Updated Hemodynamic Definition and Classification of Pulmonary Hypertension

Benoit Lechartier, MD, PhD[1,2,3,4] Mithum Kularatne, MD[1,2,3,5] Xavier Jaïs, MD[1,2,3,6]
Marc Humbert, MD, PhD[1,2,3,6] David Montani, MD, PhD[1,2,3,6]

[1] Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Bicêtre, Le Kremlin-Bicêtre, France
[2] School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France
[3] INSERM UMR_S 999 "Pulmonary Hypertension: Pathophysiology and Novel Therapies," Hôpital Marie Lannelongue, Le Plessis-Robinson, France

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Address for correspondence David Montani, MD, PhD, Service de Pneumologie, Hôpital Bicêtre, 78, Rue du général Leclerc, 94270 Le Kremlin-Bicêtre, France (e-mail: david.montani@aphp.fr).

[4] Respiratory Division, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[5] Division of Respiratory Medicine, Department of Medicine, University of Calgary, Canada
[6] European Reference Network on Rare Pulmonary Diseases (ERN-LUNG), Germany

Abstract

Pulmonary hypertension (PH) is a pathophysiological manifestation of a heterogeneous group of diseases characterized by abnormally elevated pulmonary arterial pressures diagnosed on right heart catheterization. The 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of PH provides a new hemodynamic definition to define PH by lowering the threshold of the mean pulmonary artery pressure (mPAP) to 20 mm Hg. Precapillary PH is thus now defined as a mPAP >20 mm Hg together with a normal pulmonary artery wedge pressure (<15 mm Hg) and an increased pulmonary vascular resistance (>2 Wood Units). The ESC/ERS 2022 Guidelines also introduce a revised clinical classification of PH while retaining its previous distinction between the five groups according to the underlying pathophysiology.

Keywords
- pulmonary hypertension
- definition
- classification

Pulmonary hypertension (PH) is a pathophysiological manifestation of a heterogeneous group of diseases characterized by an abnormally elevated mean pulmonary arterial pressure (mPAP) as measured by right heart catheterization (RHC).[1] Echocardiography remains the principal screening tool to raise PH suspicion, although it cannot be used to confirm the diagnosis nor decipher the underlying mechanism for the elevated mPAP.

PH leads to progressively worsening exertional dyspnea and right heart failure in untreated patients. Several mechanisms can cause an elevation of the mPAP with left heart diseases and chronic lung diseases being the most common etiologies of PH in Western countries.[2] The prevalence of these diseases increase in an aging population and recent studies indicate that the prevalence of PH has similarly increased in recent decades.[3] Each patient presenting with a suspicion for PH must be thoroughly investigated to characterize their phenotype and identify the correct underlying pathophysiological mechanisms related to their specific diagnosis. Only then can patients be appropriately managed. Recent changes in the understanding of PH have justified an update to the hemodynamic definition and classification of PH. This chapter is based on the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of PH.[1] Both the definition and classification of PH are now scientifically driven and clinically oriented.

Hemodynamic Definition

Pulmonary Hypertension, an Evolving Definition

An elevated mPAP, regardless of its value, defines a hemodynamic state and not a disease per se. The mPAP can be defined by the formula: mPAP = pulmonary vascular resistance (PVR)

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× cardiac output (CO) + left atrial pressure. This equation reveals the main pathophysiological mechanisms underlying PH: (1) elevation of the PVR due to various levels of pulmonary vasculopathy, as seen in pulmonary arterial hypertension (PAH); (2) increased CO due to hyperdynamic states and shunts; and (3) elevated pressures due to left heart diseases causing postcapillary PH. An augmented mPAP is thus present in many clinical situations and may correspond to very dissimilar pathophysiological entities, and therefore to different prognoses and management.

It was first stated in a 1961 report from the World Health Organization that the normal mPAP usually does not exceed 15 mm Hg when a subject is supine at rest.[4] In 1973 during the first World Symposium on PH (WSPH) the hemodynamic definition of PH was set arbitrarily as a mPAP $\geq$ 25 mm Hg, significantly higher than the upper limit of normal. However, since the definition was established, evidence emerged suggesting that the hemodynamic definition required refinement to better define the precapillary, postcapillary, or mixed origins of PH. The historical mPAP threshold of 25 mm Hg allowed a classical distinction between severe PH, observed secondary to appetite suppressant drugs, from usually mild PH associated with respiratory diseases. Subsequently, this threshold remained unchanged in successive international recommendations.[5]

A meta-analysis published by Kovacs et al in 1,187 healthy subjects from 47 studies revealed that the normal mPAP at rest did not exceed 14 ± 3.3 mm Hg in the supine position, independent of sex, age, and ethnicity.[6] Following this study, two standard deviations above this value was used to define the upper limit of normal as a mPAP of 20 mm Hg. Several studies have since confirmed the clinical utility of this threshold as patients with mPAP between 21 and 24 mm Hg demonstrate worse survival than subjects with mPAP $\leq$ 20 mm Hg.[7,8] The question of reducing the threshold from 25 to 20 mm Hg was previously addressed during the fifth WSPH, but some concerns were raised about the putative consequences of PH overdiagnosis together with the uncertain outcome of patients with previously termed "borderline PH" (mPAP between 21 and 24 mm Hg). In 2018, the sixth WSPH proposed to reduce the mPAP threshold to 20 mm Hg to hemodynamically define PH. Additionally, the level of PVR was included in the hemodynamic definition of PH to distinguish pre- and postcapillary PH.[9] Several robust studies have justified this revision.

Systemic sclerosis (SSc) can lead to progressive pulmonary arterial vasculopathy in affected patients. SSc patients with a mPAP between 21 and 24 mm Hg demonstrate symptoms, particularly at exercise, and may have a poorer outcome compared with patients without PH. In a multicenter prospective study among 284 SSc patients, 146 (49.2%) had mPAP $\leq$ 20 mm Hg, 19.3% between 21 and 24 mm Hg and 29.4% $\geq$ 25 mm Hg. In the 21 to 24 mm Hg group, only four patients (1.4%) had PVR values $\geq$ 3 Wood Units (WU).[10] Interestingly, 9.8% of patients presenting with mPAP 21 to 24 mm Hg and PVR $\geq$ 2 WU had a decreased 6-minute walking distance and tricuspid annular plane systolic excursion and, most importantly, had reduced long-term survival. Therefore, in SSc-PAH, a PVR threshold of $\geq$2 WU was associated with significant pulmonary vascular disease and was proposed to be a more appropriate threshold for this high-risk population.[10]

In a recent study by Kovacs et al among patients who underwent RHC for suspected PH, the 2018 definition confirmed the objectives of the 6th World Symposium by identifying patients with earlier forms of disease and a worse prognosis.[11] Based on these observations, the threshold of 20 mm Hg to define PH is no longer arbitrary but scientifically driven. In a retrospective cohort study among U.S. veterans, Maron et al analyzed the relationship between PVR and adverse clinical outcomes in PH.[12] The authors found an adjusted hazard ratio for mortality of 1.71 (confidence interval: 1.59–1.84; $p < 0.0001$) among patients with a mPAP of at least 19 mm Hg and pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mm Hg, which was validated in an external RHC cohort. The all-cause mortality hazard for PVR was increased at approximately 2.2 WU compared with PVR of 1.0 WU.[12] These data provided the first robust evidence of an adverse outcome related to mildly elevated PVR. Specifically, PVR $\geq$2.2 WU emerged as an essential determinant of outcome in PH patients.

Hemodynamic Definition of Pulmonary Hypertension in 2022

The recently updated hemodynamic definition of precapillary PH is now mPAP > 20 mm Hg together with PVR $\geq$ 2 WU in the presence of normal left heart filling pressure (pulmonary capillary wedge pressure $\leq$ 15 mm Hg) measure invasively by RHC.[1] The updated definition does not imply a necessity to treat these patients with PAH therapy; however, it favors early detection of PH for increased monitoring.

The measurement of PAWP and the calculation of PVR assist in specifying the mechanisms of PH (►**Table 1**). Precapillary PH is defined by a normal PAWP $\leq$ 15 mm Hg and elevated PVR >2 WU, whereas postcapillary PH is defined by an elevated PAWP >15 mm Hg. Postcapillary PH

Table 1 Hemodynamic definitions of pulmonary hypertension

Definitions	Hemodynamic	Clinical groups
Precapillary PH	mPAP > 20 mm Hg PAWP $\leq$ 15 mm Hg PVR > 2 WU	1, 3, 4, and 5
Isolated postcapillary PH	mPAP > 20 mm Hg PAWP > 15 mm Hg PVR $\leq$ 2 WU	2 and 5
Combined pre- and postcapillary PH	mPAP > 20 mm Hg PAWP > 15 mm Hg PVR > 2 WU	2 and 5
Exercise PH	mPAP/CO slope >3 mm Hg/L/min between rest and exercise	All groups

Abbreviations: CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood Units.
Note: Adapted from Humbert et al. 2023[1]

can be isolated with a normal PVR $\leq$ 2 WU or associated with precapillary involvement (so-called "combined" PH) if PVR is >2 WU. The prognostic impact of a moderate elevation of mPAP (21–24 mm Hg) and/or PVR (2–3 WU) raises the question of how best to manage these patients. Therapeutic trials conducted to date have not included patients with mild PH and clinical trials dedicated to this subpopulation are now warranted. Nevertheless, this new definition including lower mPAP and PVR thresholds has the advantage of identifying patients requiring close follow-up in expert centers.

Pulmonary Hypertension during Exercise

Exercise PH was part of the PH definition until 2008 when it was removed from the hemodynamic definition of PH due to a lack of robust data defining normal hemodynamic values during exercise. Indeed, numerous factors can modify mPAP during effort, not always related to the underlying pulmonary vascular disease, such as patient age or hyperdynamic state. Nevertheless, elevated mPAP during effort was associated with a poor prognosis in patients with exercise dyspnea or cardiovascular diseases.[13–17]

Several studies[17–20] have led to a better definition of an abnormal hemodynamic response during exercise, allowing the definition of exercise-induced PH to be reintroduced in the new European guidelines.[1] Exercise PH is now defined by a mPAP/CO slope >3 mm Hg/L/min between resting and exercise values, measured during RHC (►**Table 1**).[17] The mPAP/CO slope remains age-dependent, but a slope >3 mm Hg/L/min is pathological before 60 years of age and is rarely observed in healthy individuals over 60 years of age.[17] However, this definition does not differentiate between the pre- or postcapillary mechanisms causing exercise-induced PH. Further studies are needed to confirm that a PAWP/CO slope threshold >2 mm Hg/L/min might distinguish between pre- and postcapillary causes.[21,22]

Principles of the Clinical Classification of Pulmonary Hypertension

The current classification distinguishes five main clinical groups based on similar pathophysiology, etiologies, hemodynamic, and therapeutic approaches. This classification allows a rational distinction between various medical conditions where an elevated mPAP is encountered. The clinical classification of PH aims to gather etiologies that are similar in terms of clinical presentation and pathophysiological mechanisms to establish common therapeutic strategies.[1,5,9,23] This classification has evolved over time due to a better understanding of the risk factors for PH. It currently includes five major groups of PH (►**Table 2**).[1] Groups 1, 3, and 4 are characterized by precapillary involvement, group 2 by postcapillary involvement (sometimes combined with a precapillary component), and group 5 includes causes of PH that may be both pre- or postcapillary (►**Table 1**). PAH (PH group 1) encompasses a heterogeneous group of currently incurable pulmonary vascular disorders that share a similar clinical presentation, hemodynamic characteristics, and therapeutic strategy. PAH is diagnosed when the aforementioned hemodynamic criteria are met and once other causes of precapillary PH are ruled out. PAH is a rare form of PH characterized by endothelial dysfunction and progressive remodeling of small-caliber pulmonary vessels. Specific therapies targeting endothelial dysfunction (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives) are the currently available treatments for this rare form of PH.[1]

Among the causes of PAH, heritable forms, PAH associated with drug and toxic exposures, and PAH associated with various diseases such as connective tissue diseases (CTD; mainly SSc and systemic lupus erythematosus), human immunodeficiency (HIV) virus infection, portal hypertension, congenital heart disease, and bilharzia have been identified (►**Table 2**). After a thorough diagnostic workup eliminating PH groups 2 to 5 or a known etiology of PAH, these patients are classified as idiopathic (►**Table 2**). In most PH registries, idiopathic PAH represents the most common form of PAH (50–60% of cases) followed by PAH associated with CTD, congenital heart disease, and portal hypertension.[2]

Clinical and hemodynamic case A: a 22-year-old female, signs of right heart failure on presentation with occasional syncope, hemodynamics before treatment and under therapy. The first evaluation demonstrates a clearly positive vasoreactivity test corresponding to group 1.1.2 in the new classification. The second evaluation under calcium channel blocker therapy confirms a favorable hemodynamic response.

	First hemodynamic evaluation		Second evaluation after 3 mo under amlodipine 20 mg daily
	Baseline	Under NO 10 ppm	
mPAP mm Hg	52	36	23
PAWP mm Hg	9	11	4
CO L/min	3.0	3.75	4.9
CI L/min/m^2	1.53	1.91	2.6
PVR (WU)	14.3	6.7	3.9

Main Changes in the New Pulmonary Arterial Hypertension Classification

The main changes in the new classification of PAH[1] include: (1) the identification of two subgroups of idiopathic PAH according to acute vasoreactivity test response, (2) the list of genes associated with heritable forms of PAH, (3) an update of the drugs and toxins that can induce PAH, and 4) the inclusion of pulmonary veno-occlusive disease (PVOD) within group 1.

Idiopathic Pulmonary Arterial Hypertension

The new classification distinguishes two subgroups of idiopathic PAH between nonresponders and responders depending on the response at acute vasoreactivity testing (usually after nitric oxide inhalation) performed during RHC. The hemodynamic criteria for a positive vasoreactivity test are a decrease in mPAP $\geq$10 mm Hg to an absolute value of mPAP $\leq$40 mm Hg and associated with an unchanged or increased CO.[24] A positive acute vasoreactivity test identifies

Table 2 Updated clinical classification of pulmonary hypertension

Group 1 PAH
1.1 Idiopathic
1.1.1 Nonresponders at vasoreactive testing
1.1.2 Acute responders at vasoreactive testing
1.2 Heritable
1.3 Associated with drugs and toxins[α]
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
Group 2 PH associated with left heart disease
2.1 Heart failure
2.1.1 With preserved LVEF
2.1.2 With reduced or mildly reduced LVEF
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to postcapillary PH
Group 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease
3.6 Developmental lung disorders
Group 4 PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions[β]
Group 5 PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders[γ]
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, and neurofibromatosis type 1[δ]
5.3 Metabolic disorders[ε]
5.4 Chronic renal failure with or without hemodialysis
5.5 Pulmonary tumor thrombotic microangiopathy
5.6 Fibrosing mediastinitis

Abbreviations: LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.
Note: Adapted from Humbert et al. 2023[1]
[α]Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders.
[β]Other causes of pulmonary artery obstructions include sarcomas, other malignant tumors, nonmalignant tumors, arteritis without connective tissue disease, congenital pulmonary stenoses, and hydatidosis.
[γ]Including inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders.
[δ]Including sarcoidosis, pulmonary Langerhans cell histiocytosis, and neurofibromatosis type 1.
[ε]Including glycogen storage diseases and Gaucher disease. Significant changes from the 2015 Guidelines 5 are highlighted in red.

a subgroup of patients likely to benefit from calcium channel blocker therapy (administered at high doses) over the long term with an improved prognosis compared with nonresponders (cf. clinical case A). In addition to idiopathic PAH, positive acute vasoreactivity testing and long-term response to calcium channel blockers may be found in heritable or drug-induced PAH. In other conditions, such as PAH associated with CTDs, the vasoreactivity test has no diagnostic or prognostic value, which limits the performance of this test to only those patients within these three subgroups.

Heritable Pulmonary Arterial Hypertension

Heritable PAH is defined as PAH associated with mutations in PAH susceptibility genes or occurring in a familial context without an identified mutation. PAH associated genes are characterized by an autosomal dominant trait with incomplete penetrance. The new European guidelines propose an updated list of PAH susceptibility genes. This list includes some genes involved in endothelial dysfunction (*BMPR2*, *ACVRL1*, *endoglin*, *GDF2*, *SMAD9*, *CAV1*), channel function (*KCNK3*, *AQP1*, *ATP13A3*, *ABCC8*), and pulmonary vascular development (*TBX4*, *KDR*, *SOX17*). The identification of a genetic predisposition to PAH currently has limited therapeutic implications. Nevertheless, it allows for genetic counseling to family members, identification of subjects at risk, and subsequent enrolment in screening programmes.[25]

Drugs and Toxins Associated with Pulmonary Arterial Hypertension

The updated list of drugs and toxins that can induce PAH (►**Table 3**) is divided into definite and possible causes based on the strength of scientific and epidemiological evidence. Definite association between drugs and PAH comprise appetite suppressant drugs related to the amphetamine class (aminorex, dexfenfluramine, fenfluramine, benfluorex), dasatinib (a tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia), and methamphetamines, with demonstrated outbreaks particularly in the United States.[26–28] Among the possible associations are drugs that warrant special surveillance because of a suspicion of causality of these drugs (epidemiological, pharmacological, or experimental data) but have yet to be confirmed. This last category includes organic solvents such as trichloroethylene, most often inhaled during occupational exposure, which are a cause of acquired PVOD[29].

Pulmonary Arterial Hypertension with Signs of Venous and/or Capillary Involvement

Rarer forms of PAH are associated with pulmonary venous and capillary remodeling grouped in the new classification under the entity PAH with signs of venous and/or capillary

Table 3 Drugs and toxins associated with pulmonary hypertension

Definite association	Possible association
Aminorex	Alkylating agents (cyclophosphamide, mitomycin C)[α]
Benfluorex	Bosutinib
Dasatinib	Cocaine
Dexfenfluramine	Diazoxide
Fenfluramine	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Methamphetamines	Indirubin (Chinese herb Qing-Dai)
Toxic rapeseed oil	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Selective proteasome inhibitors (carfilzomib)
	Solvents (trichloroethylene)[α]
	St John's Wort

Notes: Adapted from Humbert et al. 2023[1]
[α]Association with pulmonary veno-occlusive disease.

involvement (PVOD) and/or pulmonary capillary hemangiomatosis. These patients have a particular clinical presentation (significant dyspnea, severe hypoxemia, reduced diffusion capacity for carbon monoxide, typical chest computed tomography scan abnormalities, and associated risk factors [exposure to alkylating agents, organic solvents, or a genetic form of autosomal recessive transmission linked to *EIF2AK4* gene biallelic mutations]).[30] Identification of this rare form of PAH is critical since PVOD patients have a poorer response to PAH specific treatments (with a risk of pulmonary edema) and a worse prognosis in the absence of lung transplantation.[30,31]

Other Groups of Pulmonary Hypertension (Groups 2, 3, 4, and 5)

PH associated with left heart diseases belong to group 2, which is likely the most common cause of PH worldwide.[2] It includes postcapillary PH secondary to left heart diseases with preserved or reduced left ventricular ejection fraction (LVEF), valvular diseases, and some rarer cardiac diseases. The new classification distinguishes patients with preserved LVEF ($\geq$50%) from patients with reduced ($\leq$40%) or mildly reduced LVEF (40–49%). A fluid challenge test during RHC or an exercise RHC may reveal a postcapillary phenotype (cf. clinical case B) when the PAWP is mildly elevated at rest depending on the clinical context or on the pre-test probability of postcapillary PH.[32] This can be further confirmed by a left heart catheterization to directly measure the left ventricular end-diastolic pressure (LVEDP).

Clinical and hemodynamic case B: a 57-year-old female, known for refractory systemic hypertension, reviewed for a suspicion of PAH (►**Table 4**). The baseline RHC shows borderline PAWP and LVEDP values. The fluid challenge test demonstrates a clear postcapillary phenotype with a significant increase in PAWP and a subsequent normalization of PVR.

	Baseline hemodynamic	Hemodynamic after a 500 mL NaCl fluid challenge
mPAP mm Hg	23	27
PAWP mm Hg	13	23
LVEDP mm Hg	16	–
CO L/min	4.9	4.7
CI L/min/m^2	2.7	2.6
PVR (WU)	2.0	0.9

Group 3 PH encompasses precapillary PH associated with lung diseases and/or hypoxia. Sleep apnea syndromes are no longer in the 2022 PH classification as isolated obstructive apnea syndromes are not a definite cause of PH. Instead, hypoventilation syndromes causing daytime hypercapnia belongs to PH group 3.4. It is important to emphasize that the treatment of patients in groups 2 and 3 is based primarily on optimizing the associated cardiac or respiratory diseases (cf. clinical case C).

Clinical and hemodynamic case C: a 57-year-old male known for COPD with advanced emphysema, evaluated for a suspicion of severe PH (►**Table 5**). The first RHC demonstrated a moderate-to-severe precapillary PH associated with lung disease (group 3.1). The hemodynamic evaluation after continuous oxygen therapy highlights a significant decrease in mPAP due to the reduction of hypoxic vasoconstriction.

	Baseline hemodynamic	Hemodynamic 6 months after smoking cessation and O2 therapy
mPAP mm Hg	44	31
PAWP mm Hg	15	11
CO L/min	6.2	8.1
CI L/min/m^2	3.1	4.1
PVR (WU)	4.7	2.5

Group 4 corresponds to PH associated with chronic pulmonary arterial obstructions. This group is comprised mainly of chronic thromboembolic PH (CTEPH), which requires specialized management in multidisciplinary expert centers.[33] Treatment options include surgical pulmonary endarterectomy, balloon pulmonary angioplasty, and specific treatments targeting endothelial dysfunction.[1] Other less common causes of pulmonary artery obstruction include sarcomas, other malignancies, benign tumors, arteritis without associated CTDs, congenital pulmonary artery stenosis, and hydatidosis.

The last of the five groups encompasses diseases with "multifactorial or unclear mechanisms" of PH. It includes a variety of conditions that may be complicated by complex and often multifactorial pulmonary vascular disease, such as sarcoidosis and other granulomatous diseases. The composition of group 5 was adapted in the new ESC/ERS classification

(►**Table 2**). Some hematological diseases are associated with a risk of PH, mainly chronic hemolytic or myeloproliferative disorders. Among chronic hemolytic anemias, sickle cell disease is to date the most studied and PH is present in approximately 6% of sickle cell disease patients.[34] Multifactorial mechanisms of PH in sickle cell disease have been identified, notably thrombosis, blood hyperviscosity, increased CO, endothelial dysfunction, nitric oxide deficiency, and cardiomyopathy. Myeloproliferative disorders can also cause PH by a complex pathophysiology that has not been clearly elucidated (thrombosis, endothelial dysfunction, intrapulmonary hematopoiesis).[35] PH may also be encountered in other rarer hematological disorders such as IgG4-related diseases or Castleman disease.

Certain systemic disorders such as Langerhans cell histiocytosis, sarcoidosis, or neurofibromatosis type 1 remain classified in group 5 due to the lack of robust data identifying the mechanisms for PH in these entities. Sarcoidosis-associated PH, which is seen in 6 to 20% of sarcoidosis cases, is an illustrative example of multiple mechanisms including parenchymal involvement, granulomas in small pulmonary vessels (arteries and veins), pulmonary vasculitis, fibrosing mediastinitis, lymph node extrinsic compressions of large pulmonary arteries, CTEPH, or portal hypertension.[36] PH associated with lymphangioleiomyomatosis is most often moderate and correlates with the severity of the respiratory impairment and has been reclassified as PH associated with chronic lung disease (group 3).

Metabolic disorders, mainly glycogen storage diseases or Gaucher disease, may also be accompanied by PH due to asplenia, vascular thrombosis, and pulmonary vascular remodelling.[37] PH may also complicate chronic renal failure, with or without hemodialysis, but the mechanisms remain poorly understood. It is most often a combined pre- and postcapillary PH phenotype.[38]

Tumor thrombotic microangiopathy of the lung is caused by tumor microembolism associated with fibrointimal occlusive remodeling of the small pulmonary vessels. It is a rare but severe and probably underdiagnosed cause of PH.[39]

Mediastinal fibrosis is a rare cause of PH characterized by a proliferation of fibrous tissue in the mediastinum compressing the mediastinum and bronchovascular structures, which may be pre- or postcapillary.[40] Mediastinal fibrosis can be idiopathic, caused by irradiation, infection (tuberculosis or histoplasmosis), or systemic disorders such as sarcoidosis.

Lastly, in the previous European guidelines published in 2015,[5] splenectomy and thyroid disorders were considered as PH etiologies. Current data suggest that these are not specific clinical conditions that can cause PH but rather associated comorbidities. It was thus decided to remove splenectomy and thyroid disorders from the current ESC/ERS PH classification.

Conclusion

PH is encountered in numerous medical conditions with distinct pathophysiological mechanisms, which guide PH patient management. The new definition and classification of PH take into account the recent evidence in the diagnosis and management of PH while remaining a useful clinical tool in routine medical practice. These definitions and classifications will continue to evolve in the future to keep pace with the scientific understanding of chronic pulmonary vascular diseases.

Conflict of Interest
None declared.

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