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PULMONARY HYPERTENSION – DIAGNOSTIC AND THERAPEUTIC OPTIONS

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Summary

Pulmonary hypertension is a complex group of diseases characterized by a common denominator: elevated pressure in the pulmonary circulation. The etiology of pulmonary hypertension can be very various. The first step in successful treatment of pulmonary hypertension is early detection of this serious and potentially fatal disease. Very important is the suspect about the disease and send patient to additional diagnostic procedures. The most effective diagnostic method for screening today is echocardiogram, which can indirectly measure pressures in the pulmonary circulation and evaluate function of the right ventricle. The final diagnostic method proving pulmonary hypertension is right heart catheterization. In the treatment of pulmonary hypertension different medications are used: calcium channel antagonists, prostaglandins, endothelin antagonists and inhibitors of phosphodieserase. In patients whom medical therapy is not effective lung transplantation remains a final step.

***Keywords*:** pulmonary hypertension; pulmonary pressure; treatment; idiopathic.

Introduction

Pulmonary hypertension is chronic disorder of pulmonary circulation which is characterized by elevated mean pulmonary artery pressure over 25 mmHg [1]. Disease of pulmonary vasculature leads to elevated pulmonary vascular resistance and elevated pulmonary artery pressure which consequently causes symptoms: exercise intolerance, dyspnea, weakness, presyncope and syncope and clinically meaningful right heart failure [2,3].

In the last decade, novel insights in pathogenesis and pathophysiology of pulmonary hypertension has thought us that pulmonary hypertension is a heterogeneous group of disorders. Thus, according to the etiology of the disease pulmonary hyper-

tension is divided into five groups: pulmonary arterial hypertension, pulmonary hypertension due to left heart disease, pulmonary hypertension due to lung disease and/or chronic hypoxemia, chronic thrombo-embolic pulmonary hypertension and pulmonary hypertension due to unclear and/or multifactorial mechanisms [4].

Symptoms and signs of pulmonary hypertension

Due to the fact that symptoms of the disease usually develop gradually, patients visit physicians due to the symptoms many years after pathophysiologic process which causes the diseases started. Typical symptoms which are reason for referring to physician are: exercise intolerance, shortness of breath, weakness, presyncope or syncope, dry cough and chest tightness. In the more advanced disease patient usually have peripheral edema, cynosis and finger clubbing [5,6]. Most common form of pulmonary hypertension, pulmonary hypertension due to left heart diseases, usually is manifested in worsening of respiratory function in supine position, orthopnea and paroxysmal night dyspnea, whereas, such symptoms are not present in pulmonary arterial hypertension [6].

Detailed family medical history is essential in inherited forms of pulmonary arterial hypertension [7,8]. History of cocaine, amphetamine and alcohol abuse, as well as smoking history, can be very useful in determining the etiology of pulmonary vascular disease [9,10].

Typical, but not specific signs of pulmonary hypertension can be found at detailed physical examination. Neck veins distension, positive hepato - jugular reflex, ascites, peripheral edema and finger clubbing can be found, as well as parasternal drifting due to tricuspid regurgitation. Accentuated pulmonary component of second heart tone (S2), usually narrowly torn, can be heard during auscultation. In advanced pulmonary hypertension, holo – systolic murmur of tricuspid regurgitation can be heard.

Classification and pathogenesis of pulmonary hypertension

World Health Organization in 1973 classified pulmonary hypertension in two groups: primary and secondary. Development in diagnostic procedures, and better understanding has lead to increasing knowledge about epidemiology, pathogenesis, diagnostic and treatment of pulmonary hypertension has lead to Venice classification in 1998 of pulmonary hypertension into five groups. Further understanding lead to latest classification from Nice in 2013 which is shown in *table 1.*

Regardless of the etiology of pulmonary hypertension, pulmonary hypertension is characterized by prolonged vasoconstriction, thickening and remodeling of

medium size pulmonary arteries and arterioles [2,3]. Prolonged vasoconstriction occurs due to endothelial dysfunction and misbalance between synthesis of vasoconstrictors and vasodilators. Prolonged vasoconstriction leads to increased pulmonary vascular resistance which then leads to increased right ventricular afterload resulting in concentric hypertrophy of right ventricle. Remodeling of pulmonary vasculature leads to fibrosis and obliteration of pulmonary vessels which additionally increases pressure in pulmonary artery and additionally increases afterload of the right ventricle. Increase pulmonary vascular resistance leads to decreased perfusion of pulmonary vasculature and decreased oxygenation of the blood resulting in hypoxemia.

Pathogenesis of pulmonary venous hypertension due to left heart diseases is completely different. In this form of pulmonary hypertension there is no remodeling and obstruction of pulmonary vessels. Hypertension develops due to over-volume of pulmonary vessels due to systolic and/or diastolic dysfunction of the left ventricle or due to valvular disease of the left heart [11].

In pulmonary hypertension which develops in patients with chronic lung diseases hypoxia is main pathophysiologic mechanism. Chronic hypoxia leads to prolonged vasoconstriction of pulmonary vessels and then to remodeling of vessels which is similar to remodeling in pulmonary arterial hypertension [12].

Recurrent embolism of pulmonary vessels leads to obstruction of pulmonary vasculature, increase of pulmonary vascular resistance and to chronic thrombo – embolic pulmonary hypertension (CTEPH). CTPEH is a form of pulmonary hypertension which can be successfully surgically treated with a procedure named pulmonary thromb-enderterectomy (PEA), [13].

Separate group in classification of patients with pulmonary hypertension is pulmonary hypertension due to multifactorial and/or unclear mechanisms. These forms of pulmonary hypertension are rare and represent great challenge even in specialized pulmonary hypertension centers [14].

Diagnosis

Medical history and signs and symptoms are described earlier. Pulmonary arterial hypertension, especially idiopathic, has onset in younger age so disease usually remains unrecognized for several years. Average time from first onset of symptoms to right diagnosis is more than two years.

Table 1. Classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)	
1.1	idiopathic PAH
1.2	heritable
1.2.1	BMPR2
1.2.2.	ALK1, ENG, SMAD9, CAV1, KCNK3
1.2.3.	unknown
1.3	drugs and toxins induced
1.4	associated with:
1.4.1	connective tissue diseases
1.4.2	HIV infection
1.4.3	portal hypertension
1.4.4	congenital heart diseases
1.4.5	schistosomiasis
1′	pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1′′	persistent PH of the newborn
2. Pulmonary hypertension due to left heart disease	
2.1	LV systolic dysfunction
2.2	LV diastolic dysfunction
2.3	valvular disease
2.4	congenital/acquired left heart inflow/outflow tract obstruction and congenital cardmyopathies
3. PH due to lung diseases and/or hypoxia	
3.1	COPD
3.2	interstitial lung disease
3.3	other pulmonary diseases 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 abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)	
5. PH with unclear and/or multifactorial mechanisms	
5.1	hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2	systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3	metabolic disorders: clycogen storage disease, Gaucher disease, thyroid disorders
5.4	others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

Electrocardiogram can show us signs right heart axis and enlargement and hypertrophy of right atrium and ventricle [14,15,16]. On the chest X – ray you can see enlarged right heart, dilated pulmonary arteries and reduces peripheral pulmonary vasculature [14,15,16].

Basic screening procedure is echoradiography. With echocardiography you can stated that pulmonary hypertension is likely, possible and unlikely by looking at pulmonary artery systolic pressure and tricuspid regurgitation velocity [14,17], (*table 2*).

Table 2. Likelihood of pulmonary hypertension on echocardiography

PH unlikely: systolic PA ≤ 36 mmHg, TR velocity ≤ 2.8 m/sec
PH possible: systolic PA 37 – 50 mmHg, TR velocity 2.9 – 3.4 m/sec
PH likely: systolic PA > 50 mmHg, TR velocity > 3.4 m/sec

Patients with likely or possible pulmonary hypertension should be referred to expert center where further diagnostic should be performed. Right heart catheterization is fundamental diagnostic procedure for confirmation of pulmonary hypertension with hemodynamic parameters and vasoreactivity testing. Vasoreactivity can be performed with prostanoids, adenosine and NO. Vasoreactivity testing should be done before starting any specific treatment of pulmonary hypertension [14,18].

After confirming pulmonary hypertension further test should be done to clarify etiology of pulmonary hypertension like: CT pulmonary angiography, ventilation and perfusion lung scintigraphy, pulmonary function tests, laboratory tests, genetic testing, liver test, HIV testing [14,18].

Treatment of pulmonary hypertension

Treatment starts with the treatment of underlying disease if known and general measures: oxygen, oral anticoagulants, diuretics and if needed digoxin. Specific treatment depends on vasoreactivity testing. In group of patients with pulmonary arterial hypertension specific treatment is available. In patients with positive test (unfortunately only about 10% patients) initial treatment should be calcium channel blockers [19,20,21,22]. In that group of patients, normalization of pulmonary artery pressure is expected and these patients have good prognosis. In majority of patients with negative vasoreactivity testing treatment with vasodilators should be initiated. Vasodilators can be divided into four groups according to mechanisms of action: prostacyclin analogues, endothelin antagonists, phosphodiesterase 5 inhibitors and activators of soluble guanylate – cyclase. Vasodilators are shown in *table 3*.

Treatment usually starts with monotherapy and in patients with insufficient effects combination of two or three vasodilators of different mechanisms of action is recommended [14].

In patients with failure of conservative treatment surgical procedures like ECMO support, thromb-endarterectomy, lung and/or lung and heart transplantation are indicated in selected patients [14].

Table 3. Specific vasodilators in pulmonary hypertension

Endothelin receptor antagonists	bosentan, ambrisentan, macitentan
PDE – 5 inhibitors	sildenafil, tadalafil
Prostacyclin analogues	epoprostenol, iloprost, treprostinil, beroprost
Activators of soluble guanylate – cyclase	riociguat

Follow – up

Follow up of patients is usually done with estimation of functional class, echocardiography, proNT-BNP and six-minute walking test distance. Improvement or deterioration in the distance walked in the test is today crucial for estimation of treatment efficacy [23].

Conclusion

Pulmonary hypertension is devastating, usually fatal disorder which is characterized by elevated pulmonary artery pressure and pulmonary vascular resistance which can lead to right heart failure and consequently death. Early diagnostic is crucial to improve outcome of these patients. Novel treatment options like specific pulmonary vasodilators significantly improved outcome of patients with pulmonary hypertension. Surgical procedures can be life – saving options in selected patients in whom conservative treatment has failed.

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Sažetak

Plućna hipertenzija – dijagnostičke i terapijske mogućnosti

Plućna hipertenzija složena je skupina bolesti koje karakterizira zajednički nazivnik: povišen tlak u plućnoj cirkulaciji. Etiologija plućne hipertenzije je različita. Prvi korak u uspješnom liječenju plućne hipertenzije rano je otkrivanje ove teške, i potencijalno smrtonosne bolesti. Vrlo važno je posumnjati na bolest te uputiti bolesnika na dodatne pretrage. Najučinkovitija dijagnostička metoda probira danas je ultrazvuk srca kojim se mogu indirektno izmjeriti tlakovi u plućnoj cirkulaciji te procjeniti funkcija desnog srca. Završna dijagnostička metoda kojom se dokazuje plućna hipertenzija je kateterizacija desnog srca. U liječenju plućne hipertenzije koriste se danas brojni lijekovi: antagonisti kalcijevih kanala, prostanglandini, antagonisti endotelinskih recptora i inhibitori fosfodiesteraze. U bolesnika u kojih medikamentozna terapija nije učinkovita ostaje kao zadnji korak liječenja transplantacija pluća.

***Ključne riječi*:** plućna hipertenzija; tlak, liječenje; idiopatska.

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