UPDATE

The right heart and pulmonary circulation (v)

Current Diagnostic and Prognostic Assessment of Pulmonary Hypertension

Pilar Escribano Subias,[a] Joan Albert Barberà Mir,[b] and Verónica Suberviola[c]

[a]Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain
[b]Servicio de Neumología, Hospital Clínic, Barcelona, Spain
[c]Servicio de Cardiología, Hospital Infanta Leonor, Madrid, Spain

Recently, our view of pulmonary hypertension has been changed by the significant progress made in understanding the pathobiology, epidemiology and prognosis of the disease. The increasing number of different conditions now associated with pulmonary hypertension and the appearance of new diagnostic techniques have led to a need for a systematic diagnostic approach and a new disease classification. This review article presents an update on developments in the epidemiology and pathobiology of pulmonary hypertension, on changes in the clinical classification of the disease, and on alterations in the diagnostic algorithm. In addition, it contains detailed descriptions of the treatment recommended for patients in whom an elevated systolic pulmonary pressure is discovered on echocardiography, of the differential diagnosis of pulmonary arterial hypertension and pulmonary hypertension associated with left heart disease, and of multifactorial approaches to determining prognosis, which are three of the most actively debated topics today. Finally, a care program for patients with pulmonary arterial hypertension is proposed.

Key words: *Pulmonary arterial hypertension. Epidemiology. Prognosis. Referral centre.*

Evaluación diagnóstica y pronóstica actual de la hipertensión pulmonar

Recientemente se han producido importantes avances en el conocimiento de la biopatología, la epidemiología y el pronóstico de la hipertensión pulmonar que han cambiado la perspectiva de la enfermedad. El número creciente de enfermedades asociadas a la hipertensión pulmonar y la aparición de nuevas técnicas diagnósticas obligan a sistematizar el procedimiento diagnóstico y definir una clasificación.

En esta revisión se actualizan las principales novedades en epidemiología y patobiología, las modificaciones en la clasificación clínica y los cambios en el algoritmo diagnóstico. Se desarrolla con detalle el manejo recomendado del hallazgo de presión sistólica pulmonar elevada en el ecocardiograma, el diagnóstico diferencial entre hipertensión arterial pulmonar e hipertensión pulmonar asociada a cardiopatía izquierda y la valoración multifactorial del pronóstico, que forman parte de los aspectos más controvertidos actualmente. Finalmente, se propone una organización asistencial para los pacientes con hipertensión arterial pulmonar.

Palabras clave: *Hipertensión arterial pulmonar. Epidemiología. Pronóstico. Unidad de referencia.*

INTRODUCTION

Pulmonary hypertension (PH) is defined[1] as an increase in mean pulmonary arterial pressure (PAP) >25 mmHg at rest as determined by right heart catheterization (RHC). Currently, the normal behavior of pulmonary pressure on exercise remains unknown, and it presents wide variability according to age and the degree of physical fitness in the healthy individual. Thus, a definition of PH on exercise cannot be established.

CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension can be found in different clinical conditions[3,4] and are classified into 5 groups: group 1, pulmonary arterial hypertension (PAH); group 2, pulmonary hypertension associated with left heart disease (PHLHD); group 3, pulmonary hypertension associated with lung disease or hypoxemia; group 4, chronic thromboembolic

Dr Pilar Escribano Subias is a member of the research network cooperative (REDINSCOR) of the Ministry of Health and Consumers.

Correspondence: Dra. P. Escribano Subias.
Avda. Córdoba, s/n. 28041 Madrid. Spain.
E-mail: pilar.escribano@telefonica.net

ABBREVIATIONS

CTEPH: chronic thromboembolic pulmonary hypertension
HIV: human immunodeficiency virus
IPAH: idiopathic pulmonary arterial hypertension
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
PWP: pulmonary wedge pressure
RHC: right heart catheterization

pulmonary hypertension (CTEPH); and group 5, pulmonary hypertension with unclear or multifactorial mechanisms.

This classification[1] (Table 1) is based on clinical data, and groups together the different processes and diseases that share pathophysiological mechanisms, clinical presentation and therapeutic approaches. In relation to previous classifications, substantial modifications have been made to group 1. The term familial PAH has been replaced by heritable PAH, since specific gene mutations have been identified in sporadic cases with no family history of the disease. Among the heritable forms of PAH are sporadic idiopathic PAH (IPAH) with germline mutations and clinical cases with a family background with or without identified mutations. This new category of heritable PAH does not require genetic testing, as this would not change its clinical management.

The classification of congenital heart disease underlying PAH has been updated to include a clinical version (Eisenmenger's syndrome, PH associated with systemic-to-pulmonary shunt, PH associated with small defects and PH after shunt repair) and an anatomical-pathophysiological version (Table 2) to better define each patient.

It remains difficult to classify pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis in group 1, because they share some characteristics with IPAH, but also present some differences. Finally, it was decided to include them in a different, but not entirely separate, category to that of PAH, and thus have been denominated as clinical group 1'.

TABLE 1. **Updated Classification of Pulmonary Hypertension[1]**

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK-1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3. Unknown
   1.3. Induced by drugs and toxins
   1.4. Associated with PAH
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5. Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns
   3.4. Sleep-related breathing disorder
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitudes
   3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear or multifactorial mechanisms
   5.1. Hematologic disorders: Myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic kidney failure on dialysis

ALK-1 indicates activin receptor-like kinase 1 gene; BMPR2, bone morphogenetic protein receptor, type 2; PAH, pulmonary artery hypertension; HIV, human immunodeficiency virus.

PATHOBIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension is clinically defined as a group of diseases characterized by a gradual increase in pulmonary vascular resistance leading to right ventricular failure and early death.[5] Prognosis is related to complex pathophysiological interactions between the progression (or regression) rate of the obstructive changes in pulmonary microcirculation and the response of the overloaded right ventricle (RV). The known main prognostic factors in this disease are derived from right ventricular function (hemodynamic, clinical and biochemical). The increase in afterload remains the main determinant of heart failure in patients with PAH and CTEPH, because its elimination as an outcome of lung transplantation or pulmonary

TABLE 2. **Anatomical-pathophysiological Classification of Systemic-to-Pulmonary Shunts Associated With Pulmonary Hypertension[1]**

1. Type
   1.1. Simple pre-tricuspid shunts
      1.1.1. Atrial septal defect
         1.1.1.1. Ostium secundum
         1.1.1.2. Sinus Venosus
         1.1.1.3. Ostium primum
      1.1.2. Total or partial unobstructed anomalous pulmonary venous return
   1.2. Simple post-tricuspid shunts
      1.2.1. Ventricular septal defect
      1.2.2. Patent ductus arteriosus
   1.3. Combined shunts. Describe the combination and define the predominant defect
   1.4. Complex congenital heart disease
      1.4.1. Complete atrioventricular septal defect
      1.4.2. Truncus arteriosus
      1.4.3. Single ventricle physiology with unobstructed pulmonary blood flow
      1.4.4. Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
      1.4.5. Other
2. Dimension (specify for each defect if there is more than one congenital heart disease)
   2.1. Hemodynamic (specify Qp/Qs)
      2.1.1. Restrictive
      2.1.2. Non-restrictive
   2.2. Anatomical
      2.2.1. Small to moderate (ASD<2 cm and VSD<1 cm)
      2.2.2. Large (ASD>2 cm and VSD>1 cm)
3. Direction of shunt
   3.1. Predominantly systemic-to-pulmonary
   3.2. Predominantly pulmonary-to-systemic
   3.3. Bidirectional
4. Associated cardiac and extracardiac abnormalities
5. Degree of repair
   5.1. Unoperated
   5.2. Palliated (specify types of operations; age at the time of surgery)
   5.3. Repaired (specify types of operations; age at the time of surgery)

SD indicates atrial septal defect; QP/QS, ratio of pulmonary (QP) to systemic (QS) flow in adult patients; VSD, ventricular septal defect

endarterectomy almost invariably leads to rapid recovery of RV function.

The pathophysiological basis of the increase in pulmonary vascular resistance is hypertensive vascular disease in small arteries and pulmonary arterioles. Multiple cellular and molecular factors are involved in its development that lead to remodelling of the vessel wall via 4 basic mechanisms: vasoconstriction, cell proliferation, thrombosis, and immune factors. Its origin is unknown, but a genetic predisposition facilitated and triggered by factors that lead to disease onset[6] has been suggested (Figure 1).

The different molecular mediators involved in the development of the disease, their main mechanism of action, and cell type involved are summarized in Table 3. The final outcome is a predominance of the mediators that lead to vasoconstriction, cell proliferation, and vascular thrombosis versus those which perform the opposite function. Knowledge of these mediators is not only important to understanding the natural history of the disease, but also because they are the target of different current treatments as well as being a research focus.

Genetics of Pulmonary Arterial Hypertension

Recently,[7] significant progress has been made in this field, especially in the study of *BMPR2* (bone morphogenetic protein receptor 2), *ALK-1* (activin receptor-like kinase 1) and *5-HTT* (endoglin associated with hereditary hemorrhagic telangiectasia and the serotonin transporter gene), whose LL polymorphism (2 long alleles) seems to be more common in patients with PAH than in controls.

The BMPR2 Gene

This gene codes for a membrane receptor belonging to the transforming growth factor β (TGF-β) receptor family. It is expressed in pulmonary endothelium, smooth muscle cells, and macrophages, and regulates multiple cell functions: proliferation, migration, differentiation, and apoptosis. Its mutation gives rise to haploinsufficiency, that is, low amounts of the receptor, which leads to increased cellular proliferation and the inhibition of cell apoptosis. The gene is located on the long arm of chromosome 2 (2q31,32), it has 13 exons, and up to 298 different point mutations have been described.[2]

In familial PAH, currently classified as heritable, mutations have been described in up to in 70% of cases, with autosomal dominant inheritance. Penetrance is incomplete and only 20% of these carriers will contract the disease. Another feature is the phenomenon of genetic anticipation, that is, subsequent generations will develop the disease at younger ages. Mutations have been described in approximately 20% of cases with idiopathic PAH, in 18% with anorexigen-associated PAH, and in 6% in PAH associated with congenital heart disease. In small series of cases of PAH associated with collagenosis, human immunodeficiency virus (HIV), and toxic oil syndrome, no mutations were found on the *BMPR2* gene.[7-9]

Patients carrying the mutated gene differ in some respects from those who do not carry it: the disease appears at a younger age, they have a poorer hemodynamic profile and are less likely to

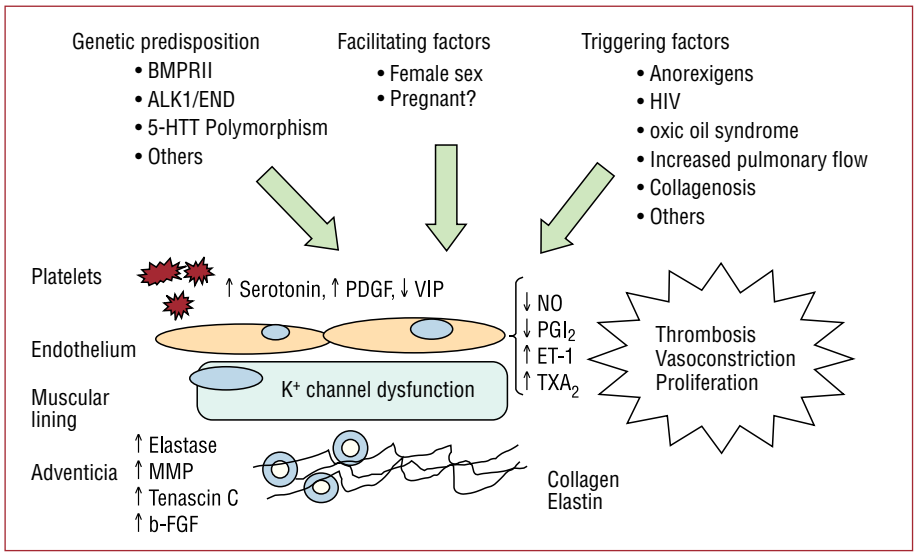

Figure 1. Pathobiological mechanisms in the development of pulmonary arterial hypertension. ALK1 indicates activin-receptor-like kinase-1; BMPR2, bone morphogenetic protein receptor 2; ENG, endoglin; ET-1, endothelin 1; b-FGF, basic fibroblast-derived growth factor; 5-HTT, serotonin transporter gene; MMP, metalloproteinases; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI2, prostacyclin; TXA2, thromboxane A2; HIV, human immunodeficiency virus; VIP, vasoactive intestinal peptide.

TABLE 3. **Main Vascular Mediators Involved in the Development of Pulmonary Arterial Hypertension and Their Effect on Pulmonary Hypertension**

Main Cell Type Affected[a]	Mediator and Change in its Activity in PAH	Vasoconstriction	Cell Proliferation	Thrombosis
Vascular space/blood platelets	↑ serotonin	↑	↑	↑
	VIP ↓	↑	↑	↑
Vascular endothelium	↓ nitric oxide	↑	NS	↑
	Prostacyclin ↓	↑	↑	↑
	Thromboxane A_2 ↑	↑	↑	↑
	Endothelin-1 ↑	↑	↑	↑
	VEGF/PDGF/EGF ↑	NS	↑	NS
Vascular smooth muscle	Rho-kinase pathway ↑	↑	↑	↑
	Angiopoietin 1 ↑	NS	↑	NS
	Kv channels ↓	↑	↑	NS
Extracellular matrix	Vascular elastance ↑	↑	↑	↑
	Tenascin-C ↑	NS	↑	NS
Inflammatory system	5 lipoxygenase ↑ (↑ IL-1b, IL-6, fractalkine RANTES, monocyte chemotactic protein-1β)	↑	↑	↑

EGF indicates epidermal growth factor; Kv, voltage-dependent potassium channels; NS, nonsignificant effect; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide.
[a]Cell type that produces the vascular mediator or the sites of its main activity.
[b]Increased interleukins in patients with pulmonary arterial hypertension. Adapted from Chan et al.[6]

respond to an acute vasodilator test; however, there are no differences in survival rates and clinical manifestations at diagnosis.[10]

EPIDEMIOLOGY OF PULMONARY HYPERTENSION

Currently, there are no comparative epidemiological data on the prevalence of the different groups of PH. In an echocardiographic study,[11] the prevalence of PH (defined by systolic PAP>40 mmHg) in 4579 patients was 10.5%. Of the 483 patients with PH, 78.7% had left heart disease (group 2), 9.7% had lung disease and hypoxemia (group 3), 4.2% had PAH (group 1), and 0.6% had CTEPH (group 4); it was not possible reach a diagnosis in the remaining 6.8%.

Group 1

Four national registries[12-15] were recently conducted and described the epidemiology of PAH.

The lowest estimated prevalence of PAH and IPAH is 15 cases/million and 5.6 cases/million, respectively, and the highest is 26 cases/million and 9 cases/million, respectively. The lowest estimated incidence of PAH was 2.4 cases/million/y and the highest was 7.6 cases/million/y. The proportion of women to men was around 2:1, and mean age at diagnosis was approximately 50 years, with an increasing number of patients older than 70 years (10%-17% according to the registries). In the Spanish Registry of Pulmonary Hypertension (Registro Español de Hipertensión Pulmonar; REHAP),[15] 34% of the patients had IPAH and 3% had a family history of PAH. In the associated PAH subgroup, 16% had connective tissue disease (especially systemic sclerosis), 17.5% had congenital heart disease, 6.4% had portal hypertension, and 5.9% had HIV infection.

It is believed that PAH is much more prevalent in emerging countries,[16] where relatively common diseases such as schistosomiasis, sickle-cell anemia, HIV infection and congenital heart disease may be complicated by PAH.

Group 2

Pulmonary hypertension associated with left heart disease is the most frequent cause of PH. Heart failure is a serious and common disease in western countries and its incidence in people older than 65 years is approximately 10/1000 population/y.[17] In 44% of the patients, left ventricular ejection fraction (LVEF) is normal, heart failure is caused by diastolic dysfunction, and is accompanied by PH in up to 83% of the patients, according to a recently published population study.[18] In 45% of the patients, heart failure is caused by systolic dysfunction and is accompanied by PH in 60% of the patients.

Group 3

Pulmonary hypertension due to lung disease or hypoxemia. In advanced chronic obstructive pulmonary disease, PH is highly prevalent (>50%), although in general it is only of moderate severity.[19] The prevalence of PH is 32%-39% in interstitial lung disease. Combined pulmonary fibrosis and emphysema is associated with a higher prevalence of PH.[20]

Group 4

The incidence of CTEPH after pulmonary embolism remains uncertain, although most experts believe that it is 0.5%-2%.[1,19] In approximately 40%-50% of the patients with CTEPH there is no clinical event compatible with deep venous thrombosis or pulmonary embolism.

The only population registry that includes CTEPH is REHAP.[15] This registry reports an incidence of 0.9 cases/million/y and a prevalence 3.2 cases/million. Of the patients with PH included in this registry, 15% had CTEPH.

DIAGNOSIS OF PULMONARY HYPERTENSION

Diagnosis is a step-wise process that begins with suspected PH, followed by confirmation of the diagnosis,[21] identification of the specific etiology (IPAH should be considered a diagnosis by exclusion) and finally assessment of severity (using clinical, echocardiographic, and hemodynamic parameters, biomarkers and exercise capacity), a key aspect in the choice of treatment and follow-up.

The diagnostic algorithm (Figure 2) begins by identifying the more common clinical groups of PH[1] (group 2, left heart disease; group 3, lung disease), then distinguishes group 4 (CTEPH) and finally makes the diagnosis and recognizes the different types in group 1 (PAH) and group 5 (miscellaneous).

Clinical suspicion of PH is based on symptoms, the presence of risk factors, the findings of physical examination and the results of simple examinations such as chest radiograph and ECG. If the initial assessment confirms the suspicion of PH, transthoracic echocardiogram, pulmonary function tests and high-resolution computed tomography (CT) of the chest are performed to identify lung disease (group 3) or left heart disease (group 2). If there is no evidence of heart or respiratory disease or PH seems "disproportional" to the severity of the underlying disease, a ventilation/perfusion lung scan (V/Q) is recommended. If the V/Q lung scan shows multiple segmental perfusion defects, CTEPH should be suspected. The final diagnosis of CTEPH requires CT pulmonary angiography, RHC, and selective pulmonary angiography. If this possibility is ruled out, and once PH is confirmed by RHC, the different types of PAH are investigated.

Some aspects relevant to diagnosis are described in the following sections.

Clinical Presentation

The initial symptom is progressive effort dyspnea. When RV dysfunction progresses, angina or effort syncope may appear due to the inability of the RV to adapt cardiac output to exercise; these symptoms occur at rest only in advanced phases. In populations at risk[1-4] of PAH (congenital heart disease, history of pulmonary embolism, connective tissue disease [CTD], HIV

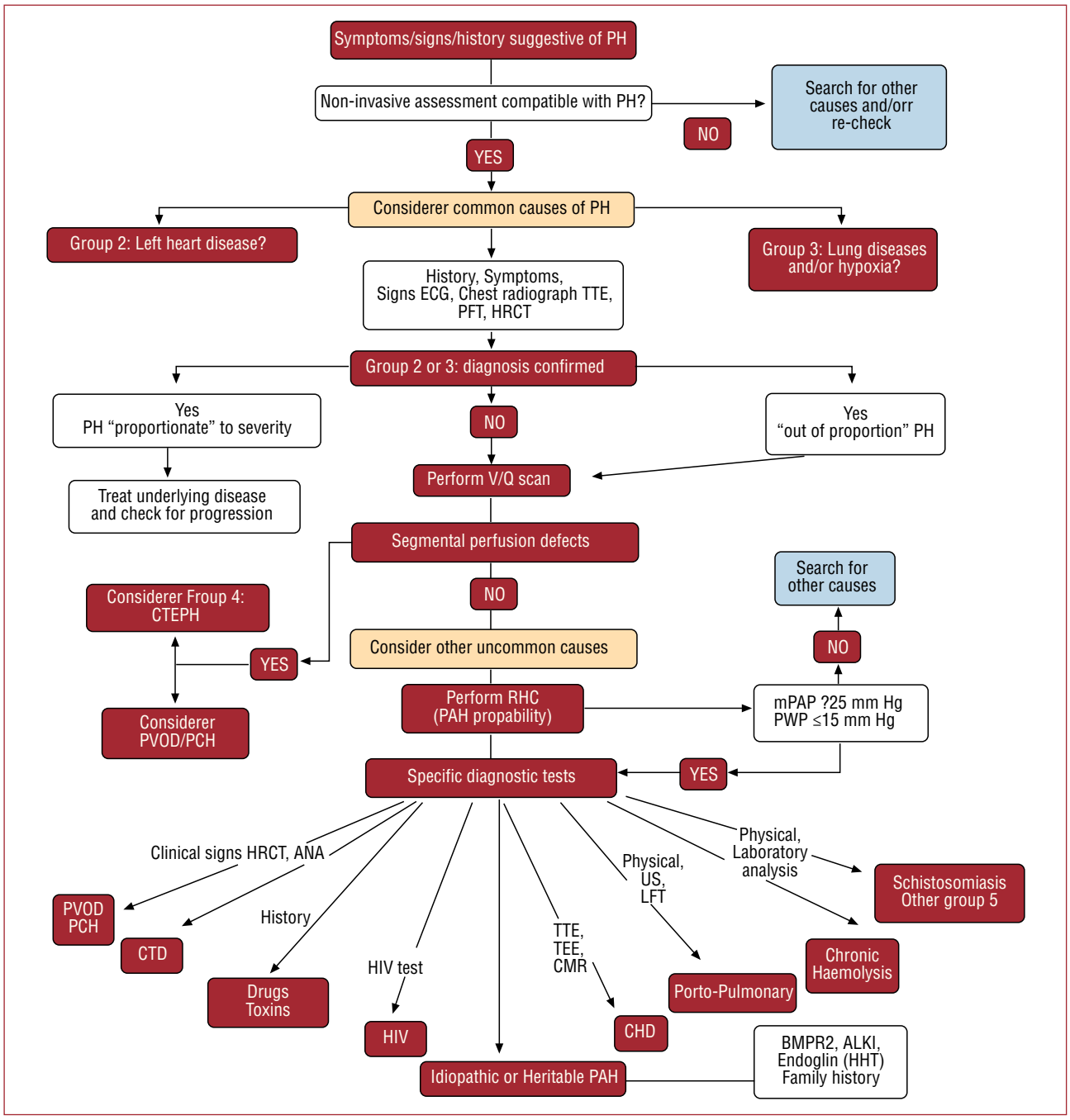

Figure 2. Diagnostic algorithm of pulmonary hypertension. ANA indicates antinuclear antibodies; RHC, right heart catheterization; TTE, transthoracic echocardiography; TEE, transesophageal echocardiogram; PVOD, pulmonary veno-occlusive disease; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PAPm, mean pulmonary arterial pressure; PWP, pulmonary wedge pressure; PFT, pulmonary function test; MRI, magnetic resonance imaging; HRCT, high-resolution computed tomography; V/Q, ventilation/perfusion; HIV, human immunodeficiency virus. Adapted from Galiè N, et al.[1] x by permission of the author, publishers and the European Society of Cardiology.

and exposure to toxic substances associated with PH), the presentation of these symptoms requires confirmation by echocardiogram. In the absence of symptoms an echocardiogram be conducted only in patients with scleroderma, liver transplant candidates, and in the relatives of patients with heritable PAH.

Transthoracic Echocardiography

This should be performed whenever PH is suspected. It provides an estimate of pulmonary artery systolic pressure (PSP), left ventricular systolic and diastolic function and valve disease and detects systemic-to-pulmonary shunt (with the use of agitated saline).

The calculation of PSP is based on the simplified Bernoulli equation, in which PSP = 4 × (maximum tricuspid regurgitation velocity)^2 + right atrial pressure (RAP). The RAP can be calculated using the diameter and the respiratory variation of the inferior vena cava, although a fixed value of 5 mmHg or 10 mmHg is often assumed. When it is difficult to measure peak tricuspid regurgitation velocity, the use of intravenous agitated saline is recommended as this significantly improves the Doppler ultrasound signal.

In general, the correlation between PSP estimated by echocardiogram and by RHC is good (0.57-0.85). However, when PSP is determined by echocardiography the hemodynamic value can be overestimated by >10 mmHg in up to 48% of patients, especially if the Doppler ultrasound recording is of poor quality.[22] Furthermore, tricuspid regurgitation is found in approximately 80% of patients with PSP >35 mmHg and the ability to analyze flow varies according to the underlying disease. Thus, in a study of 374 patients with pulmonary disease, a recording of sufficient quality to estimate PSP was only obtained in 44%.[23]

The PSP values vary according to the age and weight of the patient.[24] Thus, PSP >40 mmHg is found in 6% of individuals older than 50 years and in 5% of those with a body mass index of 30.

In view of this, PH cannot be accurately characterized using a PSP cut-off point based on Doppler ultrasound.

Other echocardiographic variables should always be considered in patients with suspected PH[1]: right heart chamber dilatation (inferior vena cava, right atrium [RA], RV and pulmonary artery), the flattening or inversion of the interventricular septum toward the LV, midsystolic collapse and a pulmonary flow acceleration time <80 ms increase the likelihood of the patient having significant PH.

Table 4 and Table 5 show the probability of a diagnosis of PAH based on echocardiographic criteria, symptoms, and risk factors, according to the current European clinical practice guidelines.[1]

If systemic-to-pulmonary shunt is detected during diagnostic study with agitated saline or PAH is suspected on the basis of clinical findings, a transesophageal echocardiogram is recommended to confirm the diagnosis. Complementary imaging techniques, such as magnetic resonance imaging, may be required in some cases especially if the systemic-to-pulmonary shunt is extracardiac or in complex congenital heart disease.[25]

If diastolic dysfunction is suspected as the origin of PH with preserved LV systolic function in the echocardiographic study, a complete study of diastolic function[26] of mitral valve flow, mitral annular flow and pulmonary vein flow by pulsed and tissue Doppler imaging is recommended. Similarly, the presence of left atrial dilatation and the degree of LV hypertrophy should be assessed.

Ventilation/Perfusion Lung Scan

This is the method of choice to exclude CTEPH during the systematic study of patients with PH. A normal- or low-probability V/Q scan[1,25] effectively excludes CTEPH with a sensitivity between 90% and 100% and a specificity between 94% and 100%.

TABLE 4. **Echocardiographic Criteria for Assessing the Probability of a Diagnosis of Pulmonary Hypertension**

	Class[a]	Level[b]
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, without additional echocardiographic variables indicative of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, but with additional echocardiographic variables indicative of PH	IIa	C
Tricuspid regurgitation velocity 2.9-3.4 m/s, PA systolic pressure 37-50 mmHg with/without additional echocardiographic variables indicative of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure >50 mmHg, with/without additional echocardiographic variables indicates of PH	I	B
Exercise Doppler echocardiography is not recommended for screening PH	III	

[a]Class of recommendation.
[b]Level of evidence.
Estimated right atrial pressure of 5 mmHg. Additional echocardiographic variables indicative of a diagnosis of pulmonary hypertension.
Adapted from Galiè et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2009;30:2493-537, by permission of the author, publishers, and the European Society of Cardiology."

TABLE 5. **Probability of a Diagnosis of Pulmonary Arterial Hypertension and Recommended Management According to Echocardiogram, Clinical Information and Risk Profile**

	Class[a]	Level[b]
Low probability of PAH		
Echocardiographic diagnosis of "PH unlikely," without symptoms: an additional work-up is not recommended	I	C
Echocardiographic diagnosis of "PH unlikely," with symptoms and concomitant disease or risk factors for group 1 (PAH): echocardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of "PH unlikely," with symptoms and absence of associated disease or risk factors for group 1 (PAH): assessment of other causes of the symptoms is recommended	I	C
Intermediate probability of PAH		
Echocardiographic diagnosis of "PH possible," without symptoms and absence of disease or risk factors for group 1 (PAH): echocardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of "PH possible," with symptoms and concomitant disease or risk factors for group 1 (PAH): RHC may be considered	IIb	C
Echocardiographic diagnosis of "possible PH," with symptoms and without associated disease or risk factors for group 1 (PAH): an alternative diagnosis and echocardiographic follow-up may be considered. If the symptoms are at least moderate, RHC may be considered	IIb	C
High probability of PAH		
Echocardiographic diagnosis of "PH likely," with symptoms and presence/absence of associated disease or risk factors for group 1 (PAH): RHC should be considered	I	C
Echocardiographic diagnosis of 'PH likely', without symptoms and presence/absence of associated disease or risk factors for group 1 (PAH): RHC should be considered	IIa	C

CPH indicates pulmonary hypertension; RHC, right heart catheterization.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from Galiè et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2009;30:2493-537, by permission of the author, publishers, and the European Society of Cardiology."

High-Resolution Computed Tomography

This is recommended at the time of initial diagnosis of patients with PH.[1] Computed tomography provides detailed images of lung parenchyma and facilitates accurate diagnosis of the interstitial lung disease (ILD) and emphysema. In patients with PAH associated with CTD and who present significant evidence of ILD, CT assesses the extent of the vascular disease and the possible fibrosis associated with the immune disease.

Computed tomography is essential when there is clinical suspicion of pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.[27] Centrilobular ground-glass opacities (diffuse centrilobular nodular opacity), subplural thickened septal lines and mediastinal lymphadenopathies are characteristic of PVOD.

Spiral CT Angiography (CT Pulmonary Angiogram)

This should be conducted in patients in whom V/Q scan is suggestive of CTEPH.

Right Heart Catheterization

Right heart catheterization is required to diagnose PAH, assess the severity of hemodynamic deterioration, and analyze the vasoreactivity of the pulmonary circulation.[1,4,28] Right heart catheterization procedures have low rates of morbidity (1.1%) and mortality (0.055%) when conducted in specialized centers.

The following variables should be recorded: PAP test (systolic, diastolic and average), right atrial pressure, pulmonary wedge pressure (PWP), and RV pressure. If possible, cardiac output should be measured in triplicate by thermodilution or by the Fick method (this is obligatory when systemic-to-pulmonary shunt is present). Similarly, superior vena cava, pulmonary artery, and systemic arterial blood oxygen saturations and pulmonary vascular resistance should be measured.

Care is needed when determining PWP, since a value <15 mmHg is required to establish the diagnosis of PAH. However, the PWP measurement method is not standardized and this has led to wide inter-observer variability.[29] Some groups conduct measurements at the end of expiration, others take measurements during an apneic pause, and yet others rely on automatic measurements provided by software programs. Intrathoracic pressures have almost no effect on intracardiac pressures at the end of expiration, and this is the correct moment to measure PWP. In addition, the catheter should be correctly positioned to guarantee

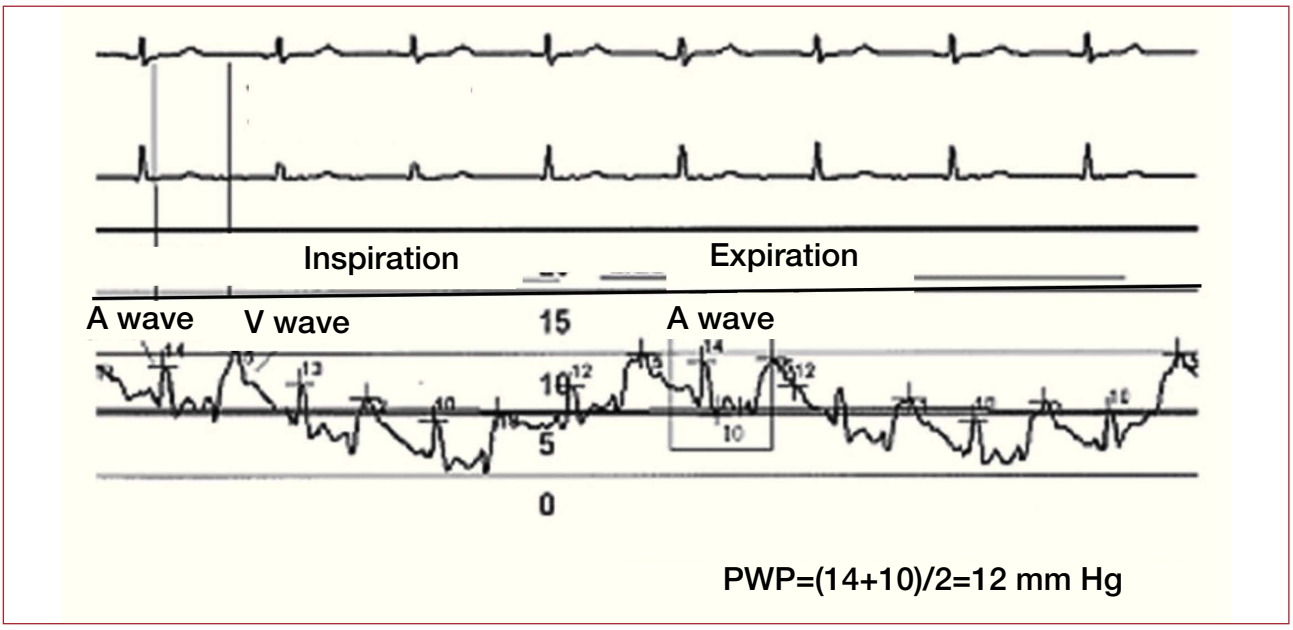

Figure 3. Pulmonary wedge pressure (PWP) tracing showing respiratory variations and the temporal relationship of the A and V waves on ECG.

good transmission of left atrial pressure through the pulmonary capillary bed. The A and V waves should be examined to ensure that they are clearly differentiated, and oximetry performed at the distal end of the catheter to confirm correct positioning (the O_2 saturation data obtained is similar to that of arterial O_2 saturation). Occasionally, the catheter should be advanced to a more distal position in the pulmonary vessel to obtain a better tracing.

The A wave is produced at the time of atrial contraction. Retrograde transmission of the wave can be observed on the PWP tracing and appears delayed at the end of QRS or immediately after this (Figure 3) in the ECG. The maximum and minimum A wave values are measured just before inspiration, and the PWP is the average of these values. The V wave is produced when blood fills the atrium and the mitral valve is closed. This is observed in the PWP recording after the T wave in the ECG. A very prominent V wave can hinder the accurate measurement of PWP and tends to appear due to severe mitral regurgitation or severe alterations in LV distensibility.

Given the steady increase in the age of patients with PH and the great number of comorbidities considered as typical risk factors of diastolic LV dysfunction, the reliable differential diagnosis of PAH and PHLHD has become increasingly important and complex, despite good techniques for measuring PEP.[19,21] Thus, the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL),[14] is being conducted in the USA. It included 2525 patients (mean age, 53 [14] years) with PAH (PWP<15 mmHg). Of these, 40% had systemic hypertension; 33%, obesity; 21%, sleep apnea; 12%, diabetes mellitus; and 4.5%, kidney failure. Patients were older than in previous registries and had a high number of risk factors for diastolic heart failure.

A hemodynamic study was recently conducted in 3920 patients with PH,[30] and analyzed the reliability of PWP to distinguish PAH and PHLHD compared to LV end-diastolic pressure (the gold standard of LV preload). Approximately half of the patients classified as having PAH based on PWP <15 mmHg, actually have PHLHD when based on the criterion of an LV end-diastolic pressure <15 mmHg. Thus, if the patient presents a clinical profile compatible with PHLHD[19] (Table 6), a direct measurement of LV end-diastolic pressure is recommended to confirm the diagnosis of PAH if PWP is <15 mmHg.

In some patients with high clinical suspicion of PHLHD who have received diuretics, low PWP and LV end-diastolic pressure values may be observed. To confirm the diagnosis of PAH, RHC with volume or exercise challenge is recommended.[1,5] These procedures have not been standardized and each cardiac catheterization laboratory has its own protocol. Catheterization with volume challenge is simpler and basically consists in the perfusion of 1000 ml of physiological saline solution over 20 min, taking measurements every 250 ml. Challenge is interrupted when PWP is >18 mmHg or symptoms appear.

TABLE 6. **Factors Indicative of Pulmonary Hypertension Associated With Left Heart Disease**

Clinical characteristics	Age >65 y
	Elevated systolic blood pressure
	Elevated pulse pressure
	Obesity
	Metabolic syndrome
	Hypertension
	Coronary artery disease
	Diabetes mellitus
	Atrial fibrillation
Echocardiography	Left atrial enlargement
	Left ventricular hypertrophy
	Presence of echocardiographic indicators of elevated left ventricular filling pressure
Interim assessment	Symptomatic response to diuretics
	Exaggerated increase in systolic blood pressure during exercise
	Reevaluation of chest radiograph compatible with heart failure

Pulmonary Vasoreactivity Testing

This should be conducted at the time of diagnosis to identify patients who may benefit from treatment with calcium channel blockers. The test should be conducted with short-acting, safe and easy to administer drugs that have few or no systemic effects. Currently, the most commonly used agent is nitric oxide; although there is wide experience with intravenous epoprostenol and intravenous adenosine, these have an increased risk of causing systemic vasodilator effects.

A positive acute response[1,4,28] (positive acute responder) is defined as a reduction in mean PAP>10 mmHg to reach an absolute value of mean PAP<40 mmHg with unchanged or increased cardiac output. Only 10% of patients with IPAH will fulfill these criteria. Only 50% of IPAH-positive acute responders are positive responders to long-term treatment with calcium channel blockers, with almost complete normalization of pulmonary pressures in the control RHC.

The usefulness of vasoreactivity testing in patients with heritable PAH, CTD or HIV is not as clear. Nevertheless, current recommendations are to perform the test and seek a long-term response to calcium channel blockers in those in whom the test is positive.

EVALUATION OF PULMONARY ARTERY HYPERTENSION PROGNOSIS

The severity of PAH is evaluated in patients after the diagnostic process and before therapeutic decision-making. The clinical assessment of the patient plays a key role in the choice of initial treatment, the evaluation of the response, and the possible intensification of therapy, if required.

The prognostic factors[31] used in PAH are based on patient cohorts and may not accurately reflect the prognosis of each individual. Scientific evidence is insufficient to be able to establish the optimal values the different parameters should reach or the relative importance of each one. Table 7 summarizes the most frequently used prognostic factors[1,4,21,28] and proposes optimal values for each parameter as an initial framework, although each pulmonary hypertension center should adapt this according to their experience and the availability of the different tests.

Clinical Profile

Age, comorbidities, and the etiology of PAH, together with the presence of heart failure and speed of progression, define how aggressive the disease is. Hemoptysis and atrial arrhythmias (fibrillation and atrial flutter) are typical of severe PAH and indicate poor prognosis.

Exercise Capacity

This is one of the most robust and classic parameters.[32] The 6-minute walking test (6MWT) is the standard test, but with increasing numbers of patients in functional class II and with a 6MWT of >400 m, better tools are needed to assess changes in exercise capacity. Cardiopulmonary exercise testing is the method of choice. Information on the prognostic value of cardiopulmonary exercise testing remains limited, but is a field expected to yield important developments in the very near future.[33]

TABLE 7. **Main Prognostic Factors in Patients With Pulmonary Arterial Hypertension**

Good Prognosis	Determinants of Prognosis	Poor Prognosis
No	Clinical evidence of heart failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)a	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardiopulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or almost normal	BNP/NT-proBNP plasma concentrations	Very elevated and increasing
No pericardial effusion	Echocardiographic findings[b]	Pericardial effusion
TAPSE[b] >2 cm		TAPSEb <1.5 cm
RAP <8 mmHg and CI >2.5 L/min/m^2	Hemodynamics	RAP >15 mmHg or CI <2 L/min/m^2

BNP indicates brain natriuretic peptide; CI, cardiac index; RAP, right arterial pressure; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class; 6MWT, 6-minute walking test.
[a]Depending on age.
[b]TAPSE and pericardial effusion have been selected because they can be measured in most patients. Adapted from McLaughlin et al.[31]

Biomarkers

N-terminal prohormone brain natriuretic peptide and brain natriuretic peptide are the most widely used biomarkers, and are considered excellent markers of the severity of RV dysfunction. Their concentrations increase when there is progressive deterioration of exercise capacity or functional class, and decrease when there is a positive response to treatment.[34]

Right Ventricle Function

Right ventricular function is the main determinant of prognosis in patients with PAH.[35] The echocardiogram is a simple and readily available tool to study the following: right chamber dilatation, LV diastolic eccentricity index, tricuspid annular plane systolic excursion,[36] TEI index (a combined myocardial performance index) and the presence of pericardial effusion which aid in assessing RV adaptation to pulmonary hypertension. It should be pointed out that estimated pulmonary systolic pressure provides null prognostic information on follow-up of these patients. Magnetic resonance imaging[25] provides a better assessment of RV function: volume, degree of hypertrophy and ejection fraction. The use of this technique for prognostic stratification of patients with PAH is still in its initial phases, but is of undoubted potential. Finally, RV hemodynamic parameters have been widely used[1,4,28] and have a clear role in the assessment of PAH severity and prognosis.

CLINICAL PATHWAY OF THE PATIENT WITH PULMONARY HYPERTENSION

Pulmonary hypertension, especially PAH and CTEPH, is a serious clinical situation. Diagnosis is usually established in advanced phases of the disease and various specialists are involved in its clinical management. Similarly, since some of the diagnostic and therapeutic procedures used are highly complex and require experienced professionals to perform them, it is recommended that patients with PAH or CTEPH should be referred to specialized centers.[1,4,28] Thus, a clinical pathway is needed to improve patient management.

Typically, suspicion of PH is diagnosed by specialists in the center nearest to the patient (local hospital). If the initial examinations lead to suspicion of PAH, CTEPH, or PH of multifactorial origin, patients should be referred for RHC at a PH center (Table 8). Right heart catheterization is not recommended before referral, except by agreement with the referral center.[1,28] Patients with heart or respiratory disease with suspected out-of-proportion PH should also be referred to a PH center.

Patients with PH can deteriorate rapidly,[28] and so it is important to establish a short timeframe in which to complete the diagnostic study and begin treatment; flexible coordination between the local hospital and reference center is essential (Table 9).

If patients live a long way from the reference center, they should also be attended by a specialist, preferably with an interest in PH, from a nearby hospital that would act as local care unit, perform follow-up and provide immediate treatment in case of complications. In these circumstances, the patient should follow a care plan agreed between the local hospital and the reference center.

In general, the clinical course of PH is one of progressive deterioration with occasional episodes of decompensation. Clinical follow-up should be maintained until death occurs or transplantation is performed. In the advanced and irreversible phases of the disease, palliative care should be mutually agreed between the patient, family, local hospital and the reference center.

TABLE 8. **Indications for Referral to a Pulmonary Hypertension Referral Center**

Patients with suspicion of PAH or PH of multifactorial origin (group 5) who present the following findings on echocardiogram:
TRV >3.4 m/s
TRV 2.9-3.4 m/s with symptoms suggestive of PH, associated disease or risk factors
TRV ≤2.8 m/s, but with echocardiographic abnormalities compatible with PH and symptoms of PH, associated disease or risk factors
Patients with suspicion of CTEPH (center with experience in pulmonary endarterectomy)
Echocardiogram with TRV ≥2.9 m/s or abnormalities compatible with PH
Perfusion defects on pulmonary scintigraphy present after more than 3 months of anticoagulant therapy
Thrombotic lesions in pulmonary arteries present after more than 3 months of anticoagulant therapy
Patients with left heart disease or respiratory disease and suspicion of out-of-proportion PH
TRV >3.4 m/s
Symptoms not explicable by underlying disease

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; TRV, tricuspid regurgitation velocity.

Reference Centers

Recently, the Spanish Society of Pneumology and Thoracic Surgery and the Spanish Society of Cardiology, in a consensus document at the national level,[28] and the European Society of Cardiology and the European Respiratory Society[28] in their international clinical guidelines, made recommendations regarding the facilities and volume of activity of the referral center specialized in PH. These are summarized in Table 10.

TABLE 9. **Timing of Procedures**

From clinical suspicion of PAH or CTEPH to echocardiographic study	Less than 4 wk
From the time of referral to the reference center for right heart catheterization	Less than 6 wk
From catheterization to the beginning of treatment	Less than 15 d
Admission to reference center in case of severe complications	Less than 2 days

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.

In particular circumstances, patients with PH require highly specialized procedures that may not form part of the functions of the referral center. These situations arise specifically in CTEPH (pulmonary endarterectomy), congenital heart disease, hereditary PAH, portal hypertension, and lung or heart and lung transplantation. The referral center and the specialized centers should act in coordination and have preestablished referral protocols to offer appropriate care to these patient.

CONCLUSIONS

Recently, significant progress has been made in understanding the pathobiology, diagnosis, epidemiology, and prognosis of patients with PAH which has led to notable improvements in the quality and efficacy of clinical care, although a cure has yet to be discovered. Correct diagnosis and an estimate of prognosis using multifactorial approaches are key aspects of this process and require experience and technical training to achieve an optimal result. Thus, a care program and a clinical pathway is warranted for patients with PAH.

TABLE 10. **Requirements and Facilities of Pulmonary Hypertension Referral Centers**

	SEPAR/SEC Consensus Document	ESC/ERS Clinical Practice Guidelines
Staff	At least 2 specialists in pneumology or cardiology with an interest and experience in PH	Similar requirements
	At least 1 registered nurse specialized in PH	Similar requirements
	Coordination with other specialists involved in the diagnosis and treatment of PH	Radiologist and cardiologist with experience in PH imaging studies
	Administrative support staff	Access to psychological support and social workers
Volume of activity	At least 30 patients with PAH or CTEPH in active follow-up	At least 50 patients with PAH or CTEPH in active follow-up
	At least 5 new patients with PAH or CTEPH per year, followed up for 3 years or more	At least 24 new patients with PAH or CTEPH per year
		At least 20 vasoreactivity tests in PAH per year
Experience and quality of care	Experience with all specific drugs	Audit of results including survival
	Regular clinical review sessions	
	Standardized operating procedures for diagnosis and treatment	
	Assess indicators of outcome (survival)	
Facilities and resources available	Specialized respiratory and cardiology departments	Similar requirements
	ICU	
	Echocardiography	
	Cardiac hemodynamics	
	Pulmonary function laboratory	
	Cardiopulmonary stress testing	
	Sleep laboratory	
	CT and spiral-CT angiography	
	Nuclear medicine	
		Contact with other services possibly situated in other centers:
	Of interest:	
	Connective tissue disease	Similar requirements
	Pulmonary endarterectomy	Similar requirements
	Lung and/or heart-lung transplantation	Similar requirements
	Congenital heart disease	Similar requirements
	Heart surgery and thoracic surgery	
	Liver transplantation/liver hemodynamics	Family planning service
	Pulmonary angiography	Genetics service
	HIV unit	
Facilities	Specialized outpatient visit	Similar requirements
	Cardiac catheterization with vasoreactivity testing	Similar requirements
	Access to all drugs specific to PAH	Similar requirements
	24-h coverage	Similar requirements
Information system	Database designed for the assessment of actions taken and their results	Outcomes auditing program
Research activity	Research projects conducted at the center, participation in clinical trials and in registries	Participation in multicenter phase II/III clinical trials
Teaching activity		Regular continuous education for all healthcare professionals
Links to patients		Links to patient associations

CT indicates computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; HIV, human immunodeficiency virus; ICU, intensive care unit; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SEPAR/SEC, Spanish Society of Pneumology and Thoracic Surgery/Spanish Society of Cardiology.

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