REGULAR ARTICLE

Sarcoidosis-Associated Pulmonary Hypertension

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Sarcoidosis is characterized by non-necrotizing granulomatous aggregations affecting a range of organs, with thoracic structures involved in 90% to 95% of cases. This granulomatous disease can impact the pulmonary vasculature via different mechanisms resulting in sarcoidosis-associated pulmonary hypertension (SAPH). These include postcapillary disease (left heart disease), immune-mediated granulomatous vasculopathy, hypoxemia, thromboembolism, pulmonary vascular compression and/or stenosis by mediastinal lymph nodes/fibrosis, or sarcoidosis-related portal hypertension. SAPH is a serious complication, especially in those with end-stage lung disease. A thorough evaluation is crucial to delineate the predominant mechanism of PH in the affected individual. The management of SAPH is complex and necessitates a personalized, multifaceted approach, targeting the specific mechanisms and underlying pathologies. Such patients are best served at specialized Pulmonary Hypertension and Sarcoidosis Centers. A notable phenotype within SAPH is the "pulmonary arteriopathy" group, characterized by milder parenchymal disease and a favorable response to PAH-targeted therapy, whereas patients with active granulomatous inflammation are likely to respond to immunosuppression. Several PAH therapies have been used to treat SAPH, however, clear direction on the use of PAH therapies in SAPH is still lacking. Patients receiving pulmonary vasodilators should be carefully monitored for potential deterioration in gas exchange or development of pulmonary edema, which could suggest underlying left heart disease or pulmonary veno-occlusive disease. Timely referral for lung transplant evaluation is crucial for those with SAPH and severe parenchymal lung disease, ensuring a comprehensive and patient-centered care approach. Much work remains to be done to understand the exact pathogenesis of SAPH, as well as to develop therapies that clearly improve outcomes for these patients.

INTRODUCTION

Sarcoidosis is a multisystem disease characterized by the aggregation of nonnecrotizing granulomas in various organs. Thoracic involvement is the most common, found in 90% to 95% of the cases.[1] The disease can affect all chest compartments, including the lung parenchyma, airways, lymph nodes and lymphatic vessels, pleural space, and pulmonary vasculature. While many patients experience spontaneous resolution of the disease, even without treatment, a subset will progress to develop severe fibrocystic disease. Approximately 5% of patients with advanced sarcoidosis succumb to the disease, primarily due to respiratory failure. Pulmonary hypertension (PH) frequently complicates sarcoidosis, especially in patients with end-stage lung disease. Epidemiologic studies have shown that the prevalence of sarcoidosis-associated PH (SAPH) depends on the stage of pulmonary disease and the diagnostic methods used to measure or estimate pulmonary vascular pressures. In a study by Iwai et al,[2] evidence of pulmonary vascular disease was found on autopsy in 5% of cases with significant parenchymal involvement. This prevalence aligns closely with the findings from a study in the Netherlands where SAPH was found in approximately 9% of patients using transthoracic echocardiography (TTE) and 3.5% by right heart catheterization (RHC).[3] However, other studies revealed a higher prevalence of SAPH. For example, a study of 162 sarcoidosis patients by Bourbonnais et al[4] revealed a SAPH prevalence of 21% by TTE and 15% by RHC. Importantly, SAPH occurs in up to 74% of patients with advanced parenchymal involvement listed for lung transplant.[5]

A recent meta-analysis by Zhang et al,[6] which included a pooled sample of 632 368 patients with sarcoidosis found a prevalence of SAPH in general sarcoidosis population to be 16.4% when estimated by TTE and 6.4% by RHC. In patients with advanced sarcoidosis; however, the prevalence of SAPH diagnosed by RHC was 62.3%.

It is important to note that PH can occur in sarcoidosis in the absence of significant parenchymal lung disease in 11% to 32% of patients.[7,8] These patients may behave clinically much like a patient with group 1 pulmonary arterial hypertension (PAH). The histopathology of the pulmonary vessels in such patients is described in Figure 2.

In addition, patients with sarcoidosis also develop left heart disease and may present with PH related to elevated left ventricular filling pressures, much like

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group 2 PH. These varying contributors and potential multifactorial influences on hemodynamics can create a challenge for the clinician attempting to parse out the relative contributions to PH of each, and further determine the best management approach. This heterogeneity adds to the complexity of these patients and is one of the reasons SAPH is categorized under group 5 PH.

PATHOGENESIS

PH is defined as an elevated mean pulmonary artery pressure (mPAP) >20 mm Hg according to the 6th World Symposium on Pulmonary Hypertension. It is categorized into 5 groups based on the underlying mechanism, as shown in Table 1. SAPH is classified under group 5 due to its often multifactorial etiology and overlapping mechanisms, as illustrated in Figure 1.[9]

Mechanisms of Pulmonary Arteriopathy

Immune-Mediated Vasculopathy: Pulmonary arteriopathy is the hallmark of PAH. It is characterized by progressive proliferative and occlusive vascular pathology that results from endothelial dysfunction, pulmonary vascular smooth muscle hyperplasia, and the proliferation of myofibroblasts. Vascular remodeling leads to excessive pulmonary vasoconstriction, intimal fibrosis, and angiogenesis. These structural changes develop under the influence of several inflammatory mediators and growth factors. A similar proliferative arteriopathy has been well recognized in SAPH and resembles PAH. T lymphocytes have been shown to play important roles in the pathogenesis of PAH. Helper T cells (Th1 and Th17 cells) produce several cytokines (interleukin[IL]-2, IL-6, tumor necrosis factor [TNF]-α,

Table 1. Classification of Pulmonary Hypertension Based on the 6th World Symposium on Pulmonary Hypertension

Group 1 PAH	1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH 1.4 PAH associated with: 1.4.1 CTD 1.4.2 HIV 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH long-term responders to calcium channel blockers 1.6 PAH with overt features of venous/capillaries involvement (PVOD/PCH)
Group 2 PH due to left heart disease	2.1 PH due to heart failure preserved LVEF 2.2 PH due to heart failure reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular disease leading to post-capillary PH
Group 3 PH due to lungs and/or hypoxia	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed obstructive/restrictive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders
Group 4 PH due to pulmonary artery obstruction	4.1 Chronic thromboembolic PH 4.2 Other. Pulmonary artery obstructions
Group 5 PH with unclear and/or multifactorial mechanisms	5.1 Hematologic disorders Hemolytic anemias Myeloproliferative disorders 5.2 Systemic and metabolic disorders Pulmonary Langerhans cell histocytosis Glycogen storage disease Neurofibromatosis Sarcoidosis 5.3 Others Chronic renal failure with or without hemodialysis Fibrosing mediastinitis 5.4 Complex congenital heart disease Segmental PH - Isolated pulmonary artery of ductal origin - Absent pulmonary artery - Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries - Hemitruncus - Other Single ventricle - Unoperated - Operated Scimitar syndrome

Abbreviations: CTD indicates connective tissue disease; HIV, human immunodeficiency virus; LVEF, left ventricle ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; - PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

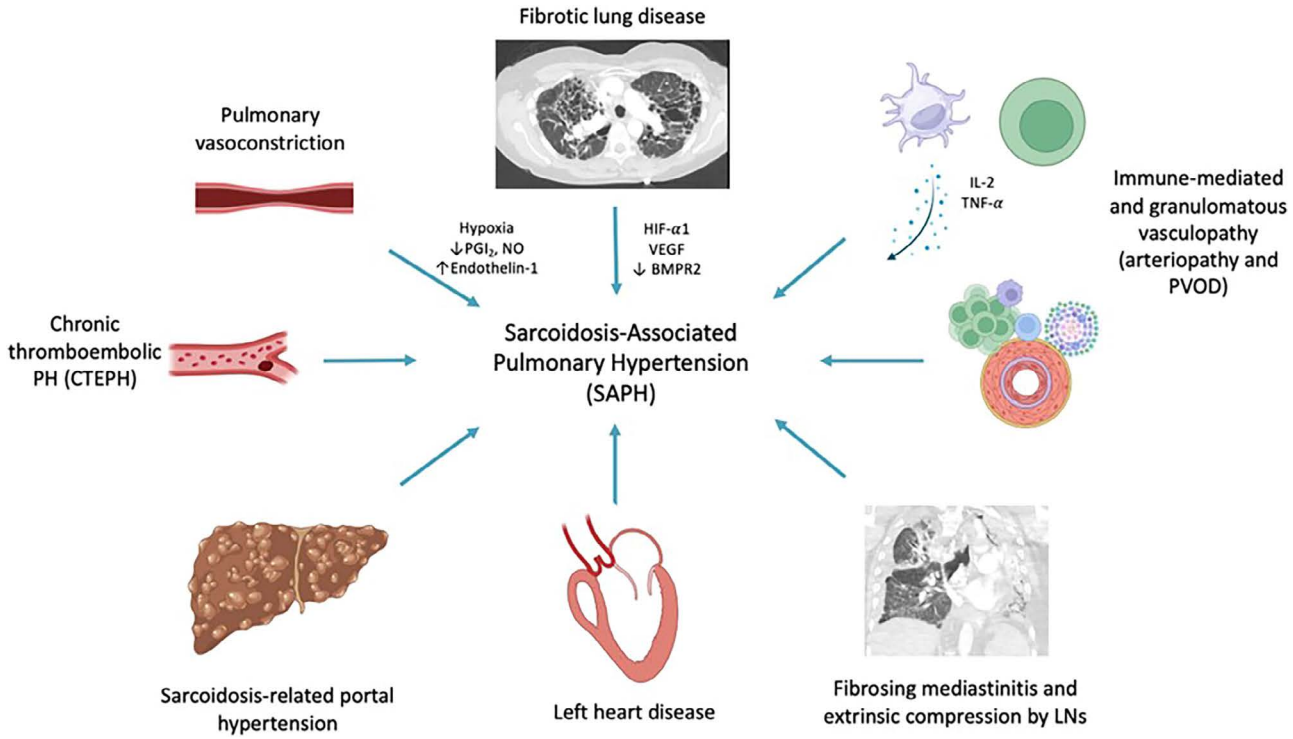

Figure 1: Multiple potential mechanisms contributing to the development of sarcoidosis-associated pulmonary hypertension (SAPH). BMPR2 indicates bone morphogenetic protein 2; CTEPH, chronic thromboembolic pulmonary hypertension; HIF, hypoxia-inducible factor; LN, lymph nodes; NO, nitric oxide; PGI_2, prostacyclin; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; VEGF, vascular endothelial growth factor. Image created with BioRender.com.

interferon-γ) that propagate the inflammatory response seen in PAH.[10,11]

In sarcoidosis, T lymphocytes, mainly CD4 cells, are known to be the primary drivers of inflammation, eventually progressing to granuloma formation. The cytokine profile in the granulomatous inflammation of sarcoidosis overlaps with that seen in PAH. IL-2 is an important growth factor released by activated immune cells, resulting in differentiation and proliferation of T lymphocytes. IL-2 levels are often elevated in patients with active and extensive granulomas due to sarcoidosis. The absence of IL-2 promotes apoptosis of activated T lymphocytes. Binding of IL-2 to its receptor on the surface of lymphocytes results in the cleavage and release of the receptor into the circulation. Therefore, soluble IL-2 receptor levels serve as a marker of T lymphocyte activation in sarcoidosis and can be used to monitor disease activity.[12,13]

In animal models of guinea pigs, IL-2 has been shown to cause pulmonary vasoconstriction and increase pulmonary capillary permeability, leading to pulmonary edema.[14] Furthermore, elevated IL-2 levels have been found in patients with heritable PAH, where they predict survival, promote expression of endothelin-1, and contribute to pulmonary hypertension.[15,16]

TNF, a major mediator of granuloma formation in sarcoidosis, has been found to drive PAH by suppressing the bone morphogenetic protein 2 (BMPR-2), which is responsible for antiproliferative signaling.[17]

Endothelial dysfunction is well recognized in sarcoidosis, possibly as a result of antibody-mediated endothelial injury.[18] There is evidence to suggest that extensive pulmonary endothelial damage may occur even before granuloma formation.[19] Pulmonary vascular remodeling seen in SAPH is propagated by serotonin-related pulmonary vascular smooth muscle hyperplasia that can be similar to that observed in patients with PAH.[20]

Granulomatous angiitis is another important manifestation of pulmonary sarcoidosis. In an autopsy study by Takemura et al,[21] a review of 40 sarcoidosis cases demonstrated granulomatous vasculitis in all cases, with occlusion of small vessels (more prominent in venules than arterioles). Obliterative pulmonary venulopathy of sarcoidosis is possibly the mechanism behind pulmonary veno-occlusive disease (PVOD), which has been described in sarcoidosis.[22,23] Plexiform lesions similar to those seen in patients with PAH have been reported but are not commonly seen in SAPH.

Granulomatous angiitis in sarcoidosis has been reported in other studies with frequency ranging from 41% to 69% of patients.[24,25] This may explain the improvement in pulmonary hemodynamic with immunosuppressive therapy noted in some patients.[26,27] The various types of arteriopathy that have been observed in SAPH are shown in Figure 2.

Imbalance in Vasoactive Substances: Pulmonary vascular homeostasis is maintained by several vasoactive substances, namely nitric oxide (NO), prostacyclin (PGI_2), endothelin (ET), and serotonin (5-HT).[28] Levels of pulmonary vasodilators (PGI_2 and NO) are reduced in patients with PAH, whereas endothelin-1, a potent vasoconstrictor with mitogenic properties, is elevated. This imbalance contributes to increased

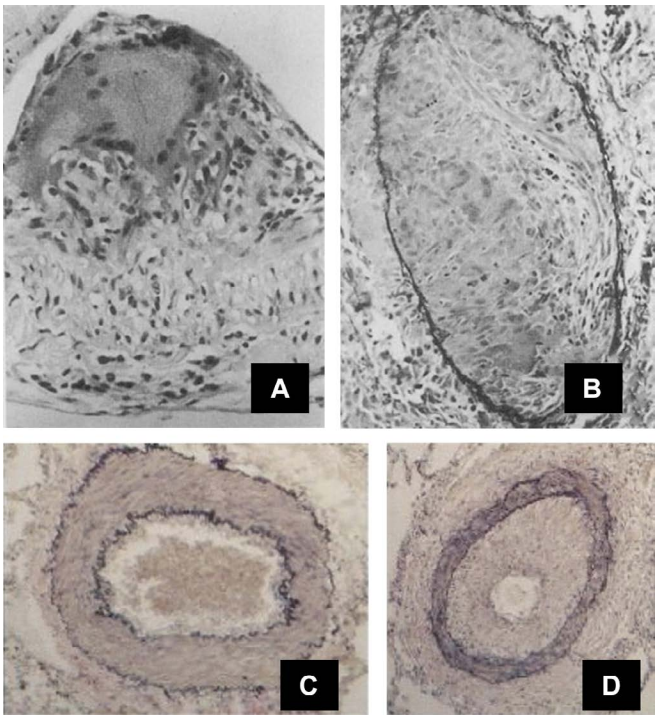

Figure 2: Various types of pulmonary vascular lesions observed in sarcoidosis-associated pulmonary hypertension. (**A**) is representative of granulomatous vascular disease. (**B**) shows venous fibrosis, much like seen in pulmonary venooclusive disease. (**C** and **D**) demonstrate nongranulomatous pulmonary arteriopathy, like that seen in traditional group 1 pulmonary arterial hypertension. Figures 2A and 2B are reprinted with permission from Rosen et al 1994[91]; Figures 2C and 2D are reprinted with permission from Pietra 2004.[92]

pulmonary vascular resistance (PVR) in PAH. Sarcoidosis patients have a similar perturbance. Prostaglandin-endoperoxidase synthase-2 (also known as cyclooxygenase-2 [COX-2]) is a key enzyme in arachidonic acid metabolism and production of prostaglandins. This enzyme is diminished in patients with sarcoidosis, impairing prostaglandin synthesis.[29] In a study by Bachwich et al,[30] prostaglandin production was significantly reduced by alveolar macrophages in patients with sarcoidosis compared to healthy volunteers Conversely, endothelin-1 levels have been shown to be elevated in the blood and bronchoalveolar lavage in patients with sarcoidosis.[31,32] NO is a potent pulmonary vasodilator that is released in inflammatory states. However, despite granulomatous inflammation in sarcoidosis, NO levels are not increased.[33] Additionally, prolonged corticosteroid therapy (for presumed active sarcoidosis) may result in NO depletion due to altered endothelial production.[34,35]

Interplay of Interstitial Lung Disease, Lymphadenopathy and PH

Destruction of the pulmonary vascular bed by fibrocystic changes is a contributing factor in the development of SAPH. Sarcoidosis is characterized by heterogeneous distribution of fibrosis, with predilection to proximal airways. This often leads to distortion of the central vasculature and altered flow, resulting in shear stress and endothelial injury.

Additionally, fibrosis alters pulmonary vascular capacitance (ie, the ability of the vessels to dilate and recoil during the cardiac cycle) and increases pulmonary vascular pressures. The development of pulmonary hypertensive lesions (fibroblast proliferation and vascular smooth muscle hyperplasia) exacerbates regional hypoxia in lung areas distal to narrowed or occluded vessels. Hypoxia due to parenchymal lung disease is likely a prominent mechanism, given the high prevalence of SAPH in patients with advanced fibrosis and chronic respiratory failure.

These pathologic processes are usually evident on radiographic studies (corresponding to Scadding stage 4) and pulmonary function tests, which may show reduced forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO). Moreover, pulmonary vasoconstriction develops secondary to alveolar hypoxia and increased pulmonary vasoreactivity.[36] Importantly, the physiologic consequences of alveolar hypoxia are far beyond simple pulmonary vasoconstriction. Hypoxia-inducible factor (HIF)-1α), a transcription factor, is highly expressed when the oxygen-sensitive α subunit is activated in response to hypoxia. HIF-1α plays a critical role in orchestrating angiogenesis, pulmonary vascular tone regulation, and cellular proliferation.[37] Expression of HIF-1α has been shown to be upregulated in patients with sarcoidosis, especially those with abnormal lung function tests, or active disease.[38,39] Under hypoxic conditions, the HIF-1α/vascular endothelial growth factor signaling pathway becomes activated in pulmonary endothelial and vascular smooth muscle cells, promoting vasoconstriction, cellular proliferation, and angiogenesis.[40] Recent studies have shown promising results with HIF inhibition in treating idiopathic PAH.[41] Whether these results translate into benefit in SAPH is still to be elucidated. HIF-1α also mediates the Th1/Th17 inflammatory response in sarcoidosis and regulates the production of several key cytokines. Lastly, in animal models, chronic hypoxia has been associated with downregulation of BMPR-2, further promoting pulmonary vascular remodeling.[42]

Extrinsic Compression/Invasion by Mediastinal Pathology: Sarcoidosis has been reported to cause extrinsic compression of pulmonary arteries by enlarged hilar and mediastinal lymph nodes, sometimes necessitating pulmonary artery stenting.[43,44]

In some cases, patients may present with a mismatched ventilation/perfusion scan, even in the absence of parenchymal fibrosis, which can lead to a misdiagnosis of chronic thromboembolic pulmonary hypertension (CTEPH).[45]

Therefore, it is crucial to carefully evaluate these patients by an experienced

team, integrating findings from chest computed tomography (CT) scan, fluorine-18-fluorodeoxyglucose positron emission tomography (FDG PET/CT), and pulmonary angiography to assess thoracic lymph nodes and establish the correct diagnosis. Mediastinal granulomatous inflammation and fibrosing mediastinitis, accompanied by pulmonary vascular invasion, may result in SAPH and can be associated with proliferative changes in the absence of parenchymal disease. Furthermore, stenosis of the pulmonary veins resulting in postcapillary pulmonary hypertension and pulmonary edema has been described in patients with fibrosing mediastinitis secondary to sarcoidosis.[46]

Chronic Thromboembolism

Sarcoidosis is sometimes considered a prothrombotic condition as several studies have shown increased prevalence of venous thromboembolic disease in the absence of other hypercoagulable states.[47,48,49]

This is likely secondary to chronic inflammation and alterations in the coagulation and fibrinolytic systems. In addition, patients with sarcoidosis have higher prevalence of antiphospholipid antibodies, which are known to be associated with arterial and venous thrombosis.[50] This increases the risk of CTEPH and adds to the mechanisms of SAPH. CTEPH in patients with sarcoidosis has been reported in a small case series.[51]

Sarcoidosis-Related Portal Hypertension

Liver involvement is common in sarcoidosis, with evidence of hepatic granulomas in 70% of cases. These are often asymptomatic but may manifest clinically in 30% of patients.[52] Portal hypertension may complicate hepatic sarcoidosis in some patients. In a retrospective study by Fauter et al,[53] 12 patients with sarcoidosis and hepatic involvement were followed for over 10 years. Nine patients developed evidence of portal hypertension (ascites, esophageal varices, or both). The development of portal hypertension increases the risk of SAPH due to endothelial injury (high cardiac output–related shear stress), dysregulated pulmonary vascular tone (increased circulating vasoconstrictors), and pulmonary emboli from portal circulation (through portosystemic shunts).

Left-Sided Heart Disease and Pulmonary Venous Hypertension

Sarcoidosis can affect the heart in approximately 20% to 25% of patients, leading to a variety of cardiac manifestations, including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, both of which can result in postcapillary PH.[54] The prevalence of postcapillary SAPH is variable. In one retrospective study, pulmonary artery wedge pressure (PAWP) was elevated in 29% of the patients with SAPH.[55] Using cardiac magnetic resonance, one study found 15% of SAPH was related to cardiac involvement by sarcoidosis.[56] In a recent study by Mathijssen et al,[57] only 7.5% of patients had postcapillary SAPH using RHC.

Notably, the detection of heart failure with preserved ejection fraction by TTE can be challenging in sarcoidosis patients. Therefore, the use of advanced imaging modalities such as echocardiography with speckle tracking analysis, cardiac magnetic resonance imaging, or even RHC may provide more insights than TTE.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of SAPH requires a high index of suspicion given the nonspecific symptoms such as dyspnea, chest pain, and palpitations. Symptoms of right heart failure (elevated jugular venous pressure, edema of the lower extremities, loud P_2, right ventricular heave) are late manifestations and lack sensitivity. Exertional syncope can be seen in patients with severe SAPH; however, syncope at rest may signify underlying arrhythmias and should prompt workup for cardiac sarcoidosis.

When evaluating patients with sarcoidosis, pulmonary function tests (spirometry, lung volumes and diffusion capacity for carbon monoxide, DLCO) and a 6-minute walk distance (6MWD) test are essential to objectively assess the physiologic impairment. Besides assessing the need for supplemental oxygen, the 6MWD test can provide valuable information such as delayed heart rate recovery, which has been linked to poor outcomes in patients with PH.[58] Features suggestive of SAPH include persistent or unexplained dyspnea, clinical signs of right-sided heart failure, resting hypoxemia, DLCO $< 60\%$ predicted, and a reduced DLCO that is out of proportion to the degree of restriction (FVC/DLCO > 1.6). In a study of 363 patients with advanced sarcoidosis, the need for supplemental oxygen was the only predictor of SAPH.[59]

Serum cardiac biomarkers such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) (or BNP) and the neutrophil:lymphocyte ratio (a surrogate for the degree of systemic inflammation in sarcoidosis) can also help identify patients with SAPH.[60] The extent of pulmonary fibrosis should be assessed with imaging studies, preferably chest CT. Extensive pulmonary fibrosis (ie, Scadding stage 4 involving $> 20\%$ of lung parenchyma) and enlarged pulmonary artery (indexed to body surface area, > 15.2 mm/m^2) should raise suspicion for SAPH.[61]

Screening asymptomatic patients for SAPH has the potential for early detection before the functional status and hemodynamics are severely impaired. Whether screening improves clinical outcome in those patients remains unknown. Doppler TTE is the first diagnostic modality to assess for SAPH when suspected based on symptoms, clinical presentation, and other diagnostic test findings. A maximum tricuspid regurgitant velocity (TRV_{max}) < 2.9 m/s makes SAPH unlikely, whereas $TRV_{max} > 3.4$ m/s or the presence of right ventricular dilation or dysfunction (eg, reduced tricuspid annular plane systolic excursion) highly suggest SAPH.[62] Patients with TRV between 2.9 and 3.4 m/s may also be considered for additional evaluation for PH by RHC (see Figure 3). For this group, a determination as to the relative severity of apparent right heart dilatation/dysfunction and pulmonary parenchymal disease should be made to assist in guiding the decision to proceed with RHC. We suggest using an FVC cutoff of 50% predicted as a guideline.

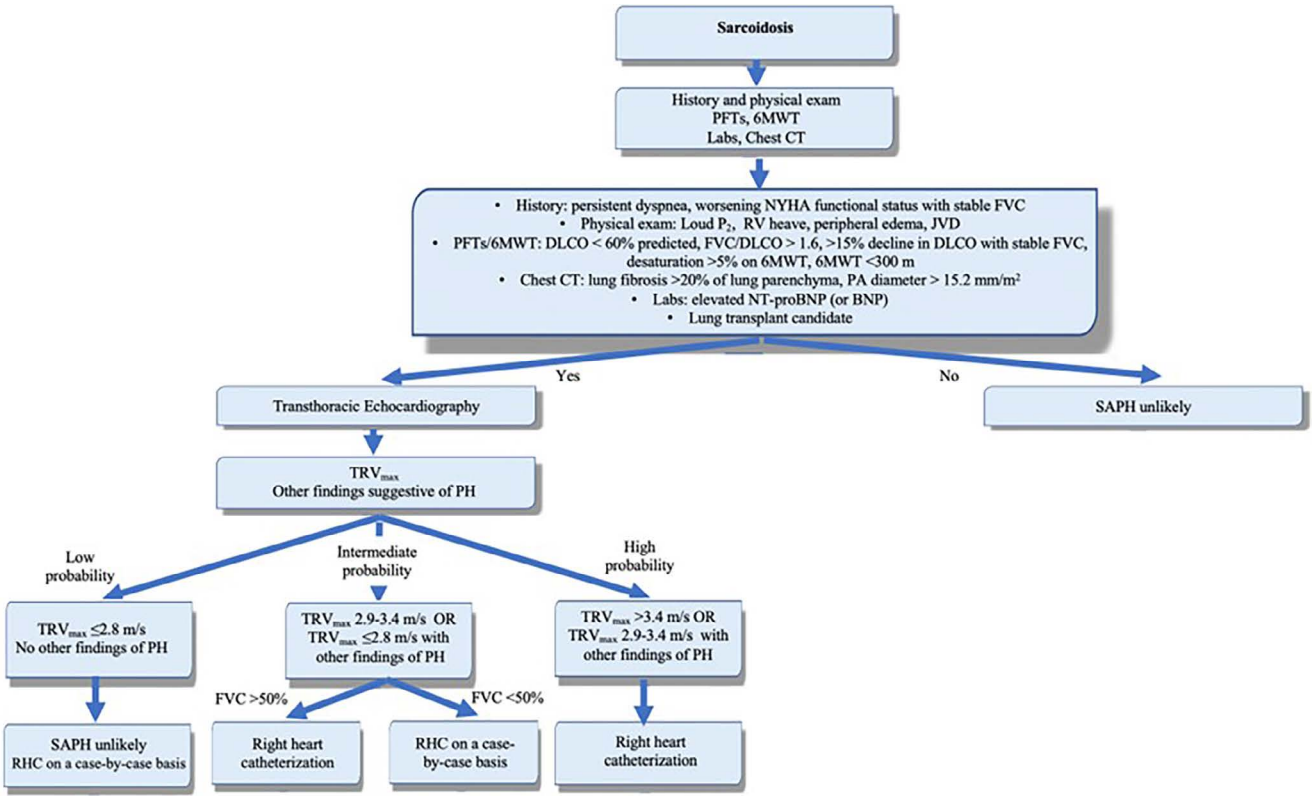

Figure 3: Proposed screening and diagnostic algorithm for the assessment of sarcoidosis-associated pulmonary hypertension (SAPH); adapted and reproduced with permission of the ERS 2024: European Respiratory Review 31 (163) 210165; DOI: 10.1183/16000617.0165-2021 Published 9 February 2022.[62] 6MWD indicates 6-minute walk distance; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; JVD, jugular venous distension; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PFT, pulmonary function test; RHC, right heart catheterization; RV, right ventricle; TRV, tricuspid regurgitant velocity.

Discretion is needed on a case-by-case basis, preferably at an expert center.[62] RHC remains the "gold standard" for confirming PH, defined as an elevated mPAP > 20 mmHg. Precapillary SAPH is characterized by an elevated PVR (> 2 Wood units) and a normal PAWP of 15 mm Hg or less. Patients with an elevated PAWP > 15 mm Hg are considered to have postcapillary SAPH. The PVR threshold to diagnose precapillary PH was recently lowered from 3 Wood units in light of studies that demonstrated increased mortality in PH patients with a PVR > 2.2 Wood units.[63]

If the PAWP is at the upper border of normal range (eg, 12-15 mm Hg) and clinical suspicion of left heart disease is high, provocative maneuvers (eg, fluid bolus or exercise) should be applied. If the post–fluid challenge (infusion of 7 mL/kg or 500 mL saline) reveals a PAWP > 18 mm Hg, it strongly suggests the presence of postcapillary PH. Alternatively, a postexercise PAWP exceeding 25 mm Hg is highly indicative of postcapillary SAPH. A fluid challenge is more practical as exercise equipment is not universally available, and interpretation is prone to error, especially in patients with large respiratory swings in pulmonary vascular pressures.

The findings (and tracings) from RHC should be carefully reviewed by a multidisciplinary team familiar with SAPH, preferably in the presence of a sarcoidosis specialist.

MANAGEMENT

Supportive Measures and Treatment of Comorbidities

Treatment of SAPH is challenging due to its multifactorial nature and often overlapping mechanisms as discussed earlier. Therefore, the most predominant contributing mechanism(s) to SAPH should be identified and treated accordingly. This includes correction of hypoxemia (if present) with supplemental oxygen and treatment of comorbid conditions that may exacerbate hypoxemia or worsen pulmonary vascular pressures (eg, obstructive sleep apnea). Left heart disease should be optimized according to current guidelines. Diuretics should be prescribed to alleviate symptoms of volume overload when necessary.

Immunosuppression and Vascular Stenting

SAPH due to mediastinal pathologies, such as fibrosing mediastinitis or lymph nodes causing compression on pulmonary vessels, is not uncommon. Therefore, chest CT and/or FDG PET/CT may be needed to rule out mediastinal pathologies. Stenosis of the pulmonary vasculature can also be visualized on chest CT. Pulmonary vascular stenting in such cases has been reported to improve hemodynamics. In a study by Liu et al,[64] pulmonary vascular distortion and compression were found in 11% of SAPH patients, all of whom demonstrated improvement in symptoms, pulmonary vascular resistance, and arterial oxygen saturation following stenting of the pulmonary arteries.

Uptake on FDG PET can help identify patients who may respond to corticosteroids (or other immunosuppressive

therapies) for shrinking large lymph nodes or treating inflammatory mediastinal pathology (ie, fibrosing mediastinitis due to sarcoidosis). It may also aid in identifying patients with active parenchymal sarcoidosis for whom optimizing immunomodulators may attenuate granulomatous vascular inflammation, resulting in improved pulmonary vascular pressures.[65]

In a study of 22 patients with severe SAPH by Nunes et al,[66] significant and sustained hemodynamic improvement was observed in 3 out of 10 patients who received high-dose corticosteroids.]

Pulmonary Vasodilators

Pulmonary arteriopathy, characterized by elevated PVR with minimal or no parenchymal disease and exclusion of other causes of PH, is an important mechanism of precapillary SAPH. The routine use of pulmonary vasodilators in SAPH is not recommended and should be reserved for select patients who exhibit the "pulmonary arteriopathy" phenotype, leading to PH that is seemingly "out of proportion" to the degree of underlying lung disease. Identifying this phenotype can be challenging, but generally patients may have significant PH (eg, mPAP > 35 mm Hg and/or cardiac index < 2.5 L/min/m^2) with less severe parenchymal disease on imaging (fibrosis on CT < 20%) or progressive right ventricle failure. In a study by Barnett et al,[67] patients with SAPH and less fibrotic disease (FVC > 50% predicted or stage 0 to 3) demonstrated more improvement in exercise capacity with PAH therapy compared to those with stage 4 or severe restriction.

While the use of PAH-targeted therapies can be justified in such patients, there is a significant concern regarding the potential for worsening gas exchange. Furthermore, the presence of left heart disease and/or PVOD also carries the risk of pulmonary edema when using pulmonary vasodilators.[68] On the other hand, these therapies may provide some benefits. A meta-analysis of 5 studies revealed that SAPH patients who received pulmonary vasodilators experienced significant improvement in hemodynamics, including mPAP, cardiac index, and PVR.[69] Additionally, a recent

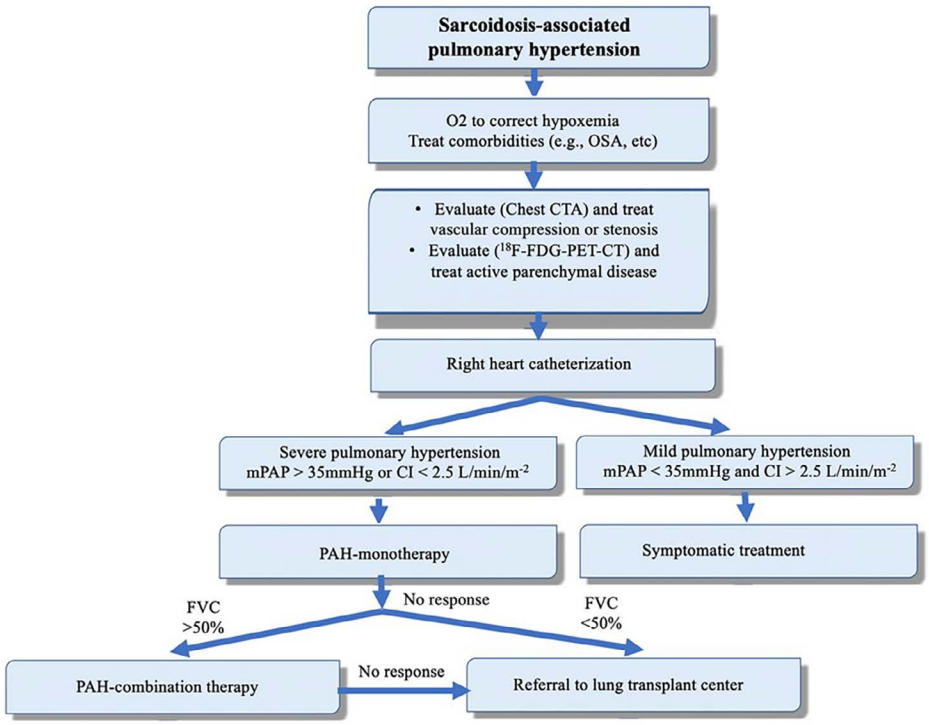

Figure 4: Proposed algorithm for management of sarcoidosis-associated pulmonary hypertension (SAPH); adapted and reproduced with permission of the ERS 2024: European Respiratory Review 31 (163) 210165; DOI: 10.1183/16000617.0165-2021 Published 9 February 2022.[62] CI indicates cardiac index; CTA, computed tomography angiography; F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography; FVC, forced vital capacity; mPAP, mean pulmonary artery pressure; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension.

study by Gayen et al[70] demonstrated that in patients with SAPH, pulmonary vasodilators may reduce hospitalization and decline in FVC, similar to the benefit observed with inhaled treprostinil in PH-interstitial lung disease (ILD). In another study, Albujoq et al[71] retrospectively evaluated 50 SAPH patients; 22 patients were treated with pulmonary vasodilators. Treatment with PAH therapy was associated with significant improvement in mPAP, BNP levels, and 6MWD.[71]

A paucity of robust data to support the use of PAH-targeted therapies in SAPH makes the selection of therapies mostly based on the severity of PH and the extent of parenchymal lung disease.[62] For example, patients with severe SAPH and mild fibrotic disease are more likely to receive intravenous prostanoids whereas patients with mild to moderate SAPH and more severe fibrotic changes tend to receive either oral therapies or inhaled prostacyclins.

Currently used PAH-specific therapies target 3 major pathways: the NO pathway (phosphodiesterase-5 inhibitors: sildenafil and tadalafil; soluble guanylate cyclase stimulators: riociguat; and inhaled NO); the endothelin pathway (endothelin receptor antagonists: bosentan, ambrisentan, macitentan), and the prostaglandin I_2 pathway (epoprostenol, treprostinil, iloprost, selexipag). Table 2 summarizes published studies evaluating PAH-specific therapies in SAPH.

Nitric oxide pathway: Phosphodiesterase-5 inhibitors (PDE5i) have been shown to have no significant impact on gas exchange in PH-ILD. This is because they exhibit a preferential vasodilatory effect in areas where NO is more available, primarily in well-ventilated areas, as oxygen is required for NO production.[72] Furthermore, PDE5i have demonstrated a favorable effect on hemodynamic measures in patients with SAPH. However, their impact on other important PH outcome variables, such as 6MWD has shown inconsistency. A small prospective open-label study conducted by Ford et al[73] evaluated tadalafil in patients with SAPH, revealing no improvement in 6MWD. Nevertheless, tadalafil was well tolerated with no

evidence of worsening ventilation/perfusion mismatch.

In another study, sildenafil was retrospectively evaluated in 19 patients with RHC-confirmed severe SAPH (median mPAP 36 mm Hg). While sildenafil resulted in significant hemodynamic improvement, including reduction in PVR by 4.9 Wood units and an improvement in cardiac index, no consistent change in 6MWD was observed.[74] However, a retrospective study that included 29 SAPH patients who were treated with sildenafil demonstrated significant improvement in 6MWD, right ventricle function by TTE, and serum BNP levels.[75] This study included patients with more severe SAPH (higher mPAP, higher PVR, and lower cardiac index) even though, similar to other studies, most patients had significant parenchymal disease (Scadding stage 3 and 4). Another agent that targets the NO pathway is riociguat, a soluble guanylate cyclase stimulator. Riociguat is contraindicated in patients with PH-ILD (not SAPH specifically) due to an increased risk of serious adverse events and mortality.[76] However, in

Table 2. Published Studies on Treatment of Sarcoidosis-Associated Pulmonary Hypertension with Pulmonary Arterial Hypertension Therapies and Relevant Characteristics and Outcomes Observed

Study	Study design	Therapy	Nol of patients	Hemodynamic effect	Clinical outcomes
Preston et al[36]	Prospective observational	iNO, CCB, epoprestenol	19	↓PVR ↓mPAP ↑CI	↑6MWD ↑functional class
Fisher et al[68]	Retrospective	Epoprestenol, treprostinil	7	↓PVR ↓mPAP ↑CI	↑functional class
Milman et al[74]	Case series	Sildenafil	12	↓PVR ↓mPAP ↑CI	⇔ 6MWD
Baughman et al[83]	Open-label	Iloprost	15	↓PVR ↓mPAP ↑CI	↑6MWD ↑functional class
Judson et al[80]	Open-label	Ambrisentan	21	—	⇔ 6MWD
Dobarro et al[69]	Retrospective	Any PAH-targeted therapy	11	↑CI	↑6MWD
Baughman et al[79]	Randomized, double-blind, placebo controlled	Bosentan	23	↓PVR ↓mPAP	⇔ 6MWD
Keir et al[75]	Retrospective	PDE5i, ERA	33	—	↑6MWD ↑TAPSE ↓BNP
Palermo et al[89]	Retrospective	Bosentan	40	↓PVR ↓mPAP	↑6MWD
Barnett et al[67]	Retrospective	Sildennafil, bosentan, epoprestenol	22	↓PVR ↓mPAP	↑6MWD
Qua et al[90]	Retrospective	Bosentan	45	—	↑6MWD
Ford et al[73]	Prospective open-label	Tadalafil	12	—	⇔ 6MWD
Bonham et al[82]	Retrospective	Epopresteol, treprostinil	26	↓PVR ↑CI	↑functionnal class ↓NT-proBNP
Boucly et al[65]	Registry	PDE5i, ERA, prostacyclin	126	↓PVR ↓mPAP ↑CI	↑functional class
Parikh et al[85]	Retrospective	Inhaled/IV prostacyclins, PDE5i, riociguat, ERA, combination therapy	74	—	↓NT-proBNP ⇔ 6MWD
Mathijssen et al[81]	Retrospective	Macitentan	6	—	↑functional class
Parsley et al[78]	Prospective open-label	iNO	8	↓mPAP ↓PVR	—
Oudiz et al[86]	Randomized, placebo-controlled trial	Bardoxolone methyl	25	—	Modest ↑6MWD
Baughman et al[77]	Randomized double-blind, placebo-controlled trial	Riociguat	16		↑6MWD Delay time to clinical worsening

Abbreviations: 6MWD indicates 6-minute walk distance; CCB, calcium-channel blockers; CI, cardiac index; ERA, endothelin receptor antagonists; iNO, inhaled nitrous oxide; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitors; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion.

a recent small (n = 16) randomized double-blind, placebo-controlled trial, riociguat was found to delay time to clinical worsening in SAPH when compared to placebo.[77] Time to clinical worsening was predefined as death, transplantation, hospitalization for progression of disease, or decrease in 6MWD of > 50 meters. Notably, 7 out of 8 patients in the riociguat group had Scadding stage 4 disease. Larger studies are needed to evaluate the efficacy and safety of riociguat in SAPH.

Inhaled NO (iNO) is a pulmonary vasodilator commonly used to assess pulmonary vasoreactivity, treat patients with PAH, and manage refractory hypoxemia in severe acute respiratory distress syndrome. The inhaled administration route ensures delivery of iNO to relatively well-ventilated lung units, reducing the risk of exacerbating hypoxemia in patients with underlying lung disease. Long-term use of iNO has been investigated in a phase 2 trial of RHC-confirmed SAPH patients. The study enrolled 8 SAPH patients, all of whom experienced significant improvement in mPAP and PVR. The drug was well tolerated, and no adverse events related to iNO were reported.[78] Other studies have also reported improvements in pulmonary hemodynamics and 6MWD with iNO in SAPH.[36] A larger trial is currently underway to validate these findings.

Endothelin Pathway: Endothelin receptor antagonists have been used in the treatment of SAPH in small case series and retrospective studies. In a retrospective study by Barnett et al,[67] SAPH patients who received PAH-specific therapies (bosentan, epoprostenol, or sildenafil) had significant improvement in their 6MWD, World Health Organization (WHO) functional class, and mPAP.

In a small randomized, double-blind, placebo-controlled study involving 23 patients treated with bosentan and 12 with placebo, bosentan was shown to significantly reduce mPAP and PVR.[79] However, no changes in 6MWD or WHO functional class were reported with bosentan. Another prospective open-label study assessed ambrisentan in 21 patients with SAPH. Ambrisentan failed to improve WHO functional class or 6MWD after 24 weeks of treatment. It is worth noting that 11 patients discontinued ambrisentan at 12 weeks, primarily due to increasing shortness of breath, which limited these findings.[80]

More recently, Mathijssen et al[81] conducted a retrospective study of macitentan in 6 patients with severe SAPH. Four patients showed improved WHO functional class and 3 had improved 6MWD. However, a major limitation was the need for increased immunosuppression due to increased sarcoidosis activity, making it unclear whether improved exercise tolerance was related to increased immunosuppressive therapy or macitentan. Additionally, 3 patients required hospitalization for volume overload during treatment. Overall, the current evidence does not support the use of endothelin receptor antagonists in SAPH.

Prostaglandin I_2 Pathway: Epoprostenol, iloprost, and treprostinil have all been used to treat patients with SAPH. In a small retrospective case series involving 7 patients treated with epoprostenol, significant improvements were observed in WHO functional classification and pulmonary hemodynamics (with a reduction in PVR of > 25%).[68] Importantly, 2 patients developed acute pulmonary edema with epoprostenol and required diuresis and reduction in the dose. Intravenous prostanoids have also been associated with a reduction in NT-proBNP.[82]

Similarly, inhaled iloprost has been showed to improve mPAP and PVR and increase the 6MWD in patients with SAPH.[83] Inhaled therapy offers an advantage, especially for patients with significant parenchymal lung disease. Currently, an ongoing open-label study is evaluating the use of inhaled treprostinil for SAPH.

Selexipag, a selective prostacyclin receptor agonist, has been used to treat SAPH in case reports and case series.[84] A randomized, placebo-controlled, trial of selexipag in SAPH was recently terminated due to slow enrollment.

Combination Therapy: Combination PAH therapy has been used in retrospective studies. However, the lack of randomized controlled trials makes it challenging to draw firm conclusions regarding the benefits of combination PAH therapy in SAPH. Parikh et al[85] published outcomes from one of the largest SAPH cohorts, consisting of 95 patients (74% with Scadding stage 4 disease). Seventy-four patients received PAH-specific therapies. Combination therapy was given to 11.6% of SAPH patients. PAH-specific therapy was not associated with death or hospitalization but did result in an improvement in NT-proBNP levels. There was no observed change in 6MWD for patients who received PAH therapy.[85] Other studies have demonstrated improvements in exercise capacity and pulmonary hemodynamics.[65]

Novel Therapies: Newer therapies for PAH have been studied in SAPH. Bardoxolone methyl, an oral antioxidant and immune modulator that inhibits the nuclear factor κB pathway, was evaluated in a randomized, placebo-controlled trial of 165 patients with PH-ILD.[86] The study included 25 patients with SAPH. After 16 weeks of treatment with bardoxolone, SAPH patients experienced a modest increase in 6MWD (17 meters with bardoxolone versus 9 meters with placebo).

Lung Transplant: In the absence of a major or disabling extrathoracic manifestations of sarcoidosis, SAPH patients who fail immunosuppression, mechanical interventions, and PAH-targeted therapy when deemed appropriate, should be considered for lung transplant. The presence of SAPH and significant lung disease (Scadding stage 4 with low FVC < 50%) is also an indication for referral for lung transplant consideration.

In summary, management of SAPH necessitates a multifaceted approach that addresses underlying pathologies and specific disease mechanisms. This includes a comprehensive evaluation to identify the most likely mechanism of PH. Patients with active granulomatous inflammation are likely to respond to immunosuppression, and those with pulmonary vascular compression or stenosis should be considered for stenting.

Patients should be carefully evaluated for postcapillary SAPH. When precapillary SAPH is confirmed, the "pulmonary arteriopathy" phenotype, characterized by less severe

Table 3. Risk Factors for Poor Outcomes in SAPH

DLCO < 35% predicted
6MWD < 300 m
Reduced 6MWD with preserved FEV_1 FVC ratio
Scadding stage 4
Precapillary SAPH (high PVR)
Elevated right atrial pressure > 15 mm Hg
Elevated NT-proBNP after treatment with PAH-specific therapies
Low cardiac index < 2.5 L/min/m^2
Presence of right-sided heart failure

Abbreviations: 6MWD indicates 6-minute walk distance; FEV_1, forced expiratory volume; FVC, forced vital capacity, NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SAPH, sarcoidosis-associated pulmonary hypertension.

parenchymal disease, should be distinguished as it tends to be more responsive to PAH-targeted therapy. Agents that target the NO pathway (especially PDE5i and iNO) and inhaled prostacyclins are well tolerated and likely beneficial. Patients treated with pulmonary vasodilators should be carefully monitored for worsening gas exchange and/or pulmonary edema (due to left heart disease or PVOD).

Timely referral for lung transplant evaluation is crucial for those with SAPH and severe parenchymal lung disease, ensuring a comprehensive and patient-centered care approach.

PROGNOSIS

The development of SAPH is associated with poor functional status, exercise-induced hypoxemia, and a 7-fold increased risk of death over 3 years.[55,87] In a study by Boucly et al[65] that included patients with severe SAPH (mPAP > 35 mm Hg), the 5-year mortality was 45% despite receiving pulmonary vasodilators. Risk factors for worse outcomes in SAPH are summarized in Table 3.[65,69,88]

CONCLUSIONS

The treatment of SAPH remains a clinical challenge with much nuance to consider due to variation in individual patient presentation. Clear direction on the use of PAH therapies in SAPH is still lacking from clinical trials conducted thus far. Given these uncertainties and the potential need for advanced therapeutics or lung transplantation evaluation, SAPH patients are likely best served by evaluation at PAH and/or sarcoidosis expert centers. Much work remains to be done to understand the exact pathogenesis of SAPH, as well as to develop therapies that clearly improve outcomes for these patients.

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