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Updated Clinical Classification of Pulmonary Hypertension

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In 1998, a clinical classification of pulmonary hypertension (PH) was established, categorizing PH into groups which share similar pathological and hemodynamic characteristics and therapeutic approaches. During the 5th World Symposium held in Nice, France, in 2013, the consensus was reached to maintain the general scheme of previous clinical classifications. However, modifications and updates especially for Group 1 patients (pulmonary arterial hypertension [PAH]) were proposed. The main change was to withdraw persistent pulmonary hypertension of the newborn (PPHN) from Group 1 because this entity carries more differences than similarities with other PAH subgroups. In the current classification, PPHN is now designated number 1. Pulmonary hypertension associated with chronic hemolytic anemia has been moved from Group 1 PAH to Group 5, unclear/multifactorial mechanism. In addition, it was decided to add specific items related to pediatric pulmonary hypertension in order to create a comprehensive, common classification for both adults and children. Therefore, congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to Group 2, and segmental pulmonary hypertension has been added to Group 5. Last, there were no changes for Groups 2, 3, and 4.
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Pulmonary hypertension (PH) was previously classified into 2 categories: 1) primary pulmonary hypertension; or 2) secondary pulmonary hypertension according to the presence of identified causes or risk factors (1).

Since the second World Symposium on pulmonary hypertension held in Evian, in 1998 (2), a clinical classification was established in order to individualize different categories of PH sharing similar pathological findings, similar hemodynamic characteristics and, similar management. Five groups of disorders that cause PH were identified: pulmonary arterial hypertension (Group 1); pulmonary hypertension due to left heart disease (Group 2);

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pulmonary hypertension due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic pulmonary hypertension (Group 4); and pulmonary hypertension due to unclear multifactorial mechanisms (Group 5). During the successive world meetings, a series of changes were carried out, reflecting some progresses in the understanding of the disease. However, the general architecture and the philosophy of the clinical classification were unchanged. The current clinical classification of pulmonary hypertension (3) is now well accepted and, widely used in the daily practice of pulmonary hypertension experts. It has been adopted by the Guidelines Committee of the Societies of Cardiology and, Pneumology (4,5). Moreover, this classification is currently used by the U.S. Food and Drug Administration and the European Agency for Drug Evaluation for the labelling of new drugs approved for pulmonary hypertension.

During the Fifth World Symposium held in 2013 in Nice, France, the consensus was to maintain the general disposition of previous clinical classification. Some modifications and updates, especially for Group 1, were proposed according to new data published in the last years. It was also decided in agreement with the Task Force on Pediatric PH to add some specific items related to pediatric pulmonary hypertension in order to have a comprehensive classification common for adults and children (Table 1).

Group 1: Pulmonary Arterial Hypertension (PAH)

Since the second World Symposium in 1998, the nomenclature of the different subcategories of Group 1 have markedly evolved and, additional modification were made in the Nice classification.

Heritable Pulmonary Hypertension

In 80% of families with multiple cases of pulmonary arterial hypertension (PAH), mutations of the bone morphogenic protein receptor type 2 (BMPR2), a member of the tumor growth factor (TGF)-beta super family, can be identified (6). In addition, 5% of patients have rare mutations in other genes belonging to the TGFβ super family: activin-like receptor kinase-1 (ALK_1) (7), endoglin (ENG) (8), and mothers against decapentaplegic 9 (Smad 9) (9). Approximately 20% of families have no detectable mutations in currently known disease-associated genes. Recently two new gene mutations have been identified: a mutation in caveolin-1 (CAV1) which encodes a membrane protein of caveolae, abundant in the endothelial cells of the lung (10), and KCNK3, a gene encoding potassium channel super family K member-3 (11). The identification of these new genes not intimately related to TGFβ signaling may provide new insights into the pathogenesis of PAH.

Abbreviations and Acronyms

CHD = congenital heart disease
HAART = highly active antiretroviral therapy
HIV = human immunodeficiency virus
IFN = interferon
PAH = pulmonary arterial hypertension
PAP = pulmonary arterial pressure
PH = pulmonary hypertension
POPH = portopulmonary hypertension
PPHN = persistent pulmonary hypertension of the newborn
PVR = pulmonary vascular resistance
SCD = sickle cell disease
Sch-PAH = schistosomiasis-associated PAH
TGF = tumor growth factor
TKI = tyrosine kinase inhibitor

Drug- and Toxin-Induced Pulmonary Hypertension

A number of drugs and toxins have been identified as risk factors for the development of PAH and were included in the previous classification (3). Risk factors were categorized according to the strength of evidence, as definite, likely, possible, or unlikely (Table 2).

A definite association is defined as an epidemic or large multicenter epidemiologic studies demonstrating an association between a drug and PAH. A likely association is defined as a single case-control study demonstrating an association or a multiple-case series. Possible is defined as drugs with similar mechanisms of action as those in the definite or likely category but which have not yet been studied. Last, an unlikely association is defined as one in which a drug has been studied in epidemiologic studies and an association with PAH has not been demonstrated.

Over the last 5 years, new drugs have been identified or suspected as potential risk factors for PAH.

Since 1976, Benfluorex (MEDIATOR, Laboratories Servier, Neuilly-Sur-Seine, France) has been approved in Europe as a hypolipidemic and hypoglycemic drug. This drug is in fact a fenfluramine derivative, and its main metabolite is norfenfluramine, similar to Isomeride. Benfluorex, due to its pharmacological properties, was withdrawn from the market in all European countries after 1998 (date of the worldwide withdrawal of fenfluramine derivatives), except in France where the drug was marketed until 2009 and was frequently used between 1998 and 2009 as a replacement for Isomeride. The first case series reporting benfluorex-associated PAH was published in 2009. In addition to 5 cases of severe PAH, 1 case of valvular disease was also reported (12). Recently, Savale et al. (13) reported 85 cases of PAH associated with benfluorex exposure, identified in the French national registry from 1999 to 2011. Of these cases, 70 patients had confirmed pre-capillary

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Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 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 diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - **2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

3. Pulmonary hypertension 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 lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

pulmonary hypertension (PH) with a median ingestion duration of 30 months and a median delay between start of exposure and diagnosis of 108 months. One-quarter of patients in these series showed coexisting PH and mild to moderate valvular heart diseases (14).

Chronic myeloproliferative (CML) disorders are a rare cause of PH, involving various potential mechanisms (Group 5) including high cardiac output, splenectomy, direct obstruction of pulmonary arteries, chronic thromboembolism, portal hypertension, and congestive heart failure. The prognosis of CML has been transformed by tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib. Although, TKIs are usually well tolerated, these agents are associated nevertheless with certain systemic side effects (edema, musculoskeletal pain, diarrhea, rash, pancytopenia, elevation of liver enzymes). It is also well established that imatinib may induce cardiac toxicity. Pulmonary complications and specifically pleural effusions have been reported more frequently with dasatinib. In addition, case reports suggested that PH may be a potential complication of dasatinib use (15).

Table 2 Updated Classification for Drug- and Toxin-Induced PAH*

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	**Interferon α and β**
SSRIs†	**Amphetamine-like drugs**
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

*Nice 2013. †Selective serotonin reuptake inhibitor (SSRIs) have been demonstrated as a risk factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in pregnant women exposed to SSRIs (especially after 20 weeks of gestation). PPHN does not strictly belong to Group 1 (pulmonary arterial hypertension [PAH]) but to a separated Group 1. Main modification to the previous Danapoint classification are in **bold**.

Montani et al. (16) recently published incidental cases of dasatinib-associated PAH reported in the French registry. Between November 2006 and September 2010, 9 cases treated with dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe precapillary PH confirmed by heart right catheterization. No other PH cases were reported with other TKIs at the time of PH diagnosis. Interestingly, clinical, functional, and hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. However, after a median follow-up of 9 months, most patients did not demonstrate complete recovery, and 2 patients died. Today, more than 13 cases have been observed in France among 2,900 patients treated with dasatinib for CML during the same period, giving the lowest estimate incidence of dasatinib-associated PAH of 0.45%. Finally, notifications of almost 100 cases of PH have been submitted for European pharmaceutical vigilance. Dasatinib is considered a likely risk factor for PH (Table 2).

Few cases of PAH associated with the use of interferon (IFN)-α or -β (17,18) have been published so far. Recently, all cases of PAH patients with a history of IFN therapy notified in the French PH registry were analyzed (19). Fifty-three patients with PAH and a history of IFN use were identified between 1998 and 2012. Forty-eight patients were treated with IFN-α for chronic hepatitis C, most of them had an associated risk factor for PH such as human immunodeficiency virus (HIV) infection and/or portal hypertension. Five other cases were treated with IFNβ for multiple sclerosis; those patients did not have any associated risks factor for PAH. The mean delay between initiation of IFN therapy and PAH diagnosis was approximately 3 years. Sixteen additional patients with previously documented PAH were treated with IFN-α for hepatitis C and showed a significant increase in pulmonary vascular resistance (PVR) within a few months of therapy initiation; in half of them, withdrawal of IFN resulted in a marked hemodynamic

improvement. Regarding a potential mechanism, several experimental studies have found that IFN-α and INF-β induced the release of endothelin-1 by pulmonary vascular cells (20).

In summary, this retrospective analysis of the French registry together with experimental data suggested that IFN therapy may be a trigger for PAH. However, most of the patients exposed to IFN also had some other risk factors for PAH, and a prospective case control study is mandatory to definitively establish a link between IFN exposure and development of PAH. At this time, IFN-α and -β are considered possible risks factors of PH.

Persistent PH of the newborn (PPHN) is a life-threatening condition that occurs in up to 2 per 1,000 live-born infants. During the past 15 years, many studies have specifically assessed the associations between use of serotonin reuptake inhibitors (SSRIs) during pregnancy and the risk of PPHN with discordant results from no association to 6-fold increased risk (21–26).

A recent study involving nearly 30,000 women who had used SSRIs during pregnancy found that every use in late pregnancy increased the risk of PPHN by more than 2-fold. Based on this large study, SSRIs can be considered a definite risk factor for PPHN (27). Whether exposure to SSRIs is associated with an increased risk of PAH in adults is unclear.

Although presently there is no demonstrated association with PAH, several drugs with mechanisms of actions similar to amphetamines, used to treat a variety of conditions including obesity (fentermine/topiramate [Qsiva]), attention deficit disorder (methylphenidate) (28), Parkinson's disease (ropinirole), and narcolepsy (mazindol), need to be monitored closely for an increase in cases of PAH.

In summary, several new drugs have recently been identified as definite, likely, or possible risk factors for PAH. In order to improve detection of potential drugs that induce PAH, it is important to outline the critical importance of obtaining a detailed history of current and prior exposure in every PAH patient. The proliferation of national and international registries should provide the unique opportunity to collect these data prospectively. In addition, one must emphasize the need to report all side effects of drugs to local pharmaceutical agencies and pharmaceutical companies.

PAH Associated With Connective Tissue Diseases

The prevalence of PAH is well established only in scleroderma, and rate of occurrence is estimated between 7% and 12% (29,30). The prognosis for patients with PAH associated with scleroderma remains poor and worse compared to other PAH subgroups. The 1-year mortality rate in patients with idiopathic PAH is approximately 15% (31) versus 30% in PAH-associated with scleroderma (32). Recent data suggest that in scleroderma, early diagnosis and early intervention may improve long-term outcome (33). Interestingly, it has been recently demonstrated that scleroderma patients with a mean pulmonary artery pressure (PAP) between 21 and 24 mm Hg are at high risk for the development of overt PH within 3 years and should be closely followed (34).

PAH Associated With HIV Infection

The prevalence of PAH associated with HIV infection has remained stable within the last decade, estimated to be 0.5% (35). Before the era of highly active antiretroviral therapy (HAART) and the development of specific PAH drugs, the prognosis for HIV-PAH was extremely poor, with a mortality rate of 50% in 1 year (36). The advent of HAART and the wide use of PAH therapies in HIV patients have dramatically improved their prognosis, and the current survival rate at 5 years in the French cohort is more than 70% (37). Interestingly, approximately 20% of these cases experience a normalization of hemodynamic parameters after several years of treatment (38).

PAH Associated With Portal Hypertension

Hemodynamic studies have shown that PAH is confirmed in 2% to 6% of patients with portal hypertension, so called portopulmonary hypertension (POPH) (39,40). The risk of developing POPH is independent of the severity of the liver disease (41). Long-term prognosis is related to the severity of cirrhosis and to cardiac function (41). There is wide discrepancy in the published survival estimates of patients with POPH. In, the U.S. REVEAL registry (42) patients with POPH had a poor prognosis, even worse that those with idiopathic PAH with a 3-year survival rate of 40% versus 64%, respectively. In the French registry, the 3-year survival rate of POPH was 68%, slightly better than that of idiopathic PAH (43). These discordant results are likely explained by important differences with respect to the severity of liver disease. In the U.S. REVEAL registry, most of these patients were referred from liver transplantation centers, whereas in the French cohort, most patients had mild cirrhosis (39–43).

PAH Associated With Congenital Heart Disease in Adults

Increasing numbers of children with congenital heart disease (CHD) now survive to adulthood. This reflects improvement in CHD management in recent decades, and both the number and complexity of adults with CHD continue to increase. It is estimated that 10% of adults with CHD may also have PAH (44). The presence of PAH in CHD has an adverse impact on quality of life and outcome (45,46).

A well-recognized clinical phenotype of patients with volume and pressure overload (i.e., with large ventricular or arterial shunts) are at much higher risk of developing early PAH than patients with volume overload only (i.e., with atrial shunts). Nevertheless, there are some exceptions, and

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we speculate that a permissive genotype might place some patients with CHD at higher risk of developing PAH. Given the prevalence of PAH among adults with CHD, we suggest that every patient with CHD merits an appropriate assessment in a tertiary setting to determine whether PAH is present. While it is anticipated that the number of patients with Eisenmenger syndrome, the extreme end of the PAH/CHD spectrum, complicated also by chronic cyanosis, will decrease in the coming years and there will be an increasing number of patients with complex and/or repaired CHD surviving to adulthood with concomitant PH (47). The present clinical subclassification of PAH associated with CHDs has evolved sensibly from 2008. It remains clinical and simple, thus widely applicable. Importantly, it is now aligned with the Nice Pediatric classification, as PAH in association with CHD is a lifelong disease (Table 3). We have proposed criteria for shunt closure in patients with net left to right shunting who may represent a management dilemma (Table 4). Other types of PH in association with CHD who do not belong to Group 1 (PAH) are included in different groups of the general clinical classification (i.e., congenital or acquired left heart inflow/outflow obstructive lesions and congenital cardiomyopathies in Group 2). Segmental PH (PH in one or more lobes of one or both lungs) is included in Group 5. In addition, some patients with PH associated with CHD are difficult to classify, such as patients with transposition of great arteries and those with PH following atrial redirection surgery or following neonatal arterial switch operation. This reinforces the need to delineate the underlying cardiac anatomy/physiology and severity of PAH/PVR in every single patient. Here we make specific reference to patients with the Fontan circulation (atrio- or cavopulmonary connections as palliation for "single ventricle" type hearts), who do not fulfill standard criteria for PH but may have an increased PVR. There are very limited surgical alternatives for this group of patients with complex anatomy/physiology. There has been some recent evidence of potential clinical response to specific PAH therapies in Fontan patients, which needs further exploration before therapeutic recommendations can been made (48,49).

Table 3 Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease*

1. Eisenmenger syndrome Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.
2. Left-to-right shunts • Correctable† • Noncorrectable Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.
3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.
4. Post-operative PAH Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

*Nice 2013.

Table 4 Criteria for Closing Cardiac Shunts in PAH Patients Associated With Congenital Heart Defects*

PVRi, Wood units/m^2	PVR, Wood units	Correctable†
<4	<2.3	Yes
>8	>4.6	No
4-8	2.3–4.6	Individual patient evaluation in tertiary centers

*Criteria: the long-term impact of defect closure in the presence of pulmonary arterial hypertension (PAH) with increased PVR is largely unknown. There are a lack of data in this controversial area, and caution must be exercised. †Correctable with surgery or intravascular nonsurgical procedure.
PVR = pulmonary vascular resistance; PVRi = pulmonary vascular resistance index.

PAH Associated With Schistosomiasis

Schistosomiasis-associated PAH (Sch-PAH) was included in Group 1 in 2008. Previously it was in Group 4 (chronic thromboembolism disease). Today, Sch-PAH is potentially the most prevalent cause of PAH worldwide. Schistosomiasis affects over 200 million people, of whom 10% develop hepatosplenic schistomiasis (50). PAH occurs almost exclusively in this population, and 5% of patients with hepatosplenic schistosomiasis may develop PAH (51). The hemodynamic profile of Sch-PAH is similar to that of POPH (52). Its mortality rate may reach up to 15% at 3 years (52). Recent uncontrolled data indicate that PAH therapies may benefit patients with Sch-PAH (53).

Chronic Hemolytic Anemia

Chronic hemolytic anemia such as sickle cell disease, thalassemia, spherocytosis, and stomatocytosis are associated with an increased risk of PH. The cause of PH is unclear and often multifactorial, including chronic thromboembolism, splenectomy, high cardiac output, left-heart disease, and hyperviscosity; the role of an inactivation of nitric oxide by free plasma hemoglobin due to chronic hemolysis is controversial (54,55).

The prevalence and characteristic of PH in chronic hemolytic anemia has been extensively studied only in sickle cell disease (SCD). In SCD, PH confirmed by right-heart catheterization and defined as a mean PAP ≥25 mm Hg occurs in 6.2% (56) to 10% of patient (57). Post-capillary PH due to left-heart disease represents the most frequent cause, with a prevalence of 3.3% (56) to 6.3% (57). The prevalence of pre-capillary PH is lower but not rare: 2.9% (56) to 3.7% (57). The classification of pre-capillary PH associated with SCD has evolved during the successive world meetings, revealing uncertainties in potential causes.

Table 5 Hemodynamic Characteristics in Patients With PH Associated With SCD in 3 Different Cohorts: France, Brazil, and United States

Characteristic	French Cohort (56) (n = 24)	Brazilian Cohort (57) (n = 8)	U.S. Cohort (62) (n = 56)
RAP, mm Hg	10 ± 6	—	10 ± 5
mPAP, mm Hg	30 ± 6	33.1 ± 8.9	36 ± 9
PCWP, mm Hg	16 ± 7	16.0 ± 5.7	16 ± 5
CO, l/min–CI, l/min/m^2*	8.7 ± 1.9	5.00 ± 1.36*	8 ± 3
PVR, dyn·s·cm^{-5}	138 ± 58	179 ± 120	229 ± 149

*Cardiac index use instead of cardiac output in the Brazilian cohort.

CI = cardiac index; CO = cardiac output; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SCD = sickle cell disease.

In the Evian classification (2), it was placed in Group 4 (chronic thromboembolism). In the Venice and Dana Point classifications (3), it was shifted to Group 1 (PAH). Pre-capillary PHs belonging to Group 1 share some characteristics: 1) histological findings of major proliferation of the wall of pulmonary arteries including plexiform lesions; 2) severe hemodynamic impairment, with PVR >3 Woods units (240 dyn·s·cm^{-5}); and 3) well-documented response to PAH-specific therapies.

In SCD, autopsy studies providing insight into the characteristics of pulmonary vascular lesions are limited. The best-documented study (58) reported 20 cases and obtained photomicrographs of the lesions; among them, 12 patients were considered having plexiform lesions. In fact, 8 of these 12 cases had histological evidence of hepatic cirrhosis, which is a major confounding factor. Moreover, the picture of the pulmonary vascular changes considered plexiform lesions were not typical and may correspond to recanalyzed thrombi (P. Dorfmüller, personal communication, February 2013). Another autopsy study of 21 cases (59) reported 66.6% of microthrombotic and/or thromboembolic lesions, whereas mild moderate or severe pulmonary vasculopathy was observed in only one-third of this population. A larger autopsy study of 306 cases of SCD patients with a clinical suspicion of PH found thromboembolic lesions in 24% but no cases of pulmonary vasculopathy lesions (60). A recent review of autopsy cases in a single tertiary center in Brazil found that pulmonary vascular injuries are quite common in patients with SCD; however, not a single case with plexiform lesions could be found (61).

Three recent hemodynamic studies provided baseline hemodynamic data in patients with SCD and PH (56–62). Findings were similar among the 3 cohorts, with a high cardiac output between 8 and 9 l/min and moderate elevation in mean PAP (from 30 to 60 mm Hg) (Table 5). SCD patients with a pre-capillary PH had a modest elevation in PVR that was 3 or 4 times less than PVR observed in other PAH subgroups (Table 6). Among the 11 patients of the French SCD cohort with a confirmed pre-capillary PH (mean pulmonary artery pressure [mPAP] ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg), no patient fulfilled the hemodynamic criteria for PAH, defined as PVR >250 dyn·s·cm^{-5} (56).

Specific therapies approved for the treatment of PAH include prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. However, none of these agents is currently approved for the treatment of PH associated with SCD due to the lack of data in this specific population. Recently, the effect of bosentan was assessed in a randomized double-blind placebo-controlled trial of patients with sickle cell disease and PH (63). Overall, bosentan appeared to be well tolerated, although the small sample size precluded an analysis of its efficacy. Another randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of sildenafil was prematurely halted after interim analysis showed that sildenafil-treated patients were likely to have more acute sickle cell pain crises (35%) than placebo-treated patients (14%) (64). Furthermore, there was no evidence of treatment-related improvement at the time of study termination (64).

In summary, pre-capillary PH associated with SCD appears significantly different from other forms of PAH in regard to pathological findings, hemodynamic characteristics, and response to PAH-specific therapies. Therefore, it was decided to move PH associated with SCD from Group 1 (PAH) to Group 5 (unclear multifactorial mechanisms).

Other PH Groups

Persistent PH of the newborn has been withdrawn from Group 1 (PAH) because this entity carries more

Table 6 Comparison of Hemodynamics at Diagnosis in Different PAH Subgroups and in Pre-Capillary PH Associated With SCD

Hemodynamic	IPAH (43) (n = 288)	CTD-PAH (43) (n = 157)	POPH (43) (n = 127)	CHD-PAH (43) (n = 35)	HIV-PAH (38) (n = 58)	PH-SCD (43,56) (n = 11)
RAP, mm Hg	8 ± 5	7 ± 5	8 ± 6	7 ± 5	8 ± 5	5 ± 2
mPAP, mm Hg	49 ± 13	41 ± 9	47 ± 12	51 ± 16	49 ± 10	28 ± 4
PCWP, mm Hg	9 ± 4	8 ± 4	9 ± 04	8 ± 4	9 ± 5	10 ± 3
Cardiac index, l/min/m^2	2.4 ± 0.8	2.8 ± 0.9	3.0 ± 1.0	3.0 ± 1.0	2.9 ± 0.7	5.8 ± 1.3
PVR, dyn·s·cm^{-5}	831 ± 461	649 ± 379	611 ± 311	753 ± 370	737 ± 328	178 ± 55

Values are mean ± SD.

CHD = congenital heart disease; CTD = connective tissue disorders; HIV = human immunodeficiency virus; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; POPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SCD = sickle cell disease.

differences than similarities with other PAH subgroups. In the current classification, PPHN is designated 1. In agreement with the pediatric classification (65), congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to Group 2. There is no change for Group 3 (PH due to lung diseases and/or hypoxia) and for Group 4 (chronic thromboembolism). In Group 5 (unclear multifactorial mechanisms) chronic hemolytic anemia and segmental PH (pediatric classification) have been included. An update for Groups 2, 3, and 4 will be published separately in the same issue of this supplement (66–68), providing some important adaptations regarding definitions and management.

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REFERENCES

1. Hatano S, Strasser T, editors. Primary Pulmonary Hypertension. Report on a WHO Meeting. Geneva: World Health Organization, 1975:7–45.
2. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43 Supl:5S–12S.
3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43–54.
4. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243–78.
5. The Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219–63.
6. Machado RD, Eickelberg O, Elliott CG, et al. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54 Suppl:S32–42.
7. Harrison RE, Flanagan JA, Sankelo M, et al. Molecular and functional analysis identifies ALK-1 as the predominant cause of pulmonary hypertension related to hereditary haemorrhagic telangiectasia. J Med Genet 2003:40865–71.
8. Chaouat A, Coulet F, Favre C, et al. Endoglin germline mutation in a patient with hereditary haemorrhagic telangiectasia and dexfenfluramine associated pulmonary arterial hypertension. Thorax 2004;59:446–8.
9. Nasim MT, Ogo T, Ahmed M, et al. Molecular genetic characterization of SMAD signaling molecules in pulmonary arterial hypertension. Hum Mutat 2011;32:1385–9.
10. Austin ED, Ma L, LeDuc C, et al. Whole exome sequencing to identify a novel gene (Caveolin-1) associated with human pulmonary arterial hypertension. Circ Cardiovasc Genet 2012;5:336–43.
11. Ma L, Roman-Campos D, Austin E, et al. A novel channelopathy in pulmonary arterial hypertension. N Engl J Med 2013;369:351–61.
12. Boutet K, Frachon I, Jobic Y, et al. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 2009;33:684–8.
13. Savale L, Chaumais M-C, Cottin V, et al. Pulmonary hypertension with benfluorex exposure. Eur Respir J 2012;40:1164–72.
14. Frachon I, Etienne Y, Jobic Y, et al. benfluorex and unexplained valvular heart disease: a case-control study. PLoS One 2010;5:e10128.
15. Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukaemia. Leuk Res 2009;33:861–4.
16. Montani D, Bergot E, Gunther S, et al. Pulmonary hypertension in patients treated by dasatinib. Circulation 2012;125:2128–37.
17. Caravita S, Secchi MB, Wu SC, et al. Sildenafil therapy for interferon-β1-induced pulmonary arterial hypertension: a case report. Cardiology 2011;120:187–9.
18. Dhillon S, Kaker A, Dosanjh A, et al. Irreversible pulmonary hypertension associated with the use of interferon alpha for chronic hepatitis C. Dig Dis Sci 2010;55:1785–90.
19. Savale L, Gunther S, Chaumais M-C, et al. Pulmonary arterial hypertension in patients treated with interferon. Available at: https://www.ersnetsecure.org/public/prg_congres.abstract?ww_i_presentation=63109. Accessed November 2013.
20. George PM, Badiger R, Alazawin, et al. Pharmacology and therapeutic potential of interferons. Pharmacol Ther 2012;135:44–53.
21. Chambers CDE, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–5.
22. Chambers CD, Hernandez-Diaz S, Van Martere LJ, et al. Serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354:579–87.
23. Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2008;14:801–6.
24. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2009;18:246–52.
25. Wichman CI, Moore KM, Lang TR, et al. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. Mayo Clin Proc 2009;84:23–7.
26. Wijson KL, Zelig CM, Harvey JP, et al. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. Am J Perinatol 2011;28:19–24.
27. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 2011;344:d8012.
28. Karaman MG, Atalay F, Tufan AE, et al. Pulmonary arterial hypertension in an adolescent treated with methylphenidate. J Child Adloesc Psychopharmacol 2010;20:229–31.
29. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792–800.
30. Mukerjee D, St. George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–93.
31. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156–63.
32. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15.
33. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522–30.
34. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum 2013;65:1074–84.
35. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med 2008;177:108–13.
36. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation 1994;89:2722–7.
37. Sitbon O, Yaïci A, Cottin V, et al. The changing picture of patients with pulmonary arterial hypertension in France. Eur Heart J 2011;32 Suppl 1:675–6.
38. Degano B, Yaïci A, Le Pavec J, et al. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. Eur Respir J 2009;33:92–8.
39. Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100:520–8.

40. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology 2003;37:401–9.
41. Le Pavec J, Souza R, Herve P, et al. Portopulmonary hypertension: survival and prognostic factors. Am J Respir Crit Care Med 2008;178:637–43.
42. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the U.S.-based REVEAL registry. Chest 2012;141:906–15.
43. Sitbon O, Yaïci A, Cottin V, et al. The changing picture of patients with pulmonary arterial hypertension in France. Eur Heart J 2011;32 Suppl 1:675–6.
44. Engelfriet PM, Duffels MG, Möller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect the Euro Heart Survey on adult congenital heart disease. Heart 2007;93:682–7.
45. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007;120:198–204.
46. Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J Am Coll Cardiol 2011;26:538–46.
47. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163–72.
48. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation 2003;107:3204–8.
49. Goldberg DJ, French B, McBride MG, et al. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: a randomized double-blind placebo-controlled crossover trial. Circulation 2011;123:1185–93.
50. World Health Organization. Shistosmiasis Fact sheet 115. Updated March 2013.
51. Lapa M, Dias B, Jardim C, Fernandes CJ, et al. Cardiopulmonary manifestations of hepatosplenic schistosomiasis. Circulation 2009;119:1518–2.
52. Dos Santos Fernandes CJ, Jardim CV, Hovnanian A, et al. Survival in schistosomiasis-associated pulmonary arterial hypertension. J Am Coll Cardiol 2010;56:715–20.
53. Fernandes CJ, Dias BA, Jardim CV, et al. The role of target therapies in schistosomiasis-associated pulmonary arterial hypertension. Chest 2012;141:923–8.
54. Bunn HF, Nathan DG, Dover GJ, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. Blood 2010;116:687–92.
55. Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med 2012;185:1154–65.
56. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365:44–53.
57. Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J 2012;39:112–8.
58. Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. Hum Pathol 2002;33:1037–43.
59. Graham JK, Mosunjac M, Hanzlick RL, et al. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. Am J Forensic Med Pathol 2007;28:168–72.
60. Manci EA, Culberson DE, Yang YM, et al. Causes of death in sickle cell disease: an autopsy study. Br J Haematol 2003;123:359–65.
61. Fonseca GH, Souza R, Salemi VM, et al. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J 2012;39:112–8.
62. Mehari A, Gladwin MT, Tian X, et al. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA 2012;307:1254–6.
63. Barst RJ, Mubarak KK, Machado RF, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. Br J Haematol 2010;149:426–35.
64. Machado RF, Barst RJ, Yovetich NA, Hassell KL. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood 2011;118:855–64.
65. Ivy D, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62 Suppl:D118–27.
66. Vachiery J-L, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013;62 Suppl:D100–8.
67. Seeger W, Adir Y, Barberà JS, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol 2013;62 Suppl:D109–16.
68. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62 Suppl:D92–9.

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