Pulmonary hypertension: classification and diagnostic algorithm

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Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death.

Recently, the diagnostic approach has been more clearly defined according to the new clinical classification and with consensus reached on algorithms of various investigative tests and procedures that exclude other causes and ensure an accurate diagnosis of PAH. The diagnostic procedures include clinical history and physical examination, ECG, chest X-ray, 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 parameters and tests that can be widely applied, have been proposed to reliably monitor the clinical course.

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Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary artery pressure (PAP) > 25 mmHg at rest or > 30 mmHg on exertion[1]. Current classification of PAH is presented in table I. Clinical conditions with PAH are classified in five categories according to similar pathologic, pathophysiologic and therapeutic characteristics. Despite possible comparable elevations of PAP and pulmonary vascular resistance in the different clinical classes, the underlying mechanisms, the diagnostic approaches and the prognostic and therapeutic implications are completely different[2].

PAH (class 1) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death[2]. The median life expectancy from the time of diagnosis in patients with idiopathic PAH, formerly termed primary PAH, before the availability of disease-specific (targeted) therapy was 2.8 years through the mid 1980's[3]. PAH includes idiopathic PAH and PAH associated with various conditions such as connective tissue diseases (CTD), congenital systemic-to-pulmonary shunts, portal hypertension and HIV infection[4]. All these conditions share equivalent obstructive pathologic changes of the pulmonary microcirculation[5] suggesting shared pathobiological processes among the disease spectrum of PAH[6]. If we include all PAH categories, the minimal prevalence of the disease has been estimated to 15 cases per million in a recent French registry[7] but with quantitative differences in the distribution and prevalence of pathological changes in the different components of the pulmonary vascular bed (arterioles, capillaries or veins). Four main pathological pictures can be identified: pulmonary arteriopathy, pulmonary occlusive venopathy (also defined pulmonary veno-occlusive disease), pulmonary microvasculopathy (also defined pulmonary capillary hemangiomatosis) and unclassifiable conditions[5]. Pulmonary arteriopathy is the most frequent pattern and its main histopathological features include medial hypertrophy, intimal thickening and complex lesions (plexiform lesions, colander lesions, arteritis) of the arterioles.

PAH is a common complication in patients affected by left heart diseases (class 2). In fact, left ventricular failure or mitral valve diseases may produce an increase in left atrial pressure, pulmonary venous pressure, pulmonary capillary pressure and in

Table I. Clinical classification of pulmonary hypertension (Venice 2003).

1.	Pulmonary arterial hypertension (PAH)
1.1.	Idiopathic (IPAH)
1.2.	Familial (FPAH)
1.3.	Associated with (APAH)
1.3.1.	Connective tissue disease
1.3.2.	Congenital systemic-to-pulmonary shunts
1.3.3.	Portal hypertension
1.3.4.	HIV infection
1.3.5.	Drugs and toxins
1.3.6.	Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4.	Associated with significant venous or capillary involvement
1.4.1.	Pulmonary veno-occlusive disease (PVO)
1.4.2.	Pulmonary capillary hemangiomatosis (PCH)
1.5.	Persistent pulmonary hypertension of the Newborn
2.	Pulmonary hypertension associated with left heart diseases
2.1.	Left-sided atrial or ventricular heart disease
2.2.	Left-sided valvular heart disease
3.	Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Sleep disordered breathing
3.4.	Alveolar hypoventilation disorders
3.5.	Chronic exposure to high altitude
3.6.	Developmental abnormalities
4.	Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1.	Thromboembolic obstruction of the proximal pulmonary arteries
4.2.	Thromboembolic obstruction of the distal pulmonary arteries
4.3.	Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5.	Miscellaneous
5.1.	Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of the pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

turn the elevation of the PAP. From the hemodynamic point of view this type of PAH is characterized by an increase of pulmonary wedge pressure and is defined as post-capillary.

PAH is relatively common in patients with chronic hypoxic lung disease of whatever cause (class 3) including chronic obstructive pulmonary disease, interstitial lung disease, ventilatory disorders, sleep hypopnea and apnea disorders and high altitude. The severity of PAH in chronic obstructive pulmonary disease is generally limited to an increase in mean PAP to 25-35 mmHg; pulmonary wedge pressure and cardiac output are normal.

Chronic thromboembolic pulmonary hypertension (CTEPH) (class 4) is the result of single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis. The natural history of pulmonary thromboemboli is to undergo total resolution, or resolution leaving minimal residua, with restoration of normal pulmonary hemodynamics. For reasons still unclear, in some patients thromboemboli fail to resolve and form endothelialized obstructions of the pulmonary vascular bed including the major branches.

A number of heterogeneous rare conditions with different clinical presentations and pathophysiologic mechanisms have been included in class 5.

Diagnostic procedures

The diagnostic process of PAH requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of PAH and the type of PAH and to evaluate the functional and hemodynamic impairment. We will describe the main characteristics of each procedure and we will discuss their sequential use in a diagnostic algorithm.

Symptoms and signs of pulmonary hypertension. Symptoms of PAH include breathlessness fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases.

Physical signs of PAH include left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricular S3. Jugular vein distension, hepatomegaly, peripheral edema, ascites and cool extremities characterize patients in a more advanced state. Lung sounds are usually normal.

Finally, PAH can be suspected when abnormal electrocardiographic, chest X-ray or echocardiographic findings are detected in the course of procedures performed for other clinical reasons.

Electrocardiography. The ECG may provide suggestive or supportive evidence of PAH by demonstrating right ventricular hypertrophy and strain, and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right-axis deviation in 79% of patients with idiopathic PAH. The ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PAH.

Chest X-ray. In 90% of idiopathic PAH patients chest X-ray is abnormal at the time of diagnosis. Findings include central pulmonary arterial dilation which contrasts with "pruning" (loss) of the peripheral blood vessels. Right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. Chest X-ray allows associated moderate-to-severe lung disease or pulmonary venous hypertension due to left heart abnormalities to be reasonably excluded (see

high-resolution computed tomography [HRCT] section).

Transthoracic Doppler echocardiography. Transthoracic Doppler echocardiography (TTE) is an excellent non-invasive screening test for patients with suspected PAH. TTE estimates pulmonary artery systolic pressure (PASP) and can provide additional information about the cause and consequences of PAH. PASP is equivalent to right ventricular systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP is estimated by measurement of the systolic regurgitant tricuspid flow velocity and an estimate of right atrial pressure. Tricuspid regurgitant jets can be assessed in the majority (74%) of patients with PAH.

According to data obtained in normal subjects[8] mild PAH can be defined as a PASP of approximately 36-50 mmHg or a resting tricuspid regurgitant velocity of 2.8-3.4 m/s (assuming a normal right atrial pressure of 5 mmHg). It should be noted that also with this definition a number of false positive diagnosis can be anticipated especially in aged subjects and confirmation with right heart catheterization is required in symptomatic patients (NYHA class II-III). In asymptomatic subjects (NYHA class I) a concomitant CTD should be excluded and echocardiography should be repeated in 6 months. Also the possibility of false negative Doppler echocardiographic results should be considered in case of high clinical suspicion[9].

Additional echocardiographic and Doppler parameters are important for diagnosis confirmation and assessment of severity of PAH including right and left ventricular dimensions and function, tricuspid, pulmonary and mitral valve abnormalities, right ventricular ejection and left ventricular filling characteristics, inferior vena cava dimensions, and pericardial effusion size[10,11].

Besides identification of PAH, TTE also allows a differential diagnosis of possible causes and virtually starts the phases III and IV of the diagnostic process. TTE can recognize left heart valvular and myocardial diseases responsible for pulmonary venous hypertension (clinical class 2), and congenital heart diseases with systemic-to-pulmonary shunts can be easily identified (clinical class 1.3.2). The venous injection of agitated saline as contrast medium can help the identification of patent foramen ovale or small sinus venosus type atrial septal defects that can be overlooked on the standard TTE examination. Transesophageal echocardiography is rarely required and is usually used to confirm the presence and assess the exact size of small atrial septal defects.

Pulmonary function tests and arterial blood gas analysis. Pulmonary function tests and arterial blood gas sample will identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (DL_{CO}) (typically in the range of 40-80% predicted) and mild to moderate reduction of lung volumes. The arterial oxygen tension is normal or only slightly lower than normal and arterial carbon dioxide tension is decreased as a result of alveolar hyperventilation. Chronic obstructive pulmonary disease as a cause of hypoxic PAH is diagnosed on the evidence of irreversible airflow obstruction[12] together with increased residual volumes, reduced DL_{CO} and normal or increased arterial carbon dioxide tension. A decrease in lung volume together with a decrease in DL_{CO} may indicate a diagnosis of interstitial lung disease. The severity of emphysema and of interstitial lung disease can be diagnosed using HRCT. If clinically suspected, screening overnight oximetry will exclude significant obstructive sleep apnea/hypopnea.

Ventilation and perfusion lung scan. In PAH the lung ventilation and perfusion (V/Q) scans may be entirely normal. However they may also show small peripheral non-segmental defects in perfusion. These are normally ventilated and thus represent V/Q mismatch. Lung V/Q scan provides a means of diagnosis of CTEPH (clinical class 4)[13]. In CTEPH the perfusion defects are usually found in lobar and segmental regions leading to segmental defects in the perfusion image. A caveat is that unmatched perfusion defects are also seen in veno-occlusive disease. Such a patient requires careful further investigation (see section on HRCT). In patients with parenchymal lung disease the perfusion defects are *matched* by ventilation defects.

High-resolution computed tomography of the lungs. HRCT provides detailed views of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema. HRCT may be indicated in cases of interstitial markings at chest X-ray without evidence of left ventricular failure. In these cases the confirmation of a diffuse central ground-glass opacification and thickening of interlobular septa suggest pulmonary veno-occlusive disease; additional findings are lymphadenopathy, pleural shadows and effusions.

Contrast-enhanced spiral computed tomography of the lungs and pulmonary angiography. Contrast-enhanced spiral (or helical) computed tomography is indicated in PAH patients when the V/Q lung scintigraphy shows segmental or subsegmental defects of perfusion with normal ventilation, i.e. evidence of a V/Q mismatch and may demonstrate central chronic pulmonary thromboemboli. Computed tomography features of chronic thromboembolic disease are complete occlusion of the pulmonary arteries, eccentric filling defects consistent with thrombi, recanalization, and stenoses or webs[13].

Traditional pulmonary angiography is still required in the work-up of CTEPH to better identify patients that can benefit from the intervention of endarterectomy[13]. Pulmonary angiography is more accurate in the identi-

fication of distal obstructions and it is indicated also in cases of inconclusive contrast-enhanced spiral computed tomography in patients with clinical and lung scintigraphy suspicion of CTEPH.

Blood tests and immunology. Routine biochemistry, hematology and thyroid function tests are required. CTD are diagnosed primarily on clinical and laboratory criteria and an autoimmune screen consists of antinuclear antibodies, including anti-centromere antibody, anti-SCL70 and RNP. About one third of patients with idiopathic PAH have positive but low antinuclear antibody titers (≥ 1:80 dilutions). Patients with substantially elevated antinuclear antibodies and/or suspicious clinical features require further serologic assessment and rheumatology consultation. Finally all patients should be consented for and undertake an HIV serology test.

Abdominal ultrasound scan. Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound scan. The use of contrast agents may improve the diagnosis. Portal hypertension can be confirmed by the detection of an increased gradient between free and occluded (wedge) hepatic vein pressure at the time of the right heart catheterization.

Exercise capacity. The objective assessment of exercise capacity in patients with PAH is an important instrument for evaluating disease severity[14] and treatment effect[15]. The most commonly used exercise tests for PAH are the 6-min walk test and cardiopulmonary exercise testing with gas exchange measurement (CPET). The 6-min walk test is technically simple, is predictive of survival in idiopathic PAH and also correlates inversely with NYHA functional status severity[14]. CPET allows measurement of ventilation and pulmonary gas exchange during exercise testing providing additional "pathophysiologic" information to that derived from standard exercise testing. However, it is more technically difficult and it may fail to confirm improvements observed with the 6-min walk test. A possible explanation may relate to a lack of sensitivity of CPET in measuring response to treatments which have less effect on maximal as opposed to submaximal exercise.

Hemodynamics. Right heart catheterization is required to confirm the diagnosis of PAH, to assess the severity of the hemodynamic impairment and to test the vasoreactivity of the pulmonary circulation.

PAH is defined by a mean PAP > 25 mmHg at rest or > 30 mmHg with exercise, by a pulmonary wedge (occluded) pressure ≤ 15 mmHg and by pulmonary vascular resistance > 3 mmHg/l/min (Wood units). Left heart catheterization is required in the rare circumstances in which a reliable pulmonary wedge pressure cannot be measured. The assessment of the pulmonary wedge pressure may allow the distinction between arterial and venous pulmonary hypertension in patients with concomitant left heart diseases.

Right heart catheterization is important also in patients with definite moderate-to-severe PAH because the hemodynamic variables have prognostic relevance[3]. Elevated mean right atrial pressure, mean PAP and reduced cardiac output and central venous oxygen saturation identify idiopathic PAH patients with the worst prognosis.

Uncontrolled studies have suggested that long-term administration of calcium channel blockers prolongs survival in acutely responsive patients compared with unresponsive patients[16]. It is generally accepted that patients who may benefit from long-term calcium channel blockers can be identified by an acute vasodilator challenge performed during right heart catheterization[17].

Acute vasodilator testing should only be done using short-acting pulmonary vasodilators at the time of the initial right heart catheterization in experienced centers to minimize the potential risks. Currently the agents used in acute testing are intravenous prostacyclin or adenosine and inhaled nitric oxide[18]. A positive acute vasoreactive response (positive acute responders) is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increase or unchanged cardiac output[19,20]. Generally, only about 10 to 15% of idiopathic PAH patients will meet these criteria[18,19]. Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of calcium channel blockers and are the only patients that can safely be treated with this type of therapy. An empiric treatment with calcium channel blockers without acute vasoreactivity test is strongly discouraged due to possible severe adverse effects.

Positive long-term responders to high-dose calcium channel blocker treatment are defined as patients being in NYHA functional class I or II with near-normal hemodynamics after several months of treatment with calcium channel blockers alone. Only about a half of idiopathic PAH positive acute responders are also positive long-term responders[19] to calcium channel blockers and only in these cases the continuation of calcium channel blockers as single treatment is warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with calcium channel blockers in patients with PAH associated with underlying processes, such as CTD or congenital heart disease is less clear as compared to idiopathic PAH[19]. However, experts suggest also in these cases to test patients for acute vasoreactivity and to look for a long-term response to calcium channel blockers in the appropriate subjects.

Diagnostic algorithm (Fig. 1). The various investigative tests can be combined in a diagnostic algorithm that for practical purposes can be divided in four steps: 1. PAH suspicion. The clinical suspicion of PAH should arise in case symptoms such as breathlessness without overt signs of specific heart or lung disease, in cases of

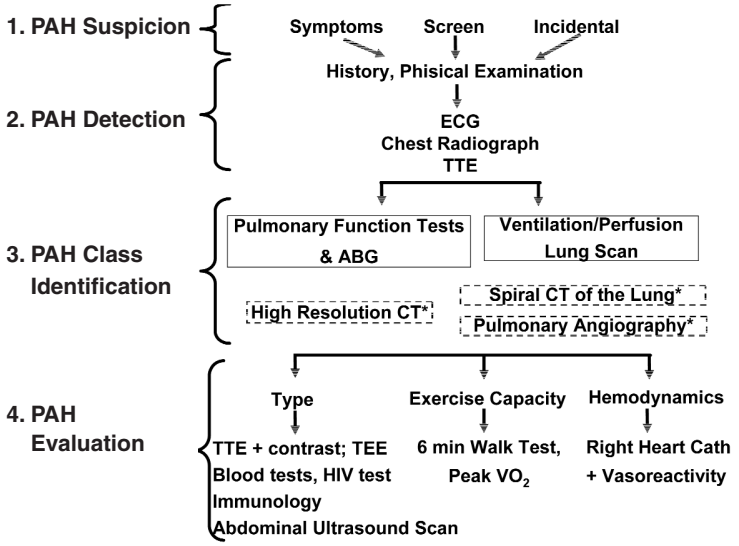

Figure 1. *Diagnostic algorithm of pulmonary hypertension. ABG = arterial blood gas analysis; CT = computed tomography; PAH = pulmonary arterial hypertension; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; VO_2 = oxygen consumption. * required in specific circumstances (see text).*

screening in predisposing conditions or in cases of incidental findings;
2. PAH detection. The detection of PAH requires investigations that are able to confirm the diagnosis of PAH such as the clinical examination, ECG, chest X-ray and TTE;
3. PAH class identification. The next step after the detection of PAH is the identification of the clinical class according to the diagnostic classification of Venice (Table I)[2]. This is accomplished by the use of essential tests such as pulmonary function tests, arterial blood gas analysis and V/Q lung scan. If required (see above), in particular circumstances additional tests can be performed such as chest HRCT, spiral computed tomography and pulmonary angiography;
4. PAH evaluation. After the diagnosis of PAH (clinical class 1) additional investigations are required for the exact identification of the type of PAH, and for the assessment of exercise capacity and hemodynamics (Fig. 1).

Evaluation of severity

In clinical practice, the prognostic value of a single variable in the individual patient may be less than the value of multiple concordant variables. Very little information is available in other conditions such as PAH associated with CTD, congenital systemic-to-pulmonary shunts, HIV infection or portal hypertension. In these circumstances, additional factors may contribute to the overall outcome. In fact, PAH associated with CTD has a worse prognosis than idiopathic PAH patients, whereas patients with PAH associated with congenital systemic-to-pulmonary shunts have a more slowly progressive course than idiopathic PAH patients.

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