

PROFESSIONAL PAPER

doi: 10.5455/medarch.2016.70.303-307

Med Arch. 2016 Aug; 70(4): 303-307

Received: APR 25, 2016 | Accepted: MAY 15, 2016

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Pulmonary Hypertension – New Trends of Diagnostic and Therapy

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ABSTRACT

Pulmonary hypertension is a pathophysiological state hemodynamically defined as the increase of the mean pulmonary arterial pressure above 25, or 30 mmHg at rest, measured by catheterization of the right heart. Laboratory findings usually reveals polycythemia, the ECG right ventricle hypertrophy, and x-ray characteristic of diseased branches (echocardiography and biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP hormones are potentially helpful tools in identifying PH). Echocardiography can be found the increase of the right atrium and ventricle, right ventricular hypertrophy, abnormal contraction of the interventricular septum, left ventricular diastolic dysfunction and decreased left ventricular size, with reduced volumes of systole and end diastole. Doppler confirming tricuspid regurgitation. Pharmacological therapy would represent a use: Calcium Channel Blockers, Prostacyclin Analogues, Endothelin Receptor Antagonists and Phosphodiesterase-5 Inhibitors. Alpha adrenergic antagonists, endothelial receptor subtype A (Bosentan, Tracleer) with treatment of the underlying disease or anticongestive therapy, are recommended. In case of inadequate response to treatment with a specific drug, guidelines recommend the combined use of drugs from the basic three groups, using their synergism.

Key words: pulmonary hypertension, treatment.

1. INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase of mean pulmonary pressure more than or equal to 25 mmHg at rest (1, 2). PH in children is mostly often related to the occurrence of heart disease and lung diseases (secondary), while it rarely occurs as a primary disorder of the pulmonary vasculature (primary)–up to 5%. Primary pulmonary hypertension can be sporadic, but familial (autosomal dominant disease with limited penetration, with mapped gene for pulmonary hypertension at chromosome 2q31/32). Secondary

pulmonary hypertension in everyday practice is most often related to congenital heart defects (CHD) with left-right shunt, connective tissue diseases, children with bronchopulmonary dysplasia, as well as children whose PH develop after surgery of congenital anomalies of the heart can be etiologically hyperkinetic, reactive and passive PH, hemodynamic capillary, precapillary and capillary. Most current is the clinical classification (Dana Point, California, 2008), which classifies PH in six groups with different pathological, pathophysiological, prognostic and therapeutic properties:

- Pulmonary arterial hypertension (PAH)—idiopathic, hereditary induced by drugs and toxins, PH associated with systemic, pulmonary, congenital anomalies of the heart, portal hypertension and chronic hemolytic anemia, and persistent pulmonary hypertension in newborns. The term pulmonary arterial hypertension (PAH) describes a sub-population of patients with PH hemodynamically characterized by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and a pulmonary vascular resistance > 3 Wood units (1).
- Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis.
- Pulmonary hypertension due to illness in the left hearth—systolic and diastolic dysfunction, valvular disease.
- Pulmonary hypertension due to lung diseases and/or hypoxemia.
- Chronic thromboembolic pulmonary hypertension.
- PH with unclear and/or multifactorial mechanisms.

Among many risk factors for pulmonary hypertension some are unambiguous (female gender, human immunodeficiency virus infection), others are very likely (amphetamines, collagen), and the third potential (cocaine, chemotherapy) or almost unlikely (oral contraceptives, antidepressants, smoking).

Pulmonary hypertension rarely occurs in adults. Pulmonary hypertension (PH) is increasingly recognized in the elderly population; however, the causes and characteristics of PH and the elderly population are not well established (data from a multicenter observational US registry suggest that idiopathic pulmonary arterial hypertension (IPAH) has an older age at diagnosis compared with the National Institute of Health registry study performed in the 1980s, with nearly 17% of the cohort ≥ 65 years of age at the time of diagnosis in the last decade) (3). In the 1980s, a US registry of patients with primary pulmonary hypertension (PH), currently referred to as idiopathic PAH (IPAH), revealed that 6% of the patients had first-degree relatives who also had PAH (4). In 2000, the influence of the BMP2 gene (BMP2 gene, a gene on chromosome 2 that encodes for bone morphogenetic protein receptor, type II (BMP2)) (4) influence is determined on the occurrence of familial pulmonary hypertension. When PAH occurs in a familial context, germline mutations in the bone morphogenetic protein receptor 2 gene are detected in at least 70% of cases (5,6). Reporting in the literature of PH incidence data at the global level is poor, in the UK, a prevalence of 97 cases per million with a female:male ratio of 1.8 has been reported (the age-standardized death rate in the USA ranges between 4.5 and 12.3 per 100,000 population) (7). In adults, pulmonary hypertension occurs in the following conditions: liver

Definition	Characteristics*	Clinical group(s) [†]
PH	mPAP ≥ 25 mmHg	All
Pre-capillary PH	mPAPm ≥ 25 mmHg PAWP ≤ 15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	mPAPm ≥ 25 mmHg PAWP > 15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG < 7 mmHg and/or PVR ≤ 3 WU	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥ 7 mmHg and/or PVR > 3 WU	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

Table 1. Haemodynamic definitions of pulmonary hypertension – ESC Guidelines 2015 (7)

diseases (chronic liver disease, liver cirrhosis), rheumatic disorders (scleroderma, systemic lupus erythematosus), lung conditions (tumors, emphysema, chronic obstructive pulmonary disease, pulmonary fibrosis), heart diseases (aortic valve disease, left heart failure, mitral valve disease), disease and thromboembolism low oxygen conditions (obesity, sleep apnea). Pulmonary hypertension within chronic obstructive pulmonary disease exists when the mean pulmonary artery pressure is above the upper limit of normal, that is when it is above 20 mmHg (Table 1.). The pH within the COPD usually have mild or moderate degree, with the systolic pressure in pulmonary artery is approximately mean 50-60mmHg and mean 35-40mmHg, wherein the pressure in the right atrium, pulmonary capillary and cardiac output is in normal range. The essence of the disease are pathological changes in the pulmonary vasculature caused by increased pressure that leads to hypertrophy and hyperplasia of the smooth muscle of blood vessels, cell intimal proliferation, accumulation of fibrous tissue in the intima and the possible creation of plexiform lesions which progress to angiomas, which eventually results in fibrinoid necrosis of the intima and media, or necrotic arteritis obliterans. Elevated vascular resistance is the result of structural changes in the pulmonary vasculature in of decreased total area and/or active constriction of pulmonary vessels (4). If the pulmonary vasculature (obstructive) disease or pulmonary sclerosis is caused by congenital anomaly of the heart is called Eisenmenger syndrome (ES).

Symptoms include chest pain under load, shortness of breath, syncope, sudden heart palpitations, chills and pain in the flanks, edema, enlargement of the liver, primarily cyanosis of the lips, hemoptysis, low pressure, dyspnea and rapid fatigue, decreased exercise tolerance. Shortness of breath occurs in about 80% of patients, at the beginning only under the load, and later under small physical stress and at rest. Patients may complain of chest pain, which resembles angina interference, but in fact is a consequence of load and ischemia of the right ventricle. In severe form occurs symptoms and signs of dysfunction and right heart failure, with the present cyanosis and finger clubbing.

2. DIAGNOSTIC METHODS

Differential diagnosis must rule out ischaemic heart disease, angina pectoris, as well as other diseases accompanied by shortness of breath and pain in the chest (peri-

carditis, pleural effusion, aortic dissection, pneumothorax or pneumonia). If the cyanosis is present it should also take into consideration hemoglobinopathies and erythrocytosis.

Laboratory findings usually reveals polycythemia, the ECG right ventricle hypertrophy, and x-ray characteristic of diseased branches. Besides clinical judgment and out-of-proportion reduction in diffusing capacity, severe hypoxaemia or exercise oxygen desaturation, echocardiography and biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP hormones are potentially helpful tools in identifying PH (8). Width of the right descending branch of the pulmonary artery at the X-ray findings greater than 16 mm and left more than 18mm, indicating the existence of pulmonary hypertension. Echocardiography can be found the increase of the right atrium and ventricle, right ventricular hypertrophy, abnormal contraction of the interventricular septum, left ventricular diastolic dysfunction and decreased left ventricular size, with reduced volumes of systole and end diastole. Doppler confirming tricuspid regurgitation. Echocardiography can be helpful in detecting the cause of suspected or confirmed PH (two-dimensional, Doppler and contrast examinations can be used to identify CHD) (7). The practical clinical value of exercise Doppler echocardiography in the identification of cases with PH limited to exercise is uncertain because of the lack of validated criteria and prospective confirmatory data (7).

Screening in the form of six-minute testing (walking-exercise test), and ultrasound evaluation of the pressure in the right ventricle based on tricuspid regurgitation or pulmonary regurgitation gradient, although this method may give false positive or false negative results as well as fluttering of the pulmonary valve indicating pulmonary hypertension, although hemodynamic data level of pulmonary hypertension and pulmonary vascular resistance can only be determined by catheterization. Perfusion scintigraphy, computerized tomography multislice MSCT, pulmonary angiography has their place in the diagnostic of patients with suspected pulmonary hypertension.

3. PULMONARY ARTERIAL HYPERTENSION (PAH)

A special interest during the last decade is directed toward pulmonary arterial hypertension (PAH), which is a rare and severe chronic disease of the lung blood vessels characterized by a progressive increase in vascular resistance. PAH is hemodynamically pathophysiological condition defined as increase of secondary pulmonary arterial pressure, at rest over 25, or after effort over 30 mmHg, measured by right heart catheterization (9). PAH is a rare disease, with an estimated prevalence ranging from 10 to 52 cases per million (10-13). PAH is classified as either primary (5%), which may be idiopathic (sporadic) and familial (autosomal dominant disease with limited penetration, with gene mapped for pulmonary hypertension on chromosome 2q31/32) and secondary PAH (95%) associated with collagen diseases, CHD left to right (L-D) shunt, portal hypertension, HIV infection, induced by drugs and toxins, as well as PAH associat-

ed with significant venous or capillary involvement, and persistent pulmonary hypertension of the newborn. A special entity is postoperative PAH (after correction of congenital anomalies of the heart). PAH with congenital heart defects in form of left-right shunt is most often caused by very early abstraction of pulmonary vasculature due to disorders of physiological processes postnatal structural conversion of the pulmonary vasculature, which in principle normally lasts until the end of the second year of life. Probably the trigger is hypoxia that stimulates pulmonary vascular vasoconstriction, and then have common flow in the form of hypertrophy and hyperplasia of the smooth muscle of blood vessels, cell intimal proliferation, accumulation of fibrous tissue in the intima and the possible creation of plexiform lesions progress to angiomatous, which eventually results in fibrinoid necrosis of the intima and media and necrotizing arteritis obliterans. Increased vascular resistance is a result of structural changes in the pulmonary vasculature in the form of reduction of the total area and/or active constriction of pulmonary vessels. PAH etiology can be hyperkinetic, reactive and passive, and hemodynamic: capillary, precapillary and postcapillary. Screening as a six-minute exercise test and ultrasound evaluation of the pressure in the right ventricle based on tricuspid regurgitation or pulmonary regurgitation gradient, the ratio of PEP/VET above 0.35, pulmonary valve fluttering, are reliable for the presence of PAH, but not sufficiently specific and sensitive. Hemodynamic data level of pulmonary hypertension and pulmonary vascular resistance can be determined only by catheterization. Evaluation of these patient's operability is performed by right cardiac catheterization, direct measurement of pressure in the lungs catheter. Quantifying levels of PAH and PVR according to Fick enables making a decision on possible correction of congenital heart anomalies. The border of operability is determined by the amount of PVR, below 8 clinical units (Wood) CHD can be surgically treated, between 8-11 clinical units are under high operational risk, and over 11 clinical units inoperable. In principle, if the pressure in the lungs upon administration of pure oxygen or other responders, decrease by more than 20% relative to the basic fixed value then a positive response and indicates that there are reserves, and that cardio-surgical procedure is possible. In addition to oxygen is used nitrous oxide, iloprost, with preference for general anesthesia and mechanical ventilation and children who respond during catheterization to vasodilator responders are still operable. Any assessment of pulmonary hypertension, except catheterization, is insufficient and should not be a parameter to decide whether someone with CHD L-D shunt and PAH can be surgically treated. The treatment is still very complex and probably PAH would be optimal therapeutic measure. During period May 1998. -January 2015 in UCC Sarajevo, from 198 diagnostic catheterization, in 61 patients with congenital heart defects, catheterization was performed in order to evaluate PAH, to decide on its operability (in 18 (29.5%) patients, the existence of fixed (irreversible) pulmonary arterial hypertension was determined, which is a contra-

indication for correction) (9). Of these 18 patients, which were monitored and treated, only 4 PAH were not proven by catheterization (9).

4. TREATMENT

From the general measures it is necessary to prohibit the physical strain that causes shortness of breath, chest pain, dizziness, and syncope. To patients with “cor pulmonale” is not recommended to stay in the mountain areas above an altitude of 1200m. Airplane travel is also not recommended if there is no possibility of oxygen inhalation of oxygen during flight. Hydrotherapy and sauna also represent a risk. The treatment is still very problematic and probably would prevent optimal therapeutic measures. The treatment is generally carried out by anti-coagulant therapy, oxygenation of the patients, diuretics and digoxin. Permanent application of oxygen shows a very good results because it improves hypoxemia and decreases pulmonary vascular resistance. Prostacyclin (intravenous or by inhalation) are provided with primary pulmonary hypertension. Inhalation of NO in the hospital setting is indicated in severe cases.

Pharmacological therapy would represent a use: Calcium Channel Blockers, Prostacyclin Analogues, Endothelin Receptor Antagonists and Phosphodiesterase-5 Inhibitors. Alpha adrenergic antagonists, endothelial receptor subtype A (Bosentan, Tracller) with treatment of the underlying disease or anticongestive therapy, are recommended. In case of inadequate response to treatment with a specific drug, guidelines recommend the combined use of drugs from the basic three groups, using their synergism. Combination therapy has become the standard of care in many PAH centers, although long-term safety and efficacy have not yet been amply explored (numerous case series have suggested that various drug combinations appear to be safe and effective) (2, 14, 15). In older children and adolescents with symptomatic polycythemia may occasionally carried out phlebotomy with volume restoration. Pulmonary hypertension has therapy that is expensive, and in general is a combination of drugs that have been tested in numerous studies (studies BREATHE-2, STEP, PACES-1, TRIUMPH-1, COMPASS, PHIRST, FREEDOM-C, VISION), and which in Bosnia and Herzegovina, are generally not available. The aforementioned general therapy is essentially a choice of doctors in our country.

Bosentan has been evaluated in PAH (idiopathic, associated with CHD, and Eisenmenger’s syndrome) in five studies (Pilot, BREATHE-1, BREATHE-2, BREATHE-5, and EARLY) that have shown improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening (2). SUPER1 study on 278 PAH patients treated with sildenafil has confirmed favorable results on exercise capacity, symptoms and hemodynamics (2,16).

The fact is that at the end the preventive measures for the occurrence of risk factors that lead to the appearance of pulmonary hypertension, to doctors remain imperative, especially at tertiary level. Improving symptoms and avoiding adverse outcomes in patients with PH requires

the following (17): (1) Understanding the optimal use of echocardiography for the diagnosis of PH; (2) Recognizing the utility and proper interpretation of invasive hemodynamic testing prior to starting pulmonary vasodilator therapy; (3) Differentiating PAH from pulmonary venous hypertension due to left heart disease; and (4) Understanding the appropriate treatment strategies for PH and the resultant right heart failure. In patients who do not respond to pharmacotherapy, and are classified as NYHA class III or IV indicated is the lung transplantation or transplantation of the heart and lungs. Prognosis of idiopathic pulmonary hypertension is poor, and life expectancy is up to eight years. Prognosis of the secondary is directly related to secondary disease (18).

The therapy of PAH patients cannot be considered as a mere prescription of drugs but is characterized by a complex strategy which includes the evaluation of severity, supportive and general measures, the assessment of vasoreactivity, the estimation of efficacy, and combination of different drugs plus interventions (in any of these steps, the knowledge and experience of the responsible physician are critical to optimize the available resources) (2).

5. CONCLUSION

Although in the treatment of PH a great progress is achieved, it is a very serious disease, not always easy to diagnose, treat, and prevent. For all these activities are necessary human resources and technical support, and a well-developed infrastructure cardiology, pediatric as well as for adults. Specific and combined therapy of PAH is expensive, and the causal treatment (heart and lungs transplantation) in our conditions (Bosnia and Herzegovina) is hardly feasible. Efforts should be made that this issue is known and ensure conditions for adequate treatment like in other Western European countries, including neighboring countries. Prevention in the form of early detection and timely correction of operational CHD with L-D shunt special risk groups (chromosopathy) appears to be the main task, using a specific therapy, and pediatric catheterization is still the gold standard in the assessment of operability of the CHD L-D shunt with PAH. In adult patients, the treatment of diseases that lead to the occurrence of pulmonary hypertension is of primary importance. In the end, the fact remains that preventive measures of risk factors that lead to the occurrence of pulmonary hypertension, remains imperative to doctors, especially at tertiary level.

• Conflict of interest: none declared.

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