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PULMONARY HYPERTENSION (JR KLINGER, SECTION EDITOR)

Medical Management of Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms (Group 5): Is There a Role for Pulmonary Arterial Hypertension Medications?

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Abstract
Purpose of Review The purpose of this review was to outline the mechanisms and to review recent literature on pulmonary arterial hypertension (PAH) medications in group 5 pulmonary hypertension (PH).
Recent Findings The first steps in management are to understand the mechanisms and hemodynamic profile and to exclude chronic thromboembolic disease. Recent studies in the past 5 years have found that PAH medications may improve hemodynamics in patients with pre-capillary pulmonary hypertension due to sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, and myeloproliferative disorders with dasatinib-induced PH. Improvements in exercise capacity are uncommon, and no survival benefit has been demonstrated. There is a risk of pulmonary edema in patients with pulmonary venous involvement or fibrosing mediastinitis when treated with PAH therapies.
Summary There is limited evidence supporting the use of PAH medications in group 5 patients, and they may be harmful in certain cases. In most patients with group 5 PH, treatment should be directed to the underlying disease with PAH therapies reserved for patients with severe pre-capillary PH.

Keywords Pulmonary arterial hypertension · PAH · Group 5 pulmonary hypertension · Hypertension treatment

This article is part of the Topical Collection on *Pulmonary Hypertension*

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Introduction

Pulmonary hypertension (PH) is classified into five groups according to similar underlying pathophysiology, hemodynamic profiles, and management strategies [1]. Group 5 consists of rare diseases that are associated with PH through multifactorial and/or poorly understood mechanisms (Table 1). Potential mechanisms vary between and within each condition, but may include pulmonary vasoconstriction, proliferation, and fibrosis of the pulmonary arteries and veins, parenchymal and vascular destruction, extrinsic compression or proximal pulmonary vessels, high cardiac output, and elevated left heart pressure (Fig. 1) [2, 3].

The objectives of the current review are to outline the pathophysiologic mechanisms of group 5 PH, to critically evaluate recent literature to address the role of therapies approved in group 1 PAH (pulmonary arterial hypertension, PAH) in each condition, and to clarify the role of other emerging or established medical therapies for group 5 PH.

Chronic Hemolytic Anemias

PH is a significant complication of chronic hemolytic anemias, particularly sickle cell disease (SCD), but also other hemolytic anemias [4–6]. The pathophysiology of PH due to chronic hemolytic anemia is not fully understood, but multiple

Table 1 5th World Symposium clinical 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

mechanisms are thought to contribute. The histological lesions observed in SCD are different than those observed in idiopathic PAH and mainly include in situ thrombosis, intimal and medial hypertrophy, and capillary hemangiomatosis [7, 8]. Moreover, hemodynamics are most often characterized by moderate elevation of pulmonary pressure with high cardiac output and/or post-capillary PH with an elevated pulmonary artery wedge pressure (PAWP) [5, 6]. Chronic hemolysis may lead to depletion of nitric oxide (NO) and its precursors, due to scavenging of endothelial derived NO by free hemoglobin, thereby impairing vascular endothelial function [9, 10]. Hemolysis promotes a hypercoagulable state via several pathways including NO depletion, platelet activation, and functional asplenia, which promote in situ thrombosis. Of note, cases of chronic thromboembolic PH (CTEPH, group 4 PH) have been reported in SCD, and some patients can be successfully treated with pulmonary endarterectomy [11] or balloon pulmonary angioplasty. The high cardiac output due to chronic anemia also may induce endothelial dysfunction from flow-induced shear stress.

In SCD, the estimated prevalence of PH ranges between 5 and 10% of patients, half of which correspond to pre-capillary PH (mPAP ≥ 25 mmHg and PAWP ≤ 15 mmHg). Because of the detrimental impact of PH on functional status and overall survival, early detection and adapted management are necessary [4, 7]. Prospective studies failed to demonstrate efficacy of PAH therapies and suggested specific safety issues in SCD patients. Two randomized, double-blind, placebo-controlled studies assessed the effect of bosentan, a dual endothelin receptor antagonist (ERA), in SCD-associated PH. The ASSET-1 and ASSET-2 studies enrolled patients with pre-capillary and post-capillary PH. Due to insufficient enrolment (n = 26), these studies were terminated early and the primary efficacy end points (pulmonary vascular resistance [PVR] and 6-minute walk distance [6MWD]) were not analyzed [12]. The effect of sildenafil, a phosphodiesterase type 5 inhibitor (PDE5i), was studied in patients with increased tricuspid regurgitation velocity and a low exercise capacity (Table 2). This study was stopped because of a significant increase in hospitalization for pain in patients treated with sildenafil [13]. Therefore, PAH medication initiation in this population should probably be discussed only on a case-by-case basis and, more specifically, should be restricted to patients with severe pre-capillary PH with cardiac output impairment. Another alternative strategy in the management of PH in these patients is to intensify treatment of the underlying disease either by the initiation of treatment with hydroxycarbamide and/or by initiating an exchange transfusion program. This alternative therapeutic approach is important to consider and must be also properly and prospectively evaluated [14•].

PH is also observed in other chronic hemolytic anemias such as hereditary spherocytosis, stomatocytosis, thalassemia, and paroxysmal nocturnal hematuria. Sildenafil therapy was evaluated in a non-randomized cohort of thalassemia patients with a Doppler-defined high risk of PH (n = 10), which resulted in improvement in New York Heart Association (NYHA) functional class and a moderate decrease in tricuspid regurgitation velocity; however, there was no improvement in 6MWD [15]. No data are available for PAH therapies in the other chronic hemolytic diseases.

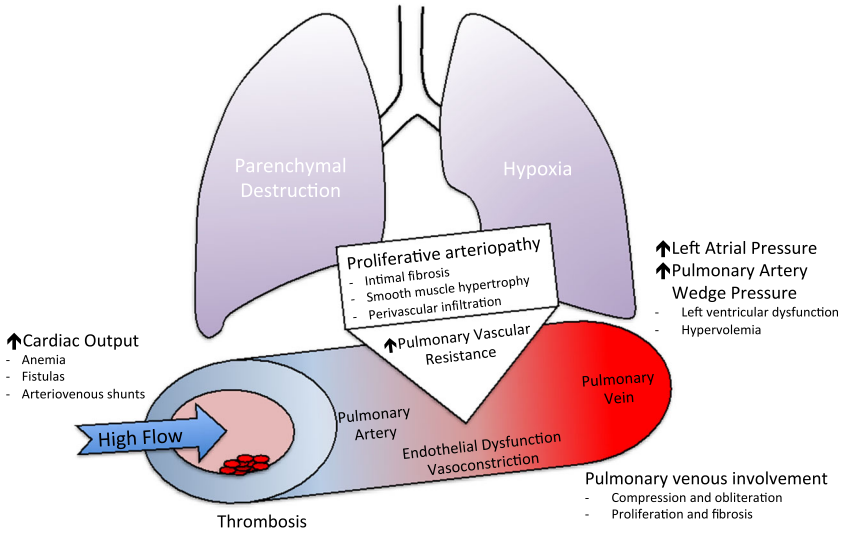

Fig. 1 Mechanisms of increased pulmonary arterial pressure in patients with group 5 pulmonary hypertension

Myeloproliferative Disorders

Myeloproliferative disorders (MPD), including chronic myelogenous leukemia (CML), polycythemia rubra vera (PRV), essential thrombocytosis (ET), and primary myelofibrosis, are clonal hematopoietic diseases which may lead to PH through several potential mechanisms (Fig. 1) [3, 16]. Hyperviscosity, platelet activation, and thrombosis occur in PRV and ET, which may lead to CTEPH [17]. Splenectomy, which may be a treatment for MPDs, is also associated with CTEPH and a plexogenic arteriopathy resembling pathologic changes observed in idiopathic PAH [18, 19]. Medications used to treat MPDs may also cause PH: pulmonary veno-occlusive disease (PVOD) has been associated with anagrelide use for MPD and myelodysplastic syndrome [20], and dasatinib, a tyrosine kinase inhibitor (TKI) used in CML, can cause pre-capillary pulmonary arterial hypertension (PAH) [21]. Portal hypertension, pulmonary infiltration by hematopoietic cells, and extramedullary hematopoiesis may also lead to pre-capillary PH [17, 22, 23]. Lastly, a high-cardiac output state may also increase pulmonary artery pressure, or can cause left ventricular dysfunction and post-capillary PH (Fig. 1) [16, 22, 24]. The incidence of pre-capillary PH in MPDs is not known as many studies demonstrating PH used only echocardiography and did not perform right heart catheterization [25–28].

Given the heterogeneity and rarity of PH in MPDs, there are limited data to guide the use of PAH-specific therapies. Generally, the prognosis of patients with MPDs and PH is

Table 2 Prospective controlled trials with specific PAH medications in sickle cell disease-associated PH

Author, date of publication	Drug	Number of patients	Inclusion criteria	Primary endpoints	Results
Barst, 2010	Bosentan	26	• ASSET 1 - mPAP ≥ 25 mmHg / PAWP ≤ 15 mmHg - PVR ≥ 160 dynes - 6MWD 150–450 m • ASSET 2 - mPAP ≥ 25 mmHg - PCWP ≤ 15 mmHg and PVR 100–160 dynes - or PAWP 16–25 mmHg and PVR ≥ 100 dynes	Change in PVR at week 16	- Studies were terminated due to slow site initiation and patient enrolment - Primary end points not analyzed - Non-significant decreases in PVR were observed with bosentan
Machado, 2011	Sildenafil	74	- TRV ≥ 2.7 m/s - 6MWD 150–500 m	Change in 6MWD at week 16	- Study was stopped early due to a higher percentage of serious adverse events in the sildenafil arm - Sildenafil appeared to increase hospitalization rates for pain in patients with SCD - No significant effect on 6MWD

6MWD six-minute walk distance, *PAWP* pulmonary artery wedge pressure, *SCD* sickle cell disease, *TRV* tricuspid regurgitation velocity

poor [29]. Cytoreductive therapy with agents such as hydroxyurea can control MPD but may not necessarily improve PH [29, 30]. A recent case report described resolution of PAH in a patient with myelofibrosis after allogeneic hematopoeitic stem cell transplant, allowing the discontinuation of PAH therapies [31]. In patients with CTEPH associated with MPDs, the treatment of choice is pulmonary endarterectomy [32]; however, some patients may not be candidates for surgery. Riociguat, a stimulator of soluble guanylate cyclase, may be considered for symptomatic patients with inoperable CTEPH or in those with residual PH post endarterectomy [33, 34]; however, there are no published data on riociguat use specifically in CTEPH related to MPDs. In patients with PAH induced by dasatinib, discontinuation of dasatinib alone may result in resolution or improvement of PAH [21, 35•]. We have recently reported 21 cases of dasatinib-induced PAH, most of which had CML. PAH therapies (n = 8) or calcium channel blockers (n = 2) were used in 10 patients with more severe hemodynamic abnormalities at baseline. Treated patients had similar long-term clinical and hemodynamic outcomes when compared to those who were untreated [35•]. We thus suggest that dasatinib-induced PAH patients with severe symptoms (NYHA III or IV) or with severe hemodynamic impairment (CI < 2.5–3.0 L/min/m^2) receive PAH therapies in addition to discontinuing dasatinib [35•, 36]. Small case series and case reports have described the use of epoprostenol, ERAs, and PDE5i in patients with pre-capillary PAH with MPDs; however, there are inadequate data to determine whether these medications are safe or effective [17, 23, 29].

In a recent study by Tabarroki et al., ruxolitinib, an oral Janus kinase (JAK) inhibitor, improved echocardiographic measures of mean right ventricular systolic pressure (RVSP) from 50.6 to 35.6 mmHg, increased NO levels, and reduced NT-pro BNP and inflammatory cytokine levels in patients with myelofibrosis and PH [37]. These results suggest that abnormal JAK signaling in myelofibrosis may promote PH through NO depletion or through elevations in key inflammatory cytokines such as interleukin (IL)-6, which is known to be involved in the pathogenesis of group 1 PAH [37–40]. Paradoxically, a patient with mild resting PH on echocardiogram (RVSP 43 mmHg) developed severe pre-capillary PH and right ventricular dysfunction shortly after starting ruxolitinib for JAK2 mutation-positive myelofibrosis, which improved significantly after stopping ruxolitinib, suggesting a drug-induced aggravation [41]. Whether the beneficial effects of ruxolitinib are limited to patients without pre-capillary PH is unclear. Right heart catheterizations were not performed in the study by Tabarroki et al. so hemodynamic profiles of PH (pre-capillary, high cardiac output, post-capillary) were not known [37].

Splenectomy

The prevalence of splenectomy is increased in cohorts of patients with idiopathic PAH and CTEPH [18, 19]. A plexogenic arteriopathy has been observed in these patients, but distal or proximal chronic thromboembolic sequela mainly characterized the vascular pathological lesions in this setting. In the international prospective CTEPH registry, 3.4% of patients had a history of splenectomy [42]. These cases were more frequently associated with non-operability, highlighting the role of in situ thrombosis in distal CTEPH. The hypercoaguable state in asplenism could be due to abnormal post-splenectomy erythrocytes and platelet microparticles [43].

The assessment of patients with post-splenectomy-associated PH is based firstly on an evaluation for post-embolic lesions. In cases with confirmed CTEPH, the management should be identical to other patients in group 4 (Table 1). Endarterectomy must be discussed for patients with proximal CTEPH. In patients with distal lesions, medical therapies and balloon pulmonary angioplasty are potential treatment options. The proportions of patients with a history of splenectomy in prospective clinical trials evaluating bosentan or riociguat in non-operable or recurrent CTEPH were not mentioned [33, 44]. Therefore, no specific data on medical therapies efficacy in this population are available.

Sarcoidosis

Pulmonary vascular involvement is frequently observed in sarcoidosis, particularly in the advanced stage of the disease. The mechanisms that lead to PH in sarcoidosis are multiple and often combined. This observation justifies the classification of sarcoidosis-associated PH as group 5 PH. In cases of post-capillary PH on right heart catheterization (mPAP ≥ 25 mmHg and PAWP > 15 mmHg), specific left heart diseases or pulmonary vein compression by fibrosing mediastinitis must be systematically sought. In the setting of pre-capillary PH (mPAP > 25 mmHg and PAWP ≤ 15 mmHg), three main mechanisms have been identified and must be discerned in order to appropriately adapt patient management [45]. Pre-capillary PH may be secondary to parenchymal fibrosis leading to vascular bed destruction and/or vascular remodeling due to chronic hypoxia. In this situation, pulmonary pressures are usually moderately elevated (< 35 mmHg) and cardiac output remains conserved for a long time, as is often observed in group 3 PH due to lung diseases (Table 1). Some patients may develop more severe pre-capillary PH, suggesting the development of a granulomatous pulmonary vasculopathy. Several studies have reported both arterial and venular involvement combining typical sarcoid granulomata in the vascular wall and pulmonary vascular remodeling, leading to progressive elevation of PVR [45–47]. The last potential

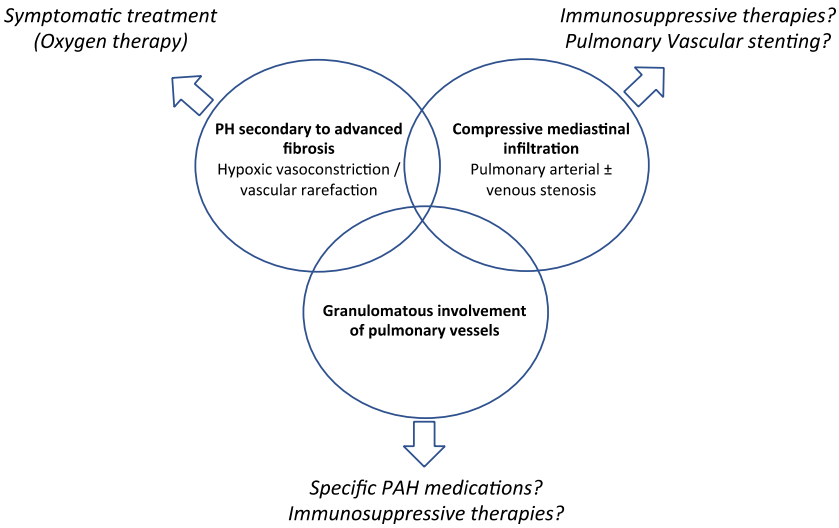

Fig. 2 Main mechanisms of pre-capillary pulmonary hypertension and specific management in sarcoidosis. *PH* pulmonary hypertension, *PAH* pulmonary arterial hypertension

mechanism of PH is compressive mediastinal infiltration by adenopathy or fibrosing mediastinitis (Fig. 2) [48•]. Whatever the identified mechanism, PH is a major prognostic factor and impairs the functional capacity of patients with sarcoidosis. The 5-year-survival rate of sarcoidosis-associated PH was approximately 40% in a previous study [49] and 55% in a more recent study from our group [50••].

Therefore, screening for PH, accurate diagnosis of PH, and selection of an optimal treatment strategy are important issues in sarcoidosis. However, recommendations on the specific management of sarcoidosis-associated PH are lacking. The therapeutic strategy for such patients is mainly based on cohort studies with low numbers, uncontrolled trials, or clinical cases whose results are sometimes discordant. The use of PAH-specific medications could be an interesting option in selected patients with specific vascular involvement, but this remains to be adequately evaluated. Only one prospective randomized controlled trial reported a beneficial effect of bosentan on pulmonary hemodynamics at 16 weeks; however, there was no improvement in exercise capacity [51••]. Similarly, other retrospective studies observed improvement in hemodynamics with different PAH-targeted medications [52] or prostacyclin therapy [53•] without clear effects on exercise capacity. In our recent study of 126 patients with sarcoidosis-associated PH from the French PH Registry, PVR significantly improved from 9.7 ± 4.4 to 6.9 ± 3.0 Wood units and NYHA functional class improved in the 97 patients who received PAH therapies, but without a significant improvement in 6MWD [50••]. A major issue with PAH-targeted therapy in patients with parenchymal lung disease is the potential risk of worsening gas exchange due to worsening ventilation/perfusion mismatch. Their impact on gas exchange should be regularly assessed irrespective of the class of drugs used. Therefore, we consider that initiation of such therapies should be avoided in cases with advanced fibrosis and severe gas exchange impairment.

The effect of immunosuppressive therapy on sarcoidosis-associated PH needs to be specifically evaluated in patients with compressive lymphadenopathy or with specific arterial involvement by an inflammatory process. 18F-FDG PET scans may be helpful to detect patients with sarcoidosis-associated PH who might respond to immunosuppressive therapy [50••]. Isolated cases of hemodynamic improvement have been reported with immunosuppressive therapies alone [45, 50••]. In cases of pulmonary vascular stenosis from external compression, therapeutic successes have been reported with pulmonary angioplasty and stenting [54, 55]. However, the hemodynamic effects and long-term efficacy of these procedures are currently unknown. Venous stenting can be complicated by recurrent stenosis or thrombosis. Because of the poor prognosis of sarcoidosis-associated PH, eligibility for lung transplantation should be assessed relatively early in the management.

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a smoking-related lung disease that is characterized by airflow obstruction, granulomatous inflammation, parenchymal nodules, and cysts. Pre-capillary PH is highly prevalent (92–100%) in advanced PLCH [56, 57]. Although many advanced patients have hypoxemia and moderate-to-severe airflow obstruction, the severity of PH is not related to the degree of airflow obstruction [56]. A diffuse proliferative vasculopathy involving pulmonary arteries and arterioles may be present in PLCH patients with severe PH, and these changes usually occur in regions unaffected by parenchymal lesions [56]. Venous fibrotic obliteration and capillary dilatation are also observed and may resemble PVOD [56, 58]. In a study by Fartoukh et al., two patients who were treated with intravenous epoprostenol developed pulmonary edema, similar to what may occur in patients with PVOD [56, 59, 60].

The occurrence of pulmonary edema may have led clinicians to consider PLCH a relative contraindication to PAH-specific therapies for some time. Long-term functional and hemodynamic benefits with bosentan were published nearly a decade later [61]. Le Pavec et al. published a retrospective cohort of 29 patients with PH related to PLCH, 14 of whom received PAH therapies [62]. Patients who received PAH therapies had more severe hemodynamics (higher mPAP and PVR) with less severe airflow obstruction and less hyperinflation than patients not treated with PAH therapies. Among treated patients, short-term improvements in functional class occurred in 67%, improvements in 6MWD of ≥ 10% occurred in 45%, and there was a 33% decrease in PVR, which were sustained at long-term re-evaluation [62]. The 1-, 3-, and 5-year survival rates in the Le Pavec et al. study were 96, 92, and 75%, respectively, and there was a trend to improved survival in patients treated with PAH therapies in univariate analysis [62]. Importantly, in contrast to the study by Fartoukh et al., patients treated with PAH therapies did not develop worsening oxygenation or pulmonary edema, suggesting that these therapies may indeed be safe and beneficial in pre-capillary PH related to PLCH [56, 62]. There have been no prospective or head-to-head comparisons of PAH-specific therapies in PLCH, but it is likely that ERAs and PDE5 inhibitors are effective. Supporting this notion is a recent case report describing the successful use of sildenafil to lower the mPAP and PVR by nearly 50% in order to bridge a 28-year-old patient with progressive PLCH-related PH who had failed oxygen, diuretics, and corticosteroids to lung transplantation [63].

Other recent case reports describe clinical responses to tadalafil [64], bosentan in conjunction with a cardiac rehabilitation program [65], sildenafil and iloprost [66], and smoking cessation [67]. In addition to corticosteroids and PAH-specific therapies, cladribine is an anti-proliferative nucleoside analogue that has been reported to improve lung disease in patients with PLCH [68–70] and also improved mPAP, PVR, and cardiac index in a patient with pre-capillary PH related to PLCH [71]. Although smoking cessation remains the most important intervention for all PLCH patients, oral PAH therapies may be considered to improve symptoms and hemodynamics and may potentially support patients with PH awaiting lung transplantation. However, because of frequent venous involvement, clinicians must be aware of the potential for pulmonary edema and monitor closely for clinical decompensation after starting PAH therapies.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease caused by neoplastic proliferation of abnormal smooth muscle cells that leads to diffuse cystic lung disease, chylous effusions and ascites, renal angiomyolipomas, and lymphangioleiomyomatosis [72•, 73]. LAM almost exclusively affects women and may occur sporadically or may be heritable in association with the tuberous sclerosis complex (TSC) [74]. Resting PH occurs in approximately 7–8% of patients with LAM; however, exertional hypoxemia and increases in pulmonary arterial pressure are common, even during low-intensity exercise [75, 76]. The prevalence of resting PH is higher (45%) in LAM patients referred for lung transplantation [77]; however, the severity of PH is generally milder (average mPAP 33 mmHg) compared to patients with end-stage PLCH (average mPAP 59 mmHg) [56].

The largest study of PH in LAM patients was from the French Registry by Cottin et al. who described the characteristics, management, and outcomes of 20 patients [78]. Most patients had severe airflow obstruction (FEV_1 < 50% predicted) and mild-moderate PH (mPAP 32 ± 6 mmHg and PVR 4.7 ± 2.3 Wood units); however, two patients had more severe "out-of-proportion" PH (mPAP > 35 mmHg with a normal FEV_1). Exercise capacity, FEV_1, $PaCO_2$, and DLCO were lower in LAM patients with PH compared to those without PH. Lung pathology showed LAM cell and perivascular epithelioid cell proliferation in addition to intimal fibrosis in some of these patients [78]. Severe PH is likely related to LAM-cell vasculopathy rather than parenchymal cystic destruction or a severe obstructive ventilatory defect and hypoxemia. Despite the presence of some pathologic similarities to group 1 PAH, such as intimal fibrosis in pulmonary arteries, the role of PAH therapies is unproven in LAM. Six patients (30%) in the series by Cottin et al. received PAH therapies (bosentan or sildenafil), with hemodynamic improvements and no detrimental effect on gas exchange or episodes of pulmonary edema, but no improvements in dyspnea or 6MWD were observed [78]. There have been no recent studies reporting the efficacy and safety of other PAH medications in LAM.

Sirolimus and everolimus inhibit the mechanistic target of rapamycin (mTOR) pathway and improve lung function, quality of life, chylous effusions, cystic lesions, and exercise capacity in patients with LAM [79–82]; however, it is unknown whether these agents have any effect on pulmonary hemodynamics in LAM patients with PH. Nevertheless, sirolimus is recommended for patients with abnormal or declining lung function or chylous effusions in recent international guidelines [72•], regardless of whether PH is present.

Metabolic Disorders and Other Etiologies

Glycogen storage diseases (GSD), lysosomal storage disorders (Gaucher disease), thyroid disorders, chronic renal failure, tumor emboli, and fibrosing mediastinitis can cause PH and are included in group 5 [1].

GSDs are genetic disorders of glycogen metabolism that lead to deposition of glycogen in multiple organs and are typically diagnosed in infancy or early childhood [83, 84]. PH has been

best characterized in patients with GSD type I [85–87] but can occur in other types. Patients with PH related to GSD type I may have pathologic changes typical of idiopathic PAH (intimal fibrosis, plexiform lesions, smooth muscle hypertrophy) [85, 87] and have dramatically elevated serum serotonin levels, suggesting common pathogenic mechanisms to idiopathic PAH [86]. Given these similarities, PAH-specific therapies may be reasonable, but there are only case reports to support their efficacy [88]. Lee et al. described two patients with GSD type III and severe pre-capillary PH: one patient was treated with intravenous epoprostenol with an initial response but died of cardiopulmonary arrest 2 years later, while a second patient had a good clinical response to sildenafil and was alive 3 years later [89].

Gaucher disease is caused by deficiency in lysosomal beta-glucosidase, which results in accumulation of glucosylceramide within cells, commonly leading to complications such as hepatosplenomegaly and bone marrow infiltration [3]. Echocardiography changes suggestive of PH are detected in 7–30% of patients with Gaucher disease [90, 91], and a plexogenic pulmonary arteriopathy similar to idiopathic PAH has been described [90, 92]. Left ventricular disease and diastolic dysfunction are other potential mechanisms of PH in Gaucher disease [93]. Splenectomy and absence of enzyme replacement are associated with the development of severe PH and death [91, 94]. The use of enzyme replacement therapy has led to lower splenectomy rates [95], and it may be expected that severe PH will become less frequent in Gaucher disease [96, 97]. However, severe PH can still occur or may worsen in patients taking enzyme replacement therapy [98]. Successful treatment with intravenous epoprostenol has been reported in patients with Gaucher disease [91, 99]. Mistry et al. reported nine patients with severe PH, six of whom were treated with enzyme replacement, epoprostenol, and anticoagulation, and they noted improvements in functional class and RVSP [91]. Bosentan and sildenafil have also been used in Gaucher patients with clinical improvements [97, 100]. A recent case report described a patient who failed to improve with intravenous treprostinil or oral PAH therapies but dramatically improved with imatinib [101]; however, this TKI is not recommended to treat PH and it has been shown to have a high rate of complications in group 1 PAH [102].

A clear link between thyroid disease and PH has been established [103–105]. Hypothyroidism and hyperthyroidism have been associated with PH via several mechanisms including autoimmunity, vascular proliferation, and high- or low-output heart failure [3, 104–106]. Autoimmune thyroid disease is also more frequent in patients with PAH [105], and low thyroid hormone levels and lack of thyroid replacement in PAH and CTEPH patients with hypothyroidism predict worse outcomes [107]. Restoration of normal thyroid function in patients with hyperthyroidism via medical treatment or surgical thyroidectomy may completely normalize pulmonary arterial pressure [108–110]. When pre-capillary PH persists despite normalization of thyroid function, PAH therapies may be introduced in accordance with current guidelines [111, 112•].

In dialysis-dependent patients with chronic kidney disease (CKD), the prevalence of PH on echocardiography increases with the severity of renal dysfunction, and the presence of PH in CKD is associated with higher mortality [113, 114]. Conversely, among patients diagnosed with PH, the presence of CKD is associated with higher mortality [115]. PH may develop in CKD for several reasons; however, it is most frequently post-capillary PH due to left ventricular systolic or diastolic dysfunction, hypervolemia, anemia, or high-output through arteriovenous fistulas [24, 113, 116]. Optimization of volume status, correction of anemia, and management of left heart disease are therefore the primary treatment strategies. Pre-capillary PH may persist in a minority after initiation of dialysis or optimization of other factors, which may warrant consideration of PAH therapy in symptomatic patients. Longer-acting PAH therapies such as tadalafil, ambrisentan, and macitentan should be avoided in patients with poor renal function. A recent case report described the addition of subcutaneous treprostinil to bosentan and sildenafil in a patient with severe pre-capillary PH on dialysis [117]. There was normalization of the patient's PVR and a decrease in mPAP from 30 to 25 mmHg, suggesting that prostanoids could be an option for patients failing oral therapy [117].

The French Registry recently reported the outcomes and management of 27 patients with PH due to fibrosing mediastinitis, which results from fibrous proliferation and compression of mediastinal vessels [48•]. Hemodynamics were consistent with pre-capillary PH, but some patients had post-capillary or combined pre- and post-capillary PH. Unfortunately, no significant improvement was observed in seven patients who received oral PAH therapies in this study and the authors cautioned the use of PAH therapies due to pulmonary venous compression and an increased risk of pulmonary edema [48•]. Corticosteroids may be effective in selected cases of fibrosing mediastinitis with PH due to sarcoidosis [48•, 50••], as discussed above, and rituximab was effective in three cases of fibrosing mediastinitis due to histoplasmosis [118]; however, none of these patients had coexisting PH. Finally, percutaneous dilation, stenting, or surgical reconstruction of pulmonary arteries and veins can be considered in certain cases with clear compression of the central vessels due to fibrosing mediastinitis [55, 119, 120].

Conclusions

Group 5 PH is a heterogeneous collection of diseases that cause PH through multifactorial and/or poorly understood mechanisms. Importantly, there is very little data to support

the use of medical therapies approved for group 1 PAH in group 5 PH patients and management is generally targeted towards the underlying disease process. Studies using PAH therapies are largely limited to registry-based case series and case reports, with only a few randomized trials being performed in this understudied group of diseases. Rational and cautious use of PAH therapies in group 5 PH must be based on an understanding of the potential underlying mechanisms in each disease subgroup and a proper assessment of hemodynamics. There is the potential for pulmonary venous involvement in many of these conditions, which could be made worse by pulmonary vasodilators.

Compliance with Ethical Standards

Conflict of Interest Dr. Humbert reports personal fees from Actelion Pharmaceuticals Ltd., grants and personal fees from Bayer, grants and personal fees from GSK, personal fees from Pfizer and United Therapeutics, during the conduct of the study; and personal fees from Novartis, outside the submitted work. Dr. Weatherald reports grants from the European Respiratory Society, grants from the Canadian Thoracic Society, grants from the Canadian Vascular Network, personal fees and non-financial support from Actelion, and personal fees and non-financial support from Bayer, outside the submitted work. Dr. Savale reports grants, personal fees and non-financial support from Actelion Pharmaceuticals, grants, personal fees and non-financial support from Bayer, grants and personal fees from Pfizer, grants, personal fees and non-financial support from GlaxoSmithKline, grants, personal fees and non-financial support from MSD, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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