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DIAGNOSTICS IN PULMONARY HYPERTENSION

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Pulmonary hypertension is a serious disease with a poor prognosis. Pulmonary hypertension is defined by a mean pulmonary arterial pressure over 25 mm Hg at rest or over 30 mm Hg during activity. According to the recent WHO classification from 2003 pulmonary hypertension can be categorized as pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic pulmonary hypertension, chronic thromboembolic pulmonary hypertension and pulmonary hypertension from other causes. Pulmonary arterial hypertension is characterized histopathologically by vasoconstriction, vascular proliferation, in situ thrombosis, and remodeling of all 3 levels of the vascular walls. These pathologic changes result in progressive increases in the mean pulmonary artery pressure and pulmonary vascular resistance, which, if untreated leads to right-ventricular failure and death. Early in the disease process, the signs and symptoms of PAH are often nonspecific, making diagnosis challenging. Patients often present with progressively worsening dyspnea and fatique. Patients with severe pulmonary arterial hypertension die of right heart failure. The diagnostic procedures include clinical history and physical examination, a standard chest radiography, electrocardiography, transthoracic Doppler echocardiography, pulmonary function tests, arterial blood gas analysis, ventilation and perfusion lung scan, high-resolution computed tomography of the lungs, contrast-enhanced spiral computed tomography of the lungs and pulmonary angiography, blood tests and immunology, abdominal ultrasound scan, exercise capacity assessment, and hemodynamic evaluation. Invasive and non-invasive markers of disease severity, either biomarkers or physiological parameter and tests that can be widely applied, have been proposed to reliably monitor the clinical course. Pulmonary biopsy is rarely indicated. Transthoracic echocardiography is a key screening tool in the diagnostic algorithm. Because transthoracic echocardiography is an inexpensive, easy, and reproducible method, it is the most commonly used noninvasive diagnostic tool to determine pulmonary arterial pressure. But it not only provides an estimate of pulmonary pressure at rest and during exercise, but it may also help to exclude any secondary causes of pulmonary hypertension, predict the prognosis, monitor the efficacy of specific therapeutic interventions, and detect the preclinical stage of the disease. In addition, the measurement of serum markers, such as brain natriuretic peptide (BNP), are diagnostically useful and of prognostic significance. Once the diagnosis and etiology of pulmonary hypertension have been established, several

parameters can predict outcome in these patients: functional class, right ventricular function, pulmonary hemodynamics, and certain laboratory parameters. Also, exercise parameters such as walking distance, peak oxygen uptake or peak systolic blood pressure can reliable predict prognosis in these patients.

Key words: *exercise capacity, pulmonary artery hypertension, six-minute walk test, Tei-Index*

INTRODUCTION

"… The pulmonary circulation in patients with chronic pulmonary disease is often considered a no-man`s land, falling between the domains of the respirologist and the cardiologist and understood only by the physiologist!" (1).

Classification of Pulmonary Hypertension

Pulmonary hypertension was previously divided into primary and secondary categories; primary pulmonary hypertension described an idiopathic hypertensive vasculopathy, exclusively affecting pulmonary circulation, whereas secondary pulmonary hypertension was associated with a causal underlying disease process (2, 3). The diagnosis of primary pulmonary was one of exclusion after ruling out all causes of pulmonary hypertension (4). The recent identification of a gene responsible for the inherited forms of this disease, along with the development of specific medical treatments and the refinement of surgical techniques, has prompted a revised classification of pulmonary hypertension (5). In 2003, Third World Symposium on pulmonary arterial hypertension held in Venice – Italy decided to maintain the general architecture and philosophy of the Evian – France classification (1998) and to propose some modifications. The aim of the modifications was to make the "Venice clinical classification" more comprehensive, easier to follow and widespread as a tool (4) (*Table 1*).

Definition and clinical symptoms

Pulmonary arterial hypertension is defined as a group of diseases characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death (6). Pulmonary hypertension is defined by a mean pulmonary arterial pressure over 25 mmHg at rest or over 30 mmHg during activity with accompanying increase of pulmonary vascular resistance over 3 WU (Wood`s unit) (2).

In its early stages pulmonary arterial hypertension may be asymptomatic. Pulmonary hypertension often presents with nonspecific symptoms. The most common symptoms – exertional dyspnea, fatique, and syncope – reflect an

Table 1. Clinical classification of Pulmonary Hypertension (PH) – Venice 2003.

Pulmonary-arterial hypertension (PAH)
Idiopathic pulmonary-arterial hypertension (IPAH) – unknown origin
Familial pulmonary-arterial hypertension (FPAH) – genetic determination
PAH associated with (APAH)
Connective tissue disease Congenital systemic to pulmonary shunts Portal hypertension HIV-infection Drugs and toxins Others (thyroid disorders, glycogen storage disease, Gaucher`s disease, ...)
PAH associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease (PVOD)
Pulmonary capillary haemangiomatosis (PCH)
Persistent pulmonary hypertension of the newborn (PPHN)PH associated with left heart disease (arterial, ventricular, valvular)
PH associated with lung respiratory diseases and/or hypoxia (COPD, interstitial lung disease, sleep disordered breathing, high altitude)
PH due to chronic thrombotic and/or embolic disease
Miscellaneous (sarcoidosis, compression of pulmonary vessels ...)

Modified from Simonneau G, Galie N, Rubin LJ et al. *J Am Coll Cardiol* 2004; 43: 5S-12S.

inability to increase cardiac output during activity. The leading symptom of pulmonary arterial hypertension is exertional dyspnea. A minority of patients may report typical angina despite normal coronary arteries. The symptoms of pulmonary hypertension can also include weakness and abdominal distension (7). Hemoptysis resulting from the rupture of distended pulmonary vessels is a rare but potentially devastating event. Raynaud`s phenomenon occurs in approximately 2% of patients with primary pulmonary hypertension, but it is more common in patients with pulmonary hypertension related to connective tissue disease. More specific symptoms may reflect the underlying cause of pulmonary hypertension (8). Symptoms at rest are reported only in very advanced cases.

Etiology and pathophysiology

The estimated incidence of primary pulmonary hypertension is 1-2 cases per 1 million persons in the general population. Pulmonary hypertension is more common in women than in men (ratio: 1.7 to 1) (9). Pulmonary hypertension is most prevalent in persons 20 to 40 years of age (3). In persons more than 50 years of age, cor pulmonale, the consequence of untreated pulmonary arterial hypertension, is the third most common cardiac disorder (after coronary and hypertensive heart disease) (9, 10). Mean life time expectancy from the time of

diagnosis in patients with idiopathic pulmonary arterial hypertension, before the availability of disease-specific targeted therapy, was 2.8 years (4).

Normal pulmonary artery systolic pressure at rest is 18 to 25 mmHg, with a mean pulmonary pressure ranging from 12 to 16 mmHg. This low pressure is due to the large cross-sectional area of the pulmonary circulation, which results in low resistance (9).

The exact processes that initiate the pathological changes seen in pulmonary arterial hypertension are still unknown, even if we now understand more of the mechanisms involved. It is recognized that pulmonary arterial hypertension has a multi-factoral pathophysiology that involves various biochemical pathways and cell types. The increase of pulmonary vascular resistance is related to different mechanisms including vasoconstriction, obstructive remodelling of the pulmonary vessel wall, inflammation and thrombosis. Pulmonary vasoconstriction is believed to be an early component of the pulmonary hypertensive process (11). In the pulmonary circulation, there is a homeostatic balance between a variety of mediators that influence vascular tone, cellular growth and coagulation. In pulmonary arterial hypertension, pulmonary endothelial cell dysfunction or injury promotes the pathological triad of vasoconstriction, cellular proliferation and thrombosis through the action of mediators such as thromboxane A_2, endothelin-1 and serotonin. Under normal circumstances, these effects are counterbalanced by prostacyclin, vasoactive intestinal peptide and nitric oxide, which tend to have opposite effects (12, 5). Irrespective of the underlying etiology of pulmonary arterial hypertension, the histological appearance of lung tissue in each of these conditions is similar and consists of intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion and plexiform lesions (5). The process of pulmonary vascular remodelling involves all layers of the vessel wall and is characterised by proliferative and obstructive changes that involve several cell types including endothelial, smooth muscle and fibroblasts (13).

Diagnostics

The clinical cardinal symptom of pulmonary hypertension is dyspnea. The diagnostic process of pulmonary hypertension requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of pulmonary hypertension and the type of pulmonary arterial hypertension and to evaluate the functional and hemodynamic impairment (*Table 2*).

Non-invasive diagnostics

Functional assessment. Patients with pulmonary hypertension can be classified according to their ability to function, modified from the New York Heart Association classification of patients with cardiac disease (*Table 3*).

Table 2. Diagnosis of pulmonary hypertension. Clinical classification: WHO/NYHA.

NON-INVASIVE
Echocardiography (TTE): for RV-size/function, TK-insufficiency, PAPs, (PAPm), Tei-index
Walking distance of 6 minutes: for severity code, therapy control and prognosis
Laboratory tests: BNP, NT-Pro-BNP, troponin
Pulmonary function: FC, FEV1, FEV1/FC, BGAs
Spiroergometry: peak VO_2, V_E/CO_2
Ventilation-perfusion lung scan: pulmonary embolism?
HR-CT of the lung: interstitial lung disease?
Exclusion: collagenosis, lupus erythematodes, HIV, congenital vitium
INVASIVE
Right cardiac catheterization: PAPs, PAPm, PCP, PVR, heart index, etc.
Pharmacological tests: O_2, NO, iloprost, prostanoids, adenosine

Table 3. Modified NYHA-classification in pulmonary hypertension.

Class I – Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatique, chest pain or pre-syncope.
Class II – Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatique, chest pain or pre-syncope.
Class III – Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatique, chest pain or pre-syncope.
Class IV – Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnea and/or fatique may be present at rest and symptoms are increased by almost any physical activity.

Hoeper M, Oudiz R, Peacock A et al. *J Am Coll Cardiol* 2004; 43: S48-S55.

Physical examination. Physical examination can reveal increased jugular venous distention, a tricuspid regurgitant holosystolic murmur and a loud P2, all suggestive of elevated right-sided pressure. Lung sounds are usually normal. Hepatomegaly, peripheral oedema, ascites and cool extremities characterize patients in a more advanced state with right ventricular failure at rest.

Electrocardiography. Electrocardiographic signs of the right heart compromise include right axis deviation, right ventricular hypertrophy, and peaked P waves. However, the electrocardiography lacks sufficient diagnostic accuracy to serve as a screening tool for the detection of pulmonary arterial hypertension. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients (7). ECG has inadequate sensitivity (55%) and

specifity (70%) (14). A normal ECG does not exclude the presence of severe pulmonary hypertension.

Chest radiography. The chest radiograph is inferior to ECG in detecting pulmonary hypertension, but it may show evidence of underlying lung disease (15). In 90% of pulmonary arterial hypertension patients the chest radiograph is abnormal at the time of diagnosis (7). The finding include central pulmonary arterial dilatation which contrasts with "pruning" of the peripheral blood vessels. A hilar-to-thoracic ratio greater than 0.44, a right descending pulmonary artery diameter of greater than 18 mm and right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. However, a normal chest radiograph does not exclude mild pulmonary hypertension including left-heart disease or pulmonary veno-occlusive disease.

Echocardiography. Transthoracic echocardiography is an excellent non-invasive screening test for the patient with suspected pulmonary hypertension. Transthoracic echocardiography estimates pulmonary artery systolic pressure and can provide additional information about the causes and consequences of pulmonary hypertension.

Pulmonary artery systolic pressure is equivalent to right ventricular systolic pressure in the absence of pulmonary outflow obstruction. With CW-Doppler-echocardiography right ventricular systolic pressure (RVSP) can be obtained by adding the estimated right atrial pressure (RAP) to the pressure gradient derived from systolic regurgitant tricuspid flow velocity *v* according the formula: RVSP = 4 v^2 + RAP. Echocardiographic estimation of the right atrial pressure by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava (*Table 4*). According to the normal ranges of Doppler-derived values of pulmonary artery pressures, mild pulmonary hypertension can be defined as pulmonary artery systolic pressures of approximately 36-50 mmHg or resting tricuspid regurgitant velocity of 2.8-3.4 m/sec assuming a normal right atrial pressure of 5 mmHg. The right ventricular systolic pressure may be underestimated in some cases because of suboptimal tracings of the regurgitation jet, of decreased tricuspid regurgitant jet velocity due to high right atrial

Table 4. Echocardiographic estimation of the right atrial pressure (RAP) by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava inferior (VCI).

VCI-diameter (cm)	Respiratory motion (%)	mRAP (mmHg)
<1.5	100	<5
1.5 - 2.5	>50	5 - 10
1.5 - 2.5	<50	10 - 15
>2.5	>50	15 - 20
>2.5 + dilated	0	>20
Hepatic vein	—	—

pressures, and poor estimation of right atrial pressures. However, in order to estimate a right ventricular systolic pressure by echocardiography, tricuspid regurgitation must be present.

Indirect signs of pulmonary hypertension are: paradoxical septal motion (septal bowling or flattering), decreased or missing collapse of the vena cava inferior, pericardial effusion, right ventricular hypertrophy and reduced right ventricular ejection time. Additional examination to the routine echocardiography is the estimation of right ventricular Tei-index (isovolumetric contraction time and relaxation time/ejection time) (24) and the "tricuspid annular plane systolic excursion" (TASPE). The peak early diastolic pulmonary regurgitation velocity is useful in estimating mean pulmonary artery pressure (mean PAP). Together with the dimension of the right atrium and pericardial effusion Tei-index and TASPE are important prognostic parameters in patients with pulmonary hypertension, while the right ventricular systolic pressure does not correlate with survival (16). Echocardiography is the most useful imaging modality for detecting pulmonary hypertension and excluding underlying cardiac disease.

Serology and biomarkers. All patients with suspected or documented pulmonary hypertension should undergo serologic testing Initial laboratory evaluation includes a complete blood count, prothrombin time, hepatic profile, and serologic studies for collagen vascular disease suggested by history or physical examination. Special autoantibodies might include antinuclear and anti-DNA (systemic lupus erythematosus), anti-Scl-70 and antinuclear (scleroderma), anticentromere (CREST syndrome), rheumatoid factor (rheumatoid arthritis), anti-Ro and anti-La (Sjogren`s syndrome), anti-Jo-1 (dermatomyositis/polymyositis) and anti-U1 RNP (mixed connective tissue disease). HIV testing should be considered in all patients, especially those with a compatible history or risk factors.

The use of plasma brain natriuretic peptide (BNP) is well established in the diagnosis and staging of patients with congestive heart failure. Recently, measurement of BNP has been shown to be a useful prognostic tool in the population of patients with primary pulmonary hypertension (17) and chronic lung diseases (18). It has been shown, that plasma BNP levels is associated with pulmonary artery pressure and pulmonary vascular resistance. Further on, there is a correlation of exercise parameters (VO_2 peak, WHO functional class, 6-minute walk). Additionally, alterations in n-terminal pro BNP reflect changes in right ventricular structure and function in pulmonary hypertension patient during treatment (19). Therefore, BNP seems to be a simple, non-invasive tool and observer independent parameter for assessing disease severity and treatment efficiency in patients with pulmonary hypertension.

Ventilation/Perfusion Scanning. Ventilation/perfusion scans are often used to rule out other causes of dyspnea. Fortunately, ventilation-perfusion lung scanning is a reliable method for differentiating chronic thromboembolism from primary pulmonary hypertension (9). Normal ventilation and quantification scans rule out

chronic thromboembolic disease (20). The finding of one or more segmental or larger perfusion defects is a sensitive marker of embolic obstruction.

Computerized tomography. Computerized tomographic (CT/MRI) scanning of the chest with high-resolution images is useful to exclude occult interstitial lung disease and mediastinal fibrosis. It also is helpful in diagnosis of pulmonary embolism. Magnetic resonance imaging can be used to assess the size and function of the right ventricle, myocardial thickness, the presence of chronic thromboembolic disease with a mosaic pattern of the lung parenchyma and cardiac and pulmonary pressures (21, 22).

Pulmonary Function Testing. The role of pulmonary function testing is to rule out parenchymal or obstructive lung disease as the cause of the patient`s symptoms. Unless hypoxia is present, pulmonary hypertension cannot be attributed to these disorders until pulmonary function is severely reduced. Some patients with pulmonary artery hypertension can have a mild decline in their total lung capacity and diffusing capacity for carbon monoxide, but the severity of these declines do not correlate with disease severity. With pulmonary function testing neither an accurate diagnosis nor adequate follow-up examinations are possible.

Six-minute walk test. Submaximal testing with a 6-minute walk test is recommended at the time of diagnosis to establish baseline functional impairment and at the follow-up to assess response to therapy and prognosis (21). The mortality risk is increased 2.4-fold in patients with pulmonary arterial hypertension who are able to walk less than 300 m in 6 minutes and 2.9-fold in those with a greater than 10% decline in arterial oxygen saturation (23). The 6-minute walk distance correlates with severity by NYHA functional class in patients with pulmonary hypertension, and patients who walk less than 332 m have a significantly lower survival rate than those who walk farther (24).

Cardiopulmonary Exercise Testing. Cardiopulmonary exercise testing (CPET) allows measurement of ventilation and pulmonary gas exchange during exercise testing providing additional “pathophysiologic” information to that derived from standard exercise testing. Cardiopulmonary exercise testing has no added value in the initial diagnostic testing of pulmonary hypertension. The most important parameters are the maximal oxygen uptake (peak VO_2) and the relation from ventilation to CO_2-relief (V_E/VCO_2). Pulmonary hypertension patients show reduced peak O_2, reduced peak work rate, reduced ratio of VO_2 increase to work rate increase, reduced anaerobic threshold and reduced peak oxygen pulse; they show also increased V_E and VCO_2 slope representative of ventilatory inefficiency (25).

Invasive diagnostics

Right Heart Catheterization. Right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension. All patients suspected of having significant pulmonary hypertension after clinical and transthoracic

echocardiographic evaluation should undergo right heart catheterization, particularly if they are candidates for treatment (21).

The modern era in cardiopulmonary medicine began in the 1940s, when Cournand and Richards pioneered right-heart catheterization. Right-heart catheterization ignited an explosion of insights into function and dysfunction of the pulmonary circulation, cardiac performance, ventilation-perfusion relationships, and lung-heart interactions. Right heart catheterization is the only method for direct proof of an increased pressure in the pulmonary circulation system. Cardiac catheterization gives information about the heart, because it is the limiting organ for performance and prognosis of pulmonary hypertension! The goals of right heart catheterization, in addition to making the diagnosis, are to measure right atrial and ventricular pressures, to detect pulmonary artery pressure (PAP systolic, PAP diastolic, PAP mean) and pulmonary artery capillary wedge pressure (PCWP), to measure pulmonary vascular and systemic vascular resistance (PVR, SVR), to calculate cardiac output/index (end organ function) by Fick principle or thermodilution, to evaluate pulmonary artery O_2-saturation, and to look for the presence of left-to-right shunts and right-to-left shunt (the latter makes left heart cardiac catheterization necessary). The significance of right heart catheterization is to assess the severity of the hemodynamic impairment, to predict the prognosis, to identify other causes of pulmonary hypertension, to monitor the etiopathology, to evaluate the right ventricular function, and to test the vasoreactivity of the pulmonary circulation.

Vasodilator testing during right-heart cardiac catheterization should only be done using short-acting vasodilators such as adenosine/epoprostenol intravenously, prostacyclin, nitric oxide or iloprost by inhalation. According to the European Society of Cardiology, a response to acute vasodilator testing includes a decrease of more than 10 mmHg in the mean pulmonary artery pressure and/or a decrease of the mean pulmonary artery pressure under 40 mmHg. Responders to acute vasodilator testing have a favorable clinical response and course when treated with calcium channel blockers, but calcium channel blockers should be strictly avoided in non-responders. There are no absolute contraindications to right heart catheterization and complications are rare, although may happen.

Disease monitoring

While echocardiography is the screening method for acquisition of pulmonary hypertension (high sensitivity), the right heart cardiac catheterization has a higher specificity and is a required method to confirm the diagnosis definitely (*Table 5*). Some patients with mild and moderate pulmonary hypertension can be managed without right heart catheterization. Those with mild to moderate pulmonary hypertension due to chronic hypoxemia (resting, exertional or noctural) can be followed with serial echocardiography for

Table 5. Pulmonary hypertension (PH): Diagnostic approach.

PH Suspicion	Symptoms & physical examination Screening procedures Incidental findings
PH Detection	ECG Chest radiography TT echocardiography
PH Class Identification	Pulmonary function tests & arterial blood gases High resolution CT Spiral CT Pulmonary Angiography/MR Angiography
PH Evaluation Type Exercise capacity Hemodynamics	 Blood tests, HIV test 6-Minute walk test, Spiroergometry Right heart catheterization & vasoreactivity

evidence of progression on appropriate oxygen and/or noctural ventilatory support. For patients with mild to moderate pulmonary hypertension by echocardiography who do not have NYHA class III symptoms, right heart cardiac catheterization can be reserved as a future option if pulmonary hypertension progresses on serial echocardiography every 3 to 6 months.

Right heart function and ejection fraction have a great importance in patients with pulmonary hypertension: clinical severity and mortality rate do increase in concert with the degree of limitation of the right ventricular function and ejection fraction. The higher the mean pulmonary arterial pressure and the pulmonary wedge pressure and the worse the right ventricular function, the higher the mortality with left heart insufficiency will be. Patients with a low ejection fraction and high pulmonary artery pressure show a particularly bad prognosis, independent from the degree of restricted left ventricular function (26) (*Table 6*).

Conclusion

Pulmonary hypertension is defined as an elevation in pulmonary arterial pressures and is characterized by symptoms of dyspnea, chest pain and syncope. If untreated, pulmonary arterial hypertension has a high mortality rate, typically from decompensated right-sided heart failure. Estimated median survival is approximately 2.8 years.

The past decade has seen major advances in our understanding of the pathophysiological mechanisms underlying the development of pulmonary arterial hypertension. The diagnosis is now more clearly defined according to a new clinical classification, and clear algorithms have been devised for the investigation. However, the prognosis of pulmonary arterial hypertension remains guarded despite recent advances and new therapeutic options.

Table 6. Estimation of prognosis in pulmonary hypertension (PH).

PARAMETERS WHICH DO CORRELATE WITH PROGNOSIS OF PH
Right Heart Cardiac Catheterisation: Cardiac output Cardiac index (CI) Right atrial pressure Mixed venous O_2-saturation Pulmonary vascular resistance (PVR)
Echocardiography: Dilatation of right atrium (RA-Area) Right ventricular Tei-Index Pericardial effusion Tricuspid annular plane systolic excursion (TASPE)
PARAMETERS WHICH DO NOT CORRELATE WITH PROGNOSIS OF PH
Right ventricular pressure Pulmonal artery pressure Pulmonary capillary wedge pressure (PWCP) Systemic vascular resistance (SVR)

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