REVIEW ARTICLE

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Diagnosis and Treatment of Pulmonary Hypertension

ABSTRACT

Pulmonary hypertension (PH) is a hemodynamic and clinical state defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest. Five groups of patients have been defined: group 1 as pulmonary arterial hypertension (PAH), group 2 as PH due to left heart disease, group 3 as PH due to lung diseases, group 4 as chronic thromboembolic PH, and group 5 as PH of other causes. PAH is a rapidly progressive and fatal disease with an incidence of 3 cases per million whereas incidence of PH due to left ventricular dysfunction is as high as 60-70% of all cases. Pulmonary capillary wedge pressure, invasively measured at rest, has been used to distinguish between pre- (≤ 15 mmHg) and post-capillary (> 15 mmHg) PH. The early clinical symptoms and signs are subtle and non-specific, such as exertional dyspnea, fatigue, pre-syncope and progressive limitation of exercise capacity so the vast majority of patients have an advanced disease with World Health Organization functional class of III or IV at first presentation. The diagnostic approach in PH has the goal to evaluate the two main anatomic components: pulmonary vasculature and right ventricle in order to establish the diagnosis and identify the group of PH. The therapy for PAH patients includes three main components: general measures and supportive therapy; initial therapy with calcium channel blockers in vasoreactive or specific drugs approved for PAH in non-vasoreactive patients either single or in combination, and lung transplantation. All patients with PAH should be referred to PH expert centers for comprehensive diagnostic and therapeutic assessment.

Keywords: Pulmonary hypertension, ventricle, pulmonary arterial pressure

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Definition

Pulmonary hypertension (PH) is an increase of the mean pressure in the pulmonary artery (mPAP) and its value ranges from 25 mmHg upwards. Depending on the hemodynamics, it is crucial to differentiate between “pre-capillary” and “post-capillary” PH.

Pre-capillary PH implies mPAP ≥ 25 mmHg and pulmonary capillary pressure (PCWP) ≤ 15 mmHg, which is why this type of hypertension is referred to as pulmonary arterial hypertension (PAH). On the other hand, post-capillary PH is defined as an increase of

mPAP ≥ 25 mmHg, whereas PCWP > 15 mmHg and it is commonly the PH resulting from the left heart weakness.¹

The increase of pulmonary vascular resistance (PVR) is the basis of vascular pathophysiology in PH and it results in the escalation of pressure in pulmonary artery, which further causes pressure-load in the right ventricle (RV). Compensatory mechanisms induce the right ventricular dilatation so the basic determinants of symptomatology and patient prognosis are actually the pulmonary arterial pressure values and RV function.

Classification of pulmonary hypertension

Over the last decade, there have been a few changes in PH classification, especially when it comes to specific groups of patients. The most recent classification was adopted at the 2013 World Symposium on Pulmonary Hypertension held in Nice, according to which PH is divided into five groups with clearly defined sub-categories (Table 1).¹

Table 1. Clinical classification of pulmonary hypertension.

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1*. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1**. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary disease with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension

4.2 Other pulmonary artery obstructions

4.2.1 Angiosarcoma

4.2.2 Other intravascular tumors

4.2.3 Arteritis

4.2.4 Congenital pulmonary arteries stenoses

4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Clinical features

Symptoms and signs of PH are usually nonspecific which frequently results in delayed diagnosis and adequate therapy application. A most common first symptom is the shortness of breath (dyspnea) during physical activity accompanied by general ailment and disability. Other symptoms which may appear later are as follows: vertigo, disturbance of consciousness, chest pain and pressure, leg swelling (a sign of right ventricular failure). Depending on to which extent the symptoms prevent patients from physical activities, we distinguish between four functional classes of patients (WHO FC) (Table 2). The functional class of patients suffering from PH is directly proportional to the survival rate so that patients from WHO FC IV have the rate of survival <40% on the three-year level.²

Table 2. World Health Organization (WHO) functional class of patients with PAH.

Functional Class	Symptoms
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnoea or fatigue, chest pain, or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Diagnosis

The PAH diagnosis begins with anamnesis, i.e. the estimation of symptoms which might indicate PH. Graph 1 displays an algorithm of procedures once we suspect of PAH. Electrocardiographic changes with patients suffering from PAH are nonspecific and they indicate the right ventricle ballast: right axis deviation, ST segment depression and/or negative T waves in right precordial leads (V1-V3), right bundle branch block. The patients showing signs of right ventricular failure suffer from the common malignant disorder of heart rhythm, which is why it is crucial to periodically perform the 24-hour ECG monitoring.

At the moment of PAH diagnosis, more than 90% patients have already experienced changes in heart and lung X-rays although these changes are of poor sensitivity.^{3,4} Typical changes are as follows: “lifting” of heart top due to right ventricular hypertrophy, right ventricular enlargement, the expansion of the main branch of pulmonary artery and/or right interlobar artery, and significant reduction of peripheral pulmonary vascular network.

Pulmonary function tests and analysis of arterial blood gas may identify the presence of respiratory diseases and pulmonary parenchyma illness. Patients suffering from PAH usually have mild to moderate lung volume reduction depending on the disease severity. The carbon monoxide diffusing capacity (DLCO) less than 45% is a bad prognosis sign and its differential diagnosis with PAH patients may indicate pulmonary veno-occlusive disease, PAH associated with scleroderma and parenchymal pulmonary disease. The chronic obstructive pulmonary disease which causes hypoxic PH is diagnosed on the basis of the irreversible airflow obstruction accompanied by an increase of residual volume, DLCO decrease, partial oxygen pressure (PaO_2), and increase of partial pressure of carbon dioxide (PaCO_2).

The transthoracic echocardiogram (TTE) is a widespread non-invasive cardiovascular diagnostic procedure pertinent for PAH patients as it helps set diagnosis and monitor the patients. TTE enables us to acquire a whole range of information as follows: evaluation of systolic, mean and diastolic pulmonary artery pressures, analysis of morphology and function of right ventricle and estimation of echocardiographic predictors of clinical outcomes in PAH patients.

Graph 1. Algorithm for diagnosing pulmonary arterial hypertension (PAH).

*p *adapted from: Galie N et al. Eur Heart J. 2016;37(1):67-119.(4)

PH, pulmonary hypertension; RV, right ventricle; V/Q scan, a lung ventilation-perfusion scan; RHC, right heart catheterization; mPAP, Mean Pulmonary Arterial Pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; CTEPH, Chronic thromboembolic pulmonary hypertension, CT, a

computed tomography

Picture 1. Echocardiographic evaluation of pulmonary artery pressure.

Picture 1 displays the usage of continuous-wave Doppler (CW) in order to show regurgitation of tricuspid (Picture 1, A) and pulmonary (Picture 1, B) valves in PAH patients. Systolic pressure in pulmonary artery (SPAP) equals the right ventricle systolic pressure (RVSP) and it is calculated

on the basis of maximum speed of tricuspid regurgitation (TRPV) and estimated right ventricle pressure (RAP) in line with the following formula: $RVSP = SPAP = 4 \times TRPV^2 + RAP$. The evaluation of the right atrial pressure (RAP) is performed on the basis of diameter of vena cava inferior (VCI) and respiratory variations of its diameter: with $IVC > 2.1$ cm diameter and $< 50\%$ diameter collapse with deep inspiration, the evaluated RAP is 15 mmHg (Picture 1, C). The diastolic pulmonary arterial pressure (DPAP) is calculated on the basis of the end-diastolic velocity of the pulmonary regurgitation (PRVED) in line with the following formula: $DPAP = 4 \times PRVED^2 + RAP$ (Picture 1, B). The mean pulmonary arterial pressure (MPAP) is calculated on the basis of systolic and diastolic pressures in line with the following formula: $MPAP = 1/3 SPAP + 2/3 DPAP$.⁴⁻⁶

High-Resolution Computed Tomography (CT) provides us with pertinent information on potential changes in pulmonary parenchyma and enables us to eliminate emphysema, bronchitis and interstitial lung disease diagnosis, infarction, and vascular and pericardial malformations. It may also be useful to diagnose pulmonary veno-occlusive disease with typical pulmonary abnormalities such as “milk glass image”, interstitial edema and bilateral interlobular septal thickening.⁷

Speaking of the acute pulmonary embolism diagnosis, the CT angiography has been a widely used method of choice and it has practically replaced the ventilation-perfusion lung scan. On the other hand, V/Q scan is a method of choice with diagnosing the chronic thromboembolic pulmonary hypertension (CTEPH).⁸⁻¹⁰ The criterion for diagnosing CTEPH on a V/Q scan is at least one massive defect after a minimum three-month effective anticoagulation therapy. The V/Q scan is 90-100% sensitive and 94-100% specific for diagnosing CTEPH. Possible errors for diagnosing CTEPH are caused by minor perfusion-like defects or nonsegmental perfusion abnormalities typical of otherwise caused PAH and pulmonary veno-occlusive disease.¹¹ In addition, the classical segmental perfusion defects may disappear during the CTEPH terminal stage.¹² Perfusion scintigraphy appears nonsegmented in cases of large central thrombotic masses in Eisenmenger syndrome or thrombus within aneurysm of pulmonary trunk or pulmonary artery branches in idiopathic PAH.¹³

Laboratory tests of blood, and biochemical and immunological tests are an integral part of etiological treatment of patients suspected of PH and other organ failures. Other routine analyses are thyroid hormone values and transaminase values, particularly after introduction of endothelin receptor antagonist therapy (ERA). Serological tests are compulsory in order to

diagnose potential connective tissue disease (CTD), hepatitis and human immunodeficiency virus (HIV) hidden behind PH. Up to 40% of patients suffering from idiopathic PAH have high antinuclear antibodies but in low titers (1:80).¹⁴

In most cases, TTE is an initial diagnostic method when there is a suspicion of PH, whereas right heart catheterization (RHC) is a necessary invasive diagnostic procedure for the definite diagnosis and evaluation of pulmonary vascular reactivity.⁴ The left heart catheterization is simultaneously performed with patients in risk of coronary heart disease or left heart insufficiency with preserved left ventricular systolic function (HFpEF). It is recommended to perform RHC at specialized clinics as the procedure itself is technically demanding and might cause serious complications. Basic parameters crucial for monitoring with RHC are as follows: mPAP (mean pulmonary arterial pressure), PCWP (pulmonary capillary wedge pressure) and PVR (pulmonary vascular resistance). If it is not possible to measure PCWP, we determine left ventricular end-diastolic pressure in left ventricle (LVEDP). Vasoreactivity tests are recommended in all patients with idiopathic PAH, hereditary PAH and PAH accompanied by usage of weight-loss medications in order to determine patients who might be introduced with calcium channel blockers (CCB). Positive vasoreactivity tests are defined as a decrease of mPAP ≥ 10 mmHg and absolute values of mPAP ≤ 40 mmHg with an increased or unaltered stroke heart volume. In order to perform a vasoreactivity test, it is advised to use nitrogen monoxide (NO) or intravenous epoprostenol, whereas we may use adenosine or inhaled iloprost as the alternative.¹⁴⁻¹⁶ CCB therapy is absolutely contraindicated if the vasoreactivity test is negative.

Therapy

PAH therapy is a complex strategy which might be divided into three basic steps as follows: the initial approach and application of general measures, introduction of CCB therapy (only patients with positive vasoreactivity test) and/or specific PAH therapies, and finally, the third step which entails monitoring of the initial therapy response, introduction of combined PAH therapy, patient care during the terminal disease stage, and determining indications for lung transplantation.

General measures and supportive therapy. The recommendation is a regular physical activity which does not provoke symptoms and mandatory avoidance of severe physical exhaustion. It has been proven that the functional capacity and life quality of PAH patients who practise controlled physical activity are better than in those patients who are physically inactive.¹⁵⁻¹⁷ PAH

patients are advised to have influenza and pneumococcal pneumonia vaccines as these cause 7% of total deaths with this group of patients.^{14,15}

PAH supporting therapy entails the oral anticoagulant therapy, oxygen therapy, right heart insufficiency therapy, and correction of anemia syndrome. The oral anticoagulant therapy is indicated only in patients with idiopathic and hereditary PAH and PAH due to weight-loss medication abuse.¹⁶⁻¹⁸ It is well-known that PAH patients also suffer from coagulation disorder and physiological fibrinolysis so it is crucial to take into account risks of venous thromboembolism (heart weakness and immobilization) and hemorrhage before the introduction of oral anticoagulant therapy. Particular caution should be paid in patients suffering from Eisenmenger syndrome.¹⁸⁻²⁰ The oxygen therapy is indicated in all PAH patients with $pO_2 < 60$ mmHg (8 kPa) as hypoxia is one of major causes of vasoconstriction and this therapy decreases PVR. The usage of diuretics is indicated in all PAH patients with signs of right heart weakness or water retention. Digoxin improves stroke volume only in cases of acute aggravation in patients suffering from idiopathic PAH but its efficiency has not been proven for chronic usage.²¹ Digoxin is administered to PAH patients with acute aggravation primarily in order to slow down ventricular response in cases of atrial cardiac rhythm disturbance. The usage of ACE inhibitors, sartans, beta blockers and ivabradine is not recommended except in cases when these are an irreplaceable comorbidity therapy (eg. arterial hypertension, coronary heart disease). Sideropenic anemia is registered with around 43% idiopathic PHA patients and 56% Eisenmenger syndrome patients, in which cases it also predicts mortality so it is crucial to monitor the iron values and substitute the treatment if necessary.²²⁻²⁴ Eisenmenger patients are a particularly sensitive group because frequent and unfounded venipuncture cause these patients severe anemia syndrome, which further increases mortality rates.²⁵ Therefore, prior to venipuncture, these patients should be examined by cardiologists specialized in PAH treatments.²⁶

Specific therapy. The specific PAH patient therapy covers the following classes of medications: CCB, endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE-5i) and guanylate cyclase stimulators (sGC), prostacyclin analogues and prostacyclin receptor antagonists. It is well-known that only few patients suffering from idiopathic PAH have positive vasoreactivity test, which is the only indication for CCB therapy. The CCBs used in PAH therapy are nifedipine, diltiazem and amlodipine. In addition, their regular dosage is 120-240 mg for nifedipine, 240-720 mg for diltiazem and up to 20 mg for amlodipine, depending

on tolerance.⁴ Endothelin receptor antagonists (ERA) are widely used in PH therapy due to the fact that these patients also suffer from activation in endothelial cells in both plasma and pulmonary tissue although it is still not quite clear if the increase of plasma endothelin-1 level causes PH or results from it.^{27,28} ERA medications used in current PH therapy for diagnostics and treatment of PAH are ambrisentan, bosentan and macitentan.⁴

The fact that pulmonary vascular network contains certain amounts of phosphodiesterase type 5 is the basis for the application of PDE-5i in PH therapy due to both consequential vasodilatation and antiproliferative effect. All three PDE-5 inhibitors approved for treatment of erectile dysfunction (sildenafil, tadalafil, vardenafil) cause massive vasodilatation of pulmonary vascular network.^{29,30} Unlike PDE-5i, sGC (riociguat) increases cyclic guanosine monophosphate production (cGMP) and causes vasodilatation and antiproliferative effect.³¹ The efficiency of riociguat application in PH therapy has been proven positive when combined with ERA or prostanoid therapy in 2.5mg three times per day dosage in sense that it improves functional capacities of patients as well as hemodynamic parameters.³² Combination of riociguat and PDE-5i therapies is contraindicated due to strong hypotension.

The usage of prostacyclin analogues and prostacyclin receptor antagonists in PH therapy is based on the role and relevance of prostacyclin in PH pathogenesis. Prostacyclin, produced primarily by endothelial cells, is a potent vasodilator and endogenous inhibitor of platelet aggregation and it also has proven cytoprotective and antiproliferative properties. Clinical use of prostacyclin in PH therapy is enabled due to synthesis of stable prostacyclin analogues which have different pharmacokinetic properties but still similar pharmacodynamic effects. Medications from this class approved for PH treatment are beraprost, epoprostenol, iloprost and treprostinil and their most common indications are for treatment of WHO FC III and IV. Selexipag, a selective IP prostacyclin receptor agonist is available for oral usage as well as monotherapy or supplement to mono and dual therapy for PH patients in WHO FC II and III with ERA and/or PDE-5i in which cases it decreases morbidity and mortality per 40%.³³

Combined therapy and transplantation. The combined PH therapy implies simultaneous usage of two or more PH medicaments from different classes in which process it is possible to initiate therapy with one medicament and then introduce medicaments from another class or initially start therapy with two medicaments from different classes. The initial combined therapy is justified by the fact that PH patients share high mortality rates

with many other malignant diseases.⁴

Balloon atrial septostomy (BAS) is a palliative method of PH treatment which results in the interatrial right-left shunt targeting at the right heart decompression, improvement of left heart function, and enhancement of stroke volume. Some published studies demonstrate benefits of this treatment with patients in WHO FC IV who show signs of right heart weakness and who are refractory to optimal medication therapy and suffer from severe syncope.³⁴⁻³⁶ In addition, the treatment is optional for patients awaiting lung transplantation who show no significant clinical improvement after the maximum combined medicament therapy.

Transplantation is a final therapy for PH patients who remain in WHO FC III or IV despite the maximum combined and supportive medicament therapy. Delayed transplantation combined with long waiting lists due to the pragmatic lack of organ donors increases mortality rates and causes clinical aggravation at the moment of transplantation. Recent data indicate additional 5-year life span with 52-75% of PH patients after transplantation and additional 10-year life span with around 45-66% of these patients.³⁷ PH patients are administered heart-lung transplantations as well as double-lung transplantations even though there is no information on the limits of irreversible stress of right ventricular systolic function and/or left ventricular diastolic function.³⁸ According to the International Registry for Heart and Lung Transplantation, most patients worldwide have double-lungs transplants.³⁹ Patients suffering from Eisenmenger syndrome and simple shunts have lung transplantations and surgical corrections of congenital heart defects or heart and lung transplantations.⁴⁰

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Dijagnostika i terapija plućne hipertenzije

SAŽETAK

Plućna hipertenzija (PH) predstavlja hemodinamski poremećaj definisan kao porast srednjeg pritiska u plućnoj arteriji od 25mmHg ili više u miru. Razlikuje se pet grupa pacijenata: grupa 1- plućna arterijska hipertenzija (PAH), grupa 2- PH kao posljedica bolesti lijevog srca, grupa 3- PH kao posljedica bolesti pluća, grupa 4 - hronična tromboembolijska PH i grupa 5- PH drugih uzroka. PAH je brzo progresivna i fatalna bolest sa incidencom od oko 3 slučaja na milion stanovnika, dok je incidenca PH kao posljedice bolesti lijevog srca prisutna kod čak 60-70% ovih pacijenata. Plućni kapilarni pritisak, mjereno invazivno u miru, omogućava razlikovanje prekapilarne (≤ 15 mmHg) i postkapilarne (>15 mmHg) PH. Rani klinički simptomi i znaci su veoma diskretni i nespecifični u obliku dispneje pri naporu, slabosti, presinkope i progresivnog smanjenja tolerancije fizičkog napora te najveći broj pacijenata ima teži stadijum bolesti sa funkcionalnom klasom Svjetske zdravstvene organizacije III ili IV pri prvom pregledu. Dijagnostički proces PH ima za cilj evaluaciju dvije osnovne anatomske komponente: plućna vaskulatura i desna komora srca sa ciljem postavljanja dijagnoze i identifikovanja grupe PH. Terapija pacijenata sa PAH se sastoji iz tri osnovna koraka: opšte mjere i suportivna terapija; inicijalna terapija blokatorima kalcijumskih kanala kod vazoreaktivnih odnosno specifičnih lijekova za PAH kod ne-vazoreaktivnih pacijenata bilo pojedinačno ili u kombinacijama te transplantacija pluća. Sve pacijente sa PAH je potrebno uputiti u ekspertске centre za dijagnostiku i liječenje PH.

Ključne riječi: Plućna hipertenzija, desna komora, plućni kapilarni pritisak