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EDITORIAL

Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed

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The growing interest in pulmonary hypertension (PH) in many medical specialties including cardiology, rheumatology and respiratory medicine, is possibly due to the recent availability of specific drugs approved for a group of rare conditions defined as pulmonary arterial hypertension (PAH). The terms ''pulmonary hypertension'' and ''pulmonary arterial hypertension'' appear to be quite similar, and this has led to confusion and ambiguity in both common clinical practice and the medical literature [1]. It is, therefore, important to clarify the different definitions of PH, the relationship between the haemodynamic measurement and the echocardiographic estimate, and the additional diagnostic methods required for the final clinical diagnosis. In addition, it is relevant to highlight the significant role of right heart catheterisation in the diagnostic algorithm of a patient with PH.

PH IS A HAEMODYNAMIC AND PATHOPHYSIOLOGICAL CONDITION

PH cannot be considered to be a specific ''disease''. PH has been defined as an increase in mean pulmonary arterial pressure ($\bar{P}$pa) $\geqslant$25 mmHg at rest, as assessed by right heart catheterisation [2–5]. Recent re-evaluation of the available data has shown that the normal $\bar{P}$pa $\pm$ SD at rest is 14 $\pm$ 3 mmHg with an upper limit of normal of ~20 mmHg [6, 7]. The significance of $\bar{P}$pa 21–24 mmHg is unclear. Patients presenting with $\bar{P}$pa in this range need further evaluation in epidemiological studies. The definition of PH on exercise as a $\bar{P}$pa >30 mmHg, as assessed by right heart catheterisation, is not supported by published data and healthy individuals can reach much higher values [6, 8]. Therefore, no definition for PH on exercise as assessed by right heart catheterisation can be provided at the present time. An additional, very important haemodynamic parameter that characterises the definitions of PH is pulmonary capillary wedge pressure (Ppcw). In fact, according to various combinations of values of Ppcw, pulmonary vascular resistance (PVR) and cardiac output, different haemodynamic types of PH can be identified and are shown in table 1. The distinction between pre-capillary (normal Ppcw) and post-capillary (elevated Ppcw) PH [9] is extremely important because the treatment strategy may differ markedly between the two haemodynamic conditions, and therapies effective in the pre-capillary form may be detrimental in the post-capillary type and *vice versa*.

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DOPPLER ECHOCARDIOGRAPHY CAN PROVIDE AN ESTIMATE OF THE LIKELIHOOD OF PH

Doppler echocardiography is not able to measure pulmonary arterial pressure (Ppa) but it provides an estimate of it by the use of the Bernoulli continuity equation and the tricuspid regurgitation velocity, which includes multiple theoretical assumptions. Even if a statistically significant correlation exists between the echocardiographic estimate and the haemodynamic assessment of Ppa, the large confidence intervals may prevent a reliable comparison in the individual patient [10]. Accordingly, the evaluation of PH by Doppler echocardiography may expose to risks of both false-negative and, in particular, false-positive diagnosis [11–13]. Whenever the exact measure of Ppa is considered relevant, right heart catheterisation should be performed. Right heart catheterisation is also able to provide a reliable assessment of Ppcw, which allows the precise identification of the haemodynamic type of pulmonary hypertension. The recent guidelines on PH from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [4, 5] have proposed arbitrary criteria for estimating the likelihood of PH based on the tricuspid regurgitation peak velocity, the correspondent Doppler-calculated systolic Ppa at rest and on additional echocardiographic parameters that might raise or reinforce the suspicion of PH (table 2). The criteria are derived both from existing data [12, 13] and expert opinion and appropriate prospective validation is required.

Other echocardiographic variables that might raise or reinforce suspicion of PH independently of tricuspid regurgitation velocity include an increased velocity of pulmonary valve regurgitation and a short acceleration time of right ventricle ejection into the pulmonary artery. Increased dimensions of right heart chambers, abnormal shape and function of interventricular septum, increased right ventricle wall thickness and dilated main pulmonary artery are also suggestive of PH, but tend to occur later in the course of the disease.

PH CAN BE FOUND IN AT LEAST 37 SYNDROMES CLASSIFIED INTO SIX CLINICAL GROUPS

The heterogeneity of clinical conditions with PH (table 3) is definitely greater than that of the haemodynamic variety of PH (table 1). In the updated clinical classification of PH (table 3) [14], 37 clinical conditions with PH are classified into six groups according to pathological, pathophysiological and therapeutic characteristics: PAH (group 1), pulmonary veno-occlusive disease (group 1′), PH due to left heart disease (group 2), PH due to lung diseases (group 3), chronic thromboembolic PH (CTEPH; group 4) and PH with unclear and/or multifactorial

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

Definition	Characteristics	Clinical group(s)#
PH	$\bar{P}_{pa}$ ⩾25 mmHg	All
Pre-capillary PH	$\bar{P}_{pa}$ ⩾25 mmHg P_{pcw} ⩽15 mmHg CO normal or reduced¶	1. PAH 3. PH due to lung diseases 4. CTEPH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	$\bar{P}_{pa}$ ⩾25 mmHg P_{pcw} >15 mmHg CO normal or reduced¶	2. PH due to left heart disease
Passive	TPG ⩽12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

All values measured at rest. $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; TPG: transpulmonary pressure gradient ($\bar{P}_{pa}$ – mean P_{pcw}); PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic PH. #: according to table 3; ¶: high CO can be present in cases of hyperkinetic conditions, such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia and hyperthyroidism, *etc.*

mechanisms (group 5). Despite possible comparable elevations of P_{pa} and PVR in the different clinical groups, the underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different. Comparative epidemiological data on the prevalence of the different groups of PH are not available. In a survey performed in an echocardiography laboratory [15], the prevalence of PH (defined as a pulmonary artery (PA) systolic pressure >40 mmHg) among 4,579 patients was 10.5%. Among the 483 cases with PH, 78.7% had left heart disease (group 2), 9.7% had lung diseases and hypoxaemia (group 3), 4.2% had PAH (group 1), 0.6% had CTEPH (group 4), and in 6.8% it was not possible to define a diagnosis.

PAH IS A CLINICAL GROUP OF RARE CONDITIONS

PAH is a clinical group of rare conditions characterised by the presence of pre-capillary PH (table 1) in the absence of other causes of pre-capillary PH, such as PH due to lung diseases (group 3), CTEPH (group 4) or other rare diseases (group 5) (table 3). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the distal pulmonary arteries (table 3).

Recent registries have described the epidemiology of PAH [16, 17]. The lowest estimate of the prevalence of PAH and idiopathic PAH are 15 cases and 5.9 cases per million adult population, respectively. The lowest estimate of PAH incidence is 2.4 cases per million adult population per year. Recent data from Scotland and other countries have confirmed that PAH prevalence is in the range of 15–50 subjects per million population in Europe [17].

In the French registry, 39.2% of patients had idiopathic PAH and 3.9% heritable PAH. In the subgroup of associated PAH, 15.3% had connective tissue diseases (mainly systemic sclerosis), 11.3% had congenital heart diseases, 10.4% had portal hypertension, 9.5% had anorexigen-associated PAH and 6.2% had HIV infection [16].

THE FINAL CLINICAL DIAGNOSIS IN THE INDIVIDUAL PATIENT WITH PH REQUIRES AN APPROPRIATE DIAGNOSTIC ALGORITHM

The confusion between ''pulmonary hypertension'' (a relatively frequent pathophysiological condition) and ''pulmonary arterial hypertension'' (a rare clinical condition) may lead to relevant diagnostic and, consequently, therapeutic errors in the individual patient. The appropriate final diagnosis of a patient with PH includes the identification of the main clinical group, the recognition of the specific clinical subtype and the evaluation of the presumptive or established haemodynamic

TABLE 2 Arbitrary criteria for estimating the likelihood of pulmonary hypertension (PH) based on tricuspid regurgitation peak velocity, correspondent Doppler-calculated pulmonary arterial systolic pressure at rest (assuming a normal right atrial pressure of 5 mmHg) and additional echocardiographic variables suggestive of PH

PH present?	Peak tricuspid regurgitant velocity $m \cdot s^{-1}$	Pulmonary artery systolic pressure mmHg	Additional echocardiographic signs of PH
Unlikely	⩽2.8	⩽35	No
Possible	⩽2.8	⩽35	Yes
	2.9–3.4	36–50	No/yes
Likely	>3.4	>50	No/yes

TABLE 3 Updated clinical classification of pulmonary hypertension (PH)

1. PAH
1.1. Idiopathic PAH
1.2.Heritable
1.2.1 BMPR2 gene mutation
1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia) gene mutation
1.2.3 Unknown
1.3. Drug- and toxin-induced
1.4. APAH
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 haemolytic anaemia
1.5. Persistent PH of the newborn
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2. PH due to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. PH due to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. CTEPH
5. PH with unclear and/or multifactorial mechanisms
5.1. Haematological disorders: myeloproliferative disorders and splenectomy
5.2. Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis and vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease and thyroid disorders
5.4. Others: tumoural obstruction, fibrosing mediastinitis and chronic renal failure on dialysis

PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor, type 2; ALK1: activin receptor-like kinase 1; APAH: associated PAH; CTEPH: chronic thromboembolic PH.

type of PH. A possible complexity is related to the potential presence of different haemodynamic forms of PH in a single clinical subtype (*e.g.* pre-capillary or post-capillary PH in patients with systemic sclerosis) or to the coexistence of different clinical conditions potentially leading to PH in the individual patient (*e.g.* lung diseases, left heart disease and HIV infection).

The diagnostic algorithm proposed in the ESC/ERS guidelines of PH is intended to facilitate the appropriate diagnosis and optimise the use of diagnostic procedures [4, 5].

In clinical practice, PH is found by Doppler echocardiography, either performed for this purpose or requested for another indication. In the majority of patients, one of the two most common clinical groups related to PH can be found (left heart disease and lung diseases) either directly by the echocardiographic examination (left heart disease), or by additional procedures already available or performed on purpose, such as chest radiograph, pulmonary function tests (including nocturnal oximetry, if required) and high-resolution computed tomography (CT) of the chest (lung diseases). In these cases, the invasive confirmation of PH is required only in specific circumstances, such as in candidates for conventional cardiac surgery, or for heart or lung transplantation, in order to stratify the surgical risk. If left heart or lung diseases are not found, or if PH seems ''out of proportion'' to their severity, less common causes of PH should be looked for. A ventilation/perfusion lung scan should be considered. If a ventilation/perfusion scan shows multiple segmental perfusion defects, a diagnosis of CTEPH (group 4) should be suspected. The final diagnosis of this condition (and the assessment of suitability for pulmonary endarterectomy) will require CT pulmonary angiography, right heart catheterisation and selective pulmonary angiography. Having excluded left heart disease, lung diseases and CTEPH, a potential diagnosis of PAH can be consistently suspected. In this case, the haemodynamic confirmation of pre-capillary PH becomes clinically significant, because this would confirm the indication for PAH-approved medications. However, the

TABLE 4 Clinical probability of pulmonary arterial hypertension (PAH) diagnosis and suggested diagnostic work-up according to the likelihood of the presence of pulmonary hypertension (PH) by Doppler echocardiography (table 2), occurrence of symptoms and risk factors, and associated conditions (table 3)

PH likelihood by echocardiography	Symptoms	Risk factors/AC	PAH probability	Work-up
Unlikely	No	Yes/no	Low	No
	Yes	Yes	Low	Echocardiographic follow-up
	Yes	No	Low	Other causes
Possible	No	No	Intermediate	Echocardiographic follow-up
	Yes	Yes	Intermediate	Right-heart catheterisation
	Yes	No	Intermediate	Echocardiographic follow-up#
Likely	Yes	Yes/no	High	Right-heart catheterisation
	No	Yes/no	High	Right-heart catheterisation

AC: associated conditions. #: consider also other causes and, if symptoms at least moderate, also right heart catheterisation.

decision to perform an invasive procedure requires a more detailed evaluation of the patient characteristics. The concept of ''clinical probability of PAH diagnosis'' has been introduced in the ESC/ERS guidelines to assist decision-making in the individual patient (table 4).

The probability is defined as low, intermediate or high according to the likelihood of presence of PH by Doppler echocardiography (table 2) and to the occurrence of symptoms and risk factors (*e.g.* anorexigen use) or associated conditions (table 3) and the specific work-up is proposed. This includes either right heart catheterisation, the Doppler echocardiographic follow-up, the suggestion for alternative diagnosis or no requirement for additional investigations. This probabilistic approach, similar to the diagnostic algorithms utilised in acute pulmonary embolism [18], is intended to reinforce the indication for right heart catheterisation only when the suspicion of a severe and rare condition, such as PAH, is present. The suggestions included in table 4 are based on expert opinion and a prospective validation is needed.

Right heart catheterisation is also very important in associated conditions, such as scleroderma, HIV infection, congenital heart diseases, portal hypertension and chronic haemolytic anaemias, in which different haemodynamic types of PH can be found (*e.g.* pre-capillary, post-capillary and hyperkinetic).

CONCLUSIONS

PH is a relatively frequent pathophysiological and haemodynamic state that can be found in multiple clinical conditions, including left heart disease and lung diseases. If the presence of PH can be estimated by Doppler echocardiography, the appropriate clinical diagnosis requires a series of investigations, which are included in a diagnostic algorithm [4, 5]. PAH is a specific clinical group of severe and rare conditions with similar pathologic, haemodynamic and therapeutic characteristics. In these cases, the confirmation of the diagnosis by right heart catheterisation is mandatory and evidence-based effective treatments are available. The lack of knowledge and application of an appropriate diagnostic algorithm may lead to confounding patients with ''pulmonary hypertension'', a frequent haemodynamic state, with subjects affected by ''pulmonary arterial hypertension'', a rare clinical entity. The direct consequence of this may be the use of drugs approved for patients with PAH in subjects with PH due to left heart disease or to lung diseases. In these conditions, the risk-to-benefit ratio of using these compounds has not yet been established appropriately [19–21].

STATEMENT OF INTEREST

A statement of interest for N. Galiè can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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