effects by binding to two distinct isoforms of the receptors in the pulmonary vascular smooth muscle cells, receptors, endothelin- A and endothelin - B. Endothelin B - receptors are also present in endothelial cells and their activation leads to the release of vasodilatory and antiproliferative agents, such as NO and prostacyclin which may compensate for the negative effect of endothelin - 1.

Among this group of drugs known: orally - active double bosentan, endothelin receptor antagonist A and B; Sitaxentan - selective orally active endothelin A

receptor antagonist; ambrisentan is ERA class no-sulfonamic, propanoic acid, a selective inhibitor of the endothelin -A receptor.

Phosphodiesterase type-5

The inhibition of cGMP - degrading enzyme phosphodiesterase type 5 leads to vasodilatation via the NO / cGMP pathway at sites of expression of this enzyme. Because pulmonary vessels contain significant amounts of phosphodiesterase type-5 inhibitors, the potential clinical benefits of phosphodiesterase type-5 were investigated in PAH. Furthermore, inhibitors of phosphodiesterase type 5 have an antiproliferative effect. All three inhibitors of phosphodiesterase type-5, approved for the treatment of erectile dysfunction, sildenafil, tadalafil, and vardenafil, cause significant pulmonary vasodilation of blood vessels with maximal effects observed after 60, 75-90 and 40-45 minutes, respectively [15]:

Sildenafil - the active oral potent and selective inhibitor of phosphodiesterase type-5, tadalafil once, single-dose selective phosphodiesterase inhibitor - type 5, is currently approved for the treatment of erectile dysfunction.

Experimental compounds and alternative medication strategies

Despite progress in the treatment of PAH physical activity, quality of life and survival of these patients remain unsatisfactory. Therefore, currently under study, additional therapeutic strategies adapted to different pathogenic mechanisms in order to improve symptoms and prognosis further. Currently, investigations of the following compounds: NO- independent stimulators and activators of cGMP inhalation vasoactive intestinal peptide receptor agonist non-prostanoide prostacyclin double cloth ERA inhibitors, tyrosine kinase inhibitor (platelet-derived growth factor) as well as serotonin antagonists.

Early stages of development are the following additional compounds inhibitors of kinase receptor inhibitors of vascular endothelial growth factor inhibitors, angiopoietin - 1 and elastase inhibitors.

In animal models were tested gene therapy strategies. Stem cell therapy was effective in a rat model and is currently being tested in a proof of concept and the selection of appropriate doses in a study of patients with PAH.

Combination Therapy

Are still many open questions regarding combination therapy, including a choice of drug combinations, the optimal timing [initial combination (in previously untreated patients) or sequential combination (depending on the answer to the first drug)], the switching and combining. If possible, when used combination therapy, patients should be treated within clinical trials or registries. Combination therapy of established PAH drugs is recommended in patients without adequate response to mono- therapy, but combination therapy should be instituted only by experienced specialists. Whether the response to monotherapy sufficient can only be resolved on an individual basis. This applies to each individual patient who, despite monotherapy and optimized background therapy has insufficient clinical response.

Drug Interactions

Significant drug interactions associated with specific PAH therapy drugs are shown in Table 20. This table is known stresses important interactions but includes theoretically untested interactions that may still be clinically significant.

Table 8.

***Potentially* significant drug interactions in PAH - targeted therapy**

PAH drug	**Interaction. Drug**	**Interaction**
Ambrisentan	Cyclosporine Ketoconazole	Caution is required when coadministered with ketoconazole ambrisentan and cyclosporine
Bosentan	Sildenafil	Sildenafil level reduced by 50%, the level of bosentan increased by 50%. Dose adjustment or selection of other medicament may not be required.
	Cyclosporine	Cyclosporine levels reduced by 50%, the level of bosentan increased by 4 times. Combination is contraindicated.
	Erythromycin	Increased levels of bosentan. When applying a short course of therapy with bosentan dose adjustment may not be necessary.
	Ketoconazole	Level bosentan increased by 2 times.
	Glibenclamide	Increasing the frequency of elevated aminotransferases. Potential reduction in hypoglycemic effect of glibenclamide. Combination is contraindicated.

	Fluconazole, Amiodarone	Significantly elevated levels of bosentan. The combination of potentially contraindicated.
	Rifampicin, Phenytoin	Level bosentan reduced by 58%. The need for regulating the unknown dose.
	CoA reductase inhibitor MMC	Level simvastatin reduced by 50%, similar effects are possible with atorvastatin.
	Warfarin	Increased metabolism of warfarin may require titration of warfarin. Intensive monitoring of warfarin is recommended after initiation, but dose adjustment is not normally required.
	Hormonal contraceptives	Reduced hormone levels. Contraception unreliable.
Sitaxentan	Warfarin	Decreased metabolism of warfarin, when appointing Sitaxentan need a dose reduction to 80% of warfarin and intensive monitoring of INR
	Cyclosporine	Dose escalation Sitaxentan combination is contraindicated.
Sildenafil	Bosentan	Sildenafil level drops to 50% level of bosentan increased by 50%. Dose adjustment or selection of another drug may not be necessary.
	CoA reductase inhibitor MMC	When competitive metabolism may increase the level of simvastatin / atorvastatin. Level of sildenafil may increase. Possible increased risk of rhabdomyolysis.
	HIV Protease Inhibitors	Ritonavir and saquinovir significantly enhance sildenafil. Usually requires dose adjustment of sildenafil.
	Phenytoin	May decrease the level of sildenafil.
	Erythromycin	With a short course of sildenafil dose adjustment may not be necessary.
	Ketoconazole	Increased doses of sildenafil. Dose adjustment may not be necessary.
	Cimetidine	Increased doses of sildenafil. Dose adjustment may not be necessary.
	Nitrates, nicorandil	Severe systemic hypotension combination is contraindicated.
Tadalafil	Bosentan	Plasma levels of tadalafil reduced by 42% without significant changes in the level of bosentan. Dose adjustment may not be necessary.
	Nitrates, nicorandil	Severe systemic hypotension combination is contraindicated.

Balloon atrial septostomy

The method represents a graduated balloon atrial septostomy, which leads to an equivalent improvement of hemodynamics and clinical symptoms. Balloon atrial septostomy (BPS), should be avoided in end-stage patients with baseline average DPP > 20 mmHg and O2 saturation at rest <80%. Before considering BPS patients should be on optimal medical therapy. The main indication in adults BPS is severe IPAH, CHD, CTD, distal CTEPH, PVOD and pulmonary capillary hemangiomatosis.

In RCTs [29,33] the impact on long-term survival of the BPS has not been established and should be regarded as BPS or intermediate palliative procedure.

Transplantation

With the advent of specific therapy of severe PAH reduced the number of patients referred to specialists in lung transplant program [42]. Long-term results of medical treatment remains uncertain, and transplantation should remain an important option for those who do not receive such therapy. Studies show that 25% of patients with IPAH specific drug therapy may not be effective and have an unfavorable prognosis [55,56]. International practical guide to assist such patients published by the International Society for Heart and Lung Transplantation [31,32].

The prognosis of PAH varies depending on the etiology of PAH associated with CTD has a worse prognosis than IPAH even when treated with prostanoids..Most unfavorable prognosis in patients with EPV and pulmonary capillary haemangiomatosis lack of effective medical treatment.

Overall 5-year survival after transplantation in PAH is 45-50 %, followed by indicators of good quality of life [1,17].

10.1.1. Treatment of pulmonary arterial hypertension associated with connective tissue diseases

- In patients with PAH associated with CTD recommended algorithm of the same patients with IPAH

- In symptomatic patients with all FTA to identify PH recommended echocardiographic screening

- CPS is shown in all cases likely PAH associated with CTD, especially if a specific drug therapy is considered

- Oral anticoagulants should be considered on an individual basis

10.1.2. Treatment of pulmonary arterial hypertension associated with portal hypertension.

Porto-pulmonary hypertension is a part of a spectrum of diseases of PAH and, in general, these patients should be treated similarly to other forms of PAH, taking into account the presence of liver disease and its implications for their treatment. Anticoagulant therapy should be avoided in patients with increased risk of bleeding.β- blockers, often used for the treatment of patients with portal hypertension, appointed to reduce the risk of bleeding from varices, but worsen hemodynamics and exercise capacity in patients with porto-pulmonary PAH [12,11].

Should be carefully monitored if treatment begins ERA because of hepatotoxicity of these compounds.

10.1.3. Treatment of pulmonary arterial hypertension associated with infection with the human immunodeficiency virus

Treatment of PAH associated with HIV infection are less well developed compared to other forms of PAH. Anticoagulant therapy is generally not recommended due to increased risk of bleeding complications and anticipated problems of drug interactions. On the results of three trials revealed that patients with HIV- PAH were insensitive to vasoreactivity test and therefore should not receive CCBs. The rest is held the same treatment as in IPAH.

10.1.4. Treatment of pulmonary arterial hypertension associated with pulmonary veins endoflebitis and pulmonary capillary haemangiomatosis. (group 1 ')

Drug therapy of EPV has been developed. Most importantly, vasodilators and especially prostanoids must be used with great caution because of the high risk of pulmonary edema. In this regard,EPV therapy should only be undertaken in centers with extensive experience in the treatment of PH, and patients should be fully informed about the risks. The only radical treatment of EPV and pulmonary capillary hemangiomatosis is a lung transplant. Patients with EPV should be sent to the transplant center for examination as soon as diagnosed.

10.2. Treatment of pulmonary arterial hypertension associated with left heart disease (group 2)

Currently, no specific treatment of PH associated with left heart disease does not exist. A number of drugs (including diuretics, nitrates, hydralazine, ACE inhibitors,β- blockers, nesiritide, and inotropic agents) or event (auxiliary device implantation of left ventricular blood flow, valvular surgery, resynchronization therapy and cardiac transplantation) may lower PAP more or less rapidly as a result of reduction filling pressure of the left heart. Thus, management of PH due to left calving heart disease, should be directed to the optimal treatment of the underlying disease. When PH contraindicated drugs for the treatment of heart failure is not present. A few studies have examined the role of drugs currently recommended for the treatment of PAH [16]. RCTs evaluating the effects of chronic use of epoprostenol and bosentan in severe heart failure were terminated early because of increased frequency of events in the study groups of drugs compared with conventional therapy. Small studies have recently suggested that sildenafil may improve exercise tolerance and quality of life in patients with PH associated with left heart disease. History of drug therapy for heart failure is full of examples where the drug has a positive effect on surrogate endpoints, but eventually turned to the detriment as phosphodiesterase type -3. Thus, the use of PAH -specific drugs is not recommended to obtain reliable data from long-term studies, especially in "disproportionate" PH associated with left heart disease. Sustained reduction of PH is expected in a few weeks or months in most patients successfully operated for mitral valve disease, even if PH is a risk factor for surgery.

10.3. Treatment of pulmonary arterial hypertension associated with lung diseases and / or hypoxia (group 3)

Currently, specific therapy PH associated with COPD or interstitial lung disease does not exist. Shown that prolonged use of O2 partially reduces the progression of PH in COPD. Nevertheless, at this treatment PAP rarely returns to normal values , and structural abnormalities of the lung vessels remain intact. In interstitial lung diseases O2 therapy prolonged role in the progression of PH is less clear. Treatment with conventional vasodilators is not recommended because they may interfere with gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction and their ineffectiveness after prolonged use. Published papers with experience of application specific PAH drug therapy is not enough. Treatment of choice in patients with COPD or interstitial lung diseases associated with hypoxemia and PH long-term therapy is O2. Using targeted therapy for PAH in patients with COPD or interstitial lung disease with a mean PAP <40 mm Hg. Art. currently not recommended because any systematic data on its safety or effectiveness absent [19,58]

10.4. Treatment of pulmonary arterial hypertension associated with chronic thromboembolic pulmonary hypertension (group 4)

Patients with CTEPH should receive lifelong anticoagulation, usually with vitamin K antagonists adjusted to a target INR between 2.0 and 3.0.

The decision on how to treat patients with CTEPH should be taken in conjunction with surgery. Selection of patients for the operation depends on the size and location of organized thrombus, the degree of PH and age related diseases. Proximal organized thrombi represent the ideal indication, while more distal obstructions may prevent a successful procedure. After an effective intervention has been a sharp drop in the LoC to nearly normal pulmonary hemodynamics. Specific PAH drug therapy may play a role in the selection of patients with CTEPH, mainly under three different scenarios: (I) if the patient is not a candidate for surgery; (II) if the preoperative treatment is deemed appropriate to improve hemodynamics and (III) if patient has symptomatic residual / recurrent PH after

pulmonary endarterectomy surgery. Several uncontrolled clinical studies suggest that prostanoids, ERAs and phosphodiesterase type-5 can provide hemodynamic and clinical benefits in patients with CTEPH, regardless of whether these patients were considered operable or inoperable. The only modern, randomized, placebo - controlled clinical trial BENEFIT, dedicated to the safety and efficacy of drug treatment examined the effects of bosentan in patients with inoperable CTEPH for 16 weeks [46]. This study showed a significant reduction in the bosentan group LSS.

Given these limited data, further studies are needed to obtain reliable conclusions about the long-term outcomes of drug therapy in patients with CTEPH. There is currently no medical treatment of CTEPH, which would be approved in Europe or the U.S.. Bilateral lung transplantation is an option for severe cases that are not suitable for PEA.

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