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Sarcoidosis-associated Pulmonary Hypertension: Pathophysiology, Diagnosis, and Treatment

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Abstract

Clinicians in pulmonary medicine frequently confront the challenge of screening, diagnosis and management of pulmonary hypertension (PH) in sarcoidosis patients who present with unexplained dyspnea. Sarcoidosis associated pulmonary hypertension (SAPH) is most prevalent in patients with pulmonary fibrosis, though it can be independent of airflow obstruction or restriction. SAPH independently associates with significantly increased mortality and decreased functional capacity, outcomes which can be mitigated by early detection and focused treatment. In this review, we discuss the pathophysiology of SAPH, which may resemble pulmonary arterial hypertension as well as secondary causes of PH. We offer a screening algorithm for SAPH, and advocate for detailed assessment of the cause of PH in each patient prior to choice of an individualized treatment plan. We note that treatment of sarcoidosis via immune suppression is typically insufficient to adequately treat SAPH. We discuss secondary causes of SAPH such as left heart disease, sleep disordered breathing, and thromboembolic disease, and the evidence for use of PH-specific therapy in select cases of SAPH. Management of SAPH by clinicians experienced in PH, with early referral to transplantation in refractory cases is advised.

Keywords

Sarcoidosis; Pulmonary hypertension; Treatment; Diagnosis; Pathophysiology

Introduction

Sarcoidosis is an immune mediated disease thought to be precipitated by unknown environmental triggers in patients with a susceptible genetic background[1,2]. The multi-systemic manifestations of sarcoidosis are unified by the presence of sterile, typically non-caseating granulomas on biopsy of involved tissue[3]. Granulomatous inflammation and fibrosis in the pulmonary vasculature, airways, interstitium and other anatomic locations results in pulmonary hypertension (PH) for a significant number of sarcoidosis patients.

The epidemiology of sarcoidosis and PH demonstrates that sarcoidosis associated pulmonary hypertension (SAPH) is prevalent, highly morbid, and deadly in patients that are

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commonly seen by pulmonologists. Between 5.7 and 28.3% of all sarcoidosis patients develop SAPH, with a wide range of prevalence reported across several single center studies[4–6]. Sarcoidosis patients with pulmonary fibrosis have the highest prevalence of SAPH[7], though SAPH can also occur in the absence of significant lung disease. In sarcoidosis patients referred for lung transplant, SAPH was present in 73.8%[8]. Patients with SAPH have higher oxygen requirements and more functional disabilities in comparison to sarcoidosis patients with end-stage lung disease but without PH[8]. SAPH ultimately results in excess mortality[9]. Patients with SAPH incur a striking 7 fold increase in risk for all-cause mortality when compared to sarcoidosis patients without PH, even when adjusted for age and pulmonary function[10].

Patients with SAPH suffer high morbidity and mortality for several reasons. First, SAPH is a complex disease mechanism. As discussed below, sarcoidosis falls within the 2013 World Health Organization (WHO) group V category of pulmonary hypertensive disorders due to multiple etiologies[11]. Thus, each sarcoidosis patient requires an individualized assessment of mechanisms driving their pulmonary hypertension. For example, SAPH can result from pulmonary vascular infiltration or obliteration, altered flow dynamics due to bulky lymphadenopathy or lung fibrosis, as well as cardiac or extra cardiac sarcoidosis. Astute clinicians recognize which factors are most contributing to SAPH for the individual, and direct the treatment plan accordingly. Secondly, treatment of SAPH is informed by a select few high-quality studies, with most evidence for PH-specific therapy extrapolated from studies in group 1 pulmonary arterial hypertension (PAH) patients. Robust phenotypic clustering of SAPH patients followed by randomized controlled trials of PH-specific therapies in SAPH remains a great unmet clinical need.

In this review we summarize an evidence based approach to diagnosis and management of SAPH. We describe the disease pathogenesis of SAPH in detail because understanding these mechanisms practically informs SAPH phenotype categorization and treatment decisions. Where appropriate, we highlight areas of controversy and future research in the field.

Pathogenesis of pulmonary hypertension in sarcoidosis

The WHO defines PH by a mean pulmonary artery pressure (MPAP) of ≥ 25 mm Hg at rest[11,12]. Exercise-based definitions are excluded due to lack of standardized exercise measurements and consensus regarding cutoff values for exercise-induced PH[11]. PH is then further divided into 5 distinct WHO groups, classified by etiology (Table 1). SAPH is classified as group V PH because of its multifactorial mechanisms. Thus management of SAPH may encompass elements of each of the other 4 categories of PH, depending on the particular clinical manifestations present in the patient. Treatment will vary based on the manifestations of sarcoidosis particular to each SAPH patient. In the following sections we will review the potential pathophysiologic manifestations of SAPH as seen in other WHO groups

Pulmonary arterial hypertension

PAH comprises a subset of PH patients that have low mean pulmonary artery (PA) wedge pressure ≤ 15 mm Hg and high pulmonary vascular resistance (PVR) >3 Wood units. PAH

patients demonstrate panvasculopathy of the pulmonary arterial circulation, with all layers of the vessels demonstrating pathology. The hallmark pathologic features of PAH include adventitial and medial thickening, smooth muscle hyperplasia, pathologic muscularization of non-muscularized arterioles, and intimal fibrosis and proliferation[13]. PAH is also characterized by marked endothelial dysfunction, including impaired nitric oxide generation and *in situ* thrombosis. In late stage disease, disorganized whorls of endothelial cells called plexiform lesions develop. Pathologic angiogenesis is also a hallmark of PAH[14]. Whether endothelial dysfunction is a primary causative feature of PH or a secondary response to elevated PA pressures remains controversial. However, it is believed that aberrant vascular remodeling over time elevates PA pressures.

On pathologic review, SAPH frequently demonstrates granulomas in the walls of the pulmonary vasculature. Granulomatous vessel involvement may affect the entirety of the pulmonary vascular tree, from elastic arteries to the collecting venules[15,16]. Granulomas are most commonly found in the lymphatic and venous systems, where they can mimic pulmonary veno-occlusive disease[16]. Granulomatous inflammation has been described in all layers of the vasculature and can circumferentially encase the vessel lumen and cause vessel fibrosis, leading to increased pulmonary vascular resistance. Some pathologic hallmarks of PAH are noted in SAPH, including the findings of plexiform lesions and intimal fibrosis[16,17].

Right heart catheterization (RHC) is required to establish the diagnosis of PH. Current guidelines recommend vasoreactivity testing for patients with idiopathic, heritable or drug toxic PH only, in an experienced center setting and in patients who are not in right heart failure. Vasoreactivity is defined by a decrease in the MPAP to ≤40 mm Hg accompanied by an absolute decrease of 10 mm Hg in response to inhaled nitric oxide or IV epoprostenol during RHC[18]. While vasoreactivity has been described in SAPH there is currently no significant amount of data regarding the benefit of calcium channel blockers in vasoreactive SAPH patients[19,20]. The vasodilatory response to inhaled nitric oxide in some patients nonetheless suggests the possibility of successfully treating select SAPH patients with pulmonary vasodilators. As in patients with PAH, patients with SAPH should never be treated *empirically* with calcium channel blockers or pulmonary vasodilators, as these may precipitate worsening heart failure or pulmonary edema when utilized in the incorrect setting.

Pulmonary hypertension secondary to left heart disease

The prevalence of cardiac sarcoidosis may be under-recognized and it is estimated that 20–25% of sarcoidosis patients have silent cardiac involvement, compared to approximately 5% with manifest disease[21]. The three most common clinical manifestations of cardiac sarcoid are conduction disease, ventricular arrhythmias, and heart failure[21]. Sarcoidosis may result in heart failure symptoms with either reduced or preserved left ventricular ejection fraction. The co-occurrence of PH in sarcoidosis patients with left heart failure is unclear, with estimates ranging from 23–79%[22]. This is true for a variety of reasons, including different diagnostic criteria between studies and heterogeneity of populations studied.

The diagnosis of left heart disease associated PH depends on having a PA wedge pressure > 15 mm Hg[11]. This retrograde transmission of pressure from the left heart is mostly driven by diastolic dysfunction, and thus the maintenance of euvolemia is a key component of management[23]. Additionally, increased retrograde pressure can trigger release of vasoconstrictive molecules that lead to a “pre-capillary” component of PH in left sided heart failure[24]. Furthermore, if pulmonary hypertension from poorly-controlled heart failure persists over time there is adaptive vascular remodeling that is likely permanent[13]. The treatment for WHO Group II PH is to treat heart failure, and thus medications such as diuretics, afterload reduction agents, and beta blockers, are the mainstays of treatment.

It is important to note that primary impact on the right ventricle from cardiac sarcoidosis is also described in patients without left ventricle involvement or pulmonary function impairment to otherwise explain significant right ventricular strain[25,26]. The management of primary right ventricular dysfunction is beyond the scope of this review.

Pulmonary hypertension due to chronic lung disease or hypoxemia

Patients who develop parenchymal lung disease from sarcoidosis are at greatest risk of developing pulmonary hypertension, and indeed the majority of patients with SAPH have evidence of pulmonary disease[7,8]. The primary mechanism for this is believed to be destruction of vasculature from the lung disease, resulting in hypoxemia from ventilation/perfusion mismatch. Thus, supplemental oxygen should be used for patients when necessary. Architectural distortion of the pulmonary vasculature can also increase PVR. Dyspnea out of proportion to lung disease and accompanied by exertional hypoxemia should raise suspicion for the development of SAPH, particularly in sarcoidosis patients whose dyspnea appears refractory to immune suppression. A formal PH workup should be pursued when there is suspicion for SAPH in patients with parenchymal lung disease, as using imaging to diagnose PH in fibrotic lung disease is not sufficiently reliable. This has been demonstrated in idiopathic pulmonary fibrosis, where radiographic markers did not predict pulmonary hypertension[27]. Additionally, there may be concomitant but separate involvement of the pulmonary vasculature and lung parenchyma in SAPH. While parenchymal lung disease is strongly associated with SAPH, a full evaluation of potential causes of PH should be pursued given the multiple etiologies by which sarcoidosis may cause SAPH.

Sarcoidosis patients are also noted to have increased rates of sleep disordered breathing[28–30]. As a result, their risk of developing PH secondary to nocturnal hypoxemia from obstructive sleep apnea is increased and is further compounded by the potential worsening of obstructive sleep apnea from corticosteroids used to treat the disease[30]. Patients who have congestive heart failure also have a higher risk of sleep-disordered breathing, thus providing another mechanism by which sarcoidosis may contribute to the development of PH[31].

Pulmonary hypertension due to chronic thromboembolic disease (CTEPH)

Sarcoidosis confers an elevated risk of venous thromboembolism, thought to be commensurate with active inflammation promoting a hypercoagulable state[32]. Swigris et al. found pulmonary embolism in 2.5% of United States decedents with sarcoidosis[33]. A recent

analysis of the Olmstead county cohort in Minnesota elucidated a 3 fold increase in hazard ratio of venous thromboembolism for patients with sarcoidosis[34], while in the United Kingdom, sarcoidosis patients under age 65 had a risk ratio of 2.0 for pulmonary embolism (95% CI: 1.1–3.4)[35]. Therefore, sarcoidosis patients are at increased risk of developing CTEPH. CTEPH presents on a spectrum ranging from central obstruction of the pulmonary vasculature to small emboli distributed among the microvasculature. Central emboli may be amenable to pulmonary endarterectomy, while disease of the microvasculature requires lifelong anticoagulation and is best detected through ventilation-perfusion scan. An additional medical treatment for CTEPH is the soluble guanylyl cyclase activator riociguat, which in studies of non-sarcoidosis PH was associated with improved WHO functional class, increased 6 minute walk distance, and improved hemodynamics[36]. Riociguat is currently considered appropriate for use in patients with CTEPH who are non-operable candidates or who have failed pulmonary endarterectomy. Concordant with guidelines for PH evaluation, ventilation perfusion scanning to detect CTEPH is warranted in all patients with PH. If indeterminate or multiple perfusion defects are present, CT angiography, followed by referral to a CTEPH center is advised[37,38].

Other Mechanisms of SAPH

Sarcoidosis may present with marked thoracic lymphadenopathy and fibrosing mediastinitis. In these cases, architectural distortion on major branches of the pulmonary circulation imposes a physical impedance to pulmonary blood flow, leading to pulmonary stenosis and segmental pulmonary hypertension[39,40]. The presence of significant thoracic lymphadenopathy or a chest bruit are clues to anatomic pulmonary arterial obstruction. PA stenting has been demonstrated to be effective by several groups, achieving sustained decrease in the PA pressure[41,42].

Although liver involvement has been well-described, cirrhosis is a rare complication of sarcoidosis, comprising fewer than 1% of cases[43]. No cases of portopulmonary hypertension definitively attributed to sarcoidosis have been reported, although a different cause of hypoxemia, the hepatopulmonary syndrome, has been described[43,44]. While the possibility of portopulmonary hypertension should be considered in sarcoidosis patients with cirrhosis, the overall incidence of this etiology appears to be quite rare.

Lastly, chronic anemia can lead to high output heart failure. Patients with sarcoidosis may have a mild degree of anemia from their disease which can be exacerbated by agents commonly used to treat sarcoidosis such as methotrexate or azathioprine.

Screening for SAPH

The gold standard for the diagnosis of pulmonary hypertension is RHC. This section focuses on key aspects of the patient’s clinical presentation and screening tests when considering referral for RHC. Figure 1 summarizes a SAPH screening algorithm for sarcoidosis patients presenting with dyspnea.

Symptomatology and exam

The symptoms of sarcoidosis and pulmonary hypertension may be difficult to distinguish, but the clinician should have a low threshold of suspicion for SAPH and be vigilant for worsening dyspnea or signs of right sided heart failure. Exertional dyspnea is a common complaint in pulmonary sarcoidosis, cardiac sarcoidosis, and in pulmonary hypertension, thus confounding the diagnosis of SAPH[1,12]. Similarly, chest pain and palpitations are also reported in both diseases independently. Exertional syncope is one criteria for WHO functional class IV PH, but may also occur due to cardiac conduction disease in sarcoidosis.

Signs of pulmonary hypertension on physical exam include a loud P2, evidence of right sided volume overload such as elevated jugular venous pressure or peripheral edema, and a right ventricular heave, but these are often findings that are discovered late in the disease course. A systematic review revealed that the presence of a loud P2 or a right-sided 4th heart sound were the best physical exam correlates of PH, but most reliable in the hands of a specialist[45].

Pulmonary Function Testing

Patients with sarcoidosis undergo routine pulmonary function tests (PFTs), which may provide clues to the presence of PH. Diffusing capacity of the lung for carbon monoxide (DLCO), forced vital capacity (FVC), and 6 minute walk test (6MWT) have all been noted to be decreased in patients with SAPH[4]. Additionally, ambulating hypoxemia is a key feature of PH. In a study of 162 patients with sarcoidosis, Bourbonnais et al demonstrated that oxygen desaturation below 90% on 6MWT correlated with an odds ratio of 12.1 (CI 3.7–19.7) of having SAPH, with a DLCO <60% predicted demonstrating an odds ratio of 7.3 of having PH[4]. Mirsaedi and others also identified 6MWT desaturation and low DLCO as the strongest correlates with PA systolic pressure as measured by echocardiography[46]. Among the different parameters for PFT it is logical that DLCO and 6MWT desaturation would be the strongest predictors of SAPH since they can reflect capillary destruction from high pulmonary pressures and circulatory insufficiency, respectively. Additionally, a focus on these parameters may help modulate suspicion when other PFT results are also abnormal.

Imaging

The presence of advanced lung disease on chest x-ray has been associated with SAPH by several groups[5,7]. However, SAPH can also exist in isolation of significant lung disease[47]. The presence of significant parenchymal lung disease in patients with sarcoidosis should lead to the obtaining of computed tomography (CT) scan of the chest. Often this imaging has occurred earlier in a patient’s disease course before the diagnosis of sarcoidosis is made.

Numerous studies have investigated the utility of CT scan for the detection of PH, with reported associations between PA diameter and the ratio of PA to aorta[27,48,49]. In a study specific to sarcoidosis in which over half the patients exhibited Scadding stage IV disease, Huitema and colleagues found CT-measured PA diameter corrected for body surface area was the best predictor of SAPH,[50]. This recent study counters earlier literature questioning the reliability of CT scanning for detection of PH in patients with pulmonary fibrosis. While RHC remains the gold standard for PH diagnosis and radiographic results can only be

suggestive, enlarged PA diameter on CT scan should heighten the clinicians' pre-test probability of PH being present and prompt further workup.

Echocardiography

Echocardiography remains the most common way to screen for PH of all causes[51]. It is particularly useful in sarcoidosis because of the simultaneous need for assessment of cardiac sarcoidosis. Bertoli and colleagues were the first to report on the use of echocardiography in SAPH[52].

Echocardiography remains a *screening* test which should not be used for PH *diagnosis* due to several limitations. One notable pitfall is the use of echocardiography in the presence of fibrotic lung disease, which compromises the accuracy of echocardiography to estimate MPAP. In a cross-sectional study of idiopathic pulmonary fibrosis patients with RHC data and echocardiograms, Nathan and colleagues found that only 40% of patients had echocardiograms that reasonably estimated MPAP[53]. In addition to this pitfall, not all patients have a regurgitant tricuspid jet which is required for estimation of PA pressure, nor adequate windows for echocardiographic estimation of right heart parameters. Despite these limitations, high estimated pulmonary pressures are likely still helpful. Baughman and colleagues reported an estimated PA systolic pressure > 50 by echocardiogram was associated with worse mortality, while when under 30 mortality was unchanged[54]. Early detection of PH and cardiac sarcoidosis by noninvasive cardiac imaging is an area of active research. For example, echocardiography derived global longitudinal peak systolic strain (GLS) can be used in the assessment of early RV dysfunction in sarcoidosis patients who do not otherwise demonstrate cardiac involvement or pulmonary hypertension[55]. GLS on echocardiography is associated with cardiac sarcoidosis on MRI, and high GLS associates with increased risk of adverse cardiovascular events in patients with preserved left ventricular ejection fraction[56].

Treatment of SAPH

The pathophysiology of SAPH holds relevance for treatment. With the exception of CTEPH, the only approved medical therapies PH are for group I, or pre-capillary PAH. In PH secondary to left heart disease or chronic lung disease current recommendations are to treat the underlying cause of disease. However, treatment of sarcoidosis alone may be insufficient. For example, steroid use does not affect the burden of disease in the pulmonary vasculature of sarcoidosis patients on autopsy[16]. Furthermore, in the largest cohort study of SAPH patients, only 4/11 patients treated with immunosuppression alone saw improvements in hemodynamics[57]. Since granulomatous involvement of the pulmonary vasculature as well as evidence of vasoreactivity suggest that SAPH may in some cases behave similarly to PAH, multiple groups have investigated PAH-directed therapies in the treatment of SAPH.

The selection of patients is paramount when planning the start of PAH therapies for SAPH. Because of the multiple pathophysiologic mechanisms that mediate SAPH, many patients may not respond to PH-specific therapy. Some SAPH patients, notably those with pulmonary veno-occlusive pathophysiology, acutely worsen with pulmonary vasodilator (PV) therapy[58]. Nevertheless, PVs have demonstrated efficacy in several small studies

conducted at expert centers, where patients with a pre-capillary SAPH phenotype most similar to PAH were carefully selected. Additional treatments for secondary PH, including diuretics for volume optimization, surgery or anticoagulation for thromboembolic disease, treatment of sleep disordered breathing, and stenting for mechanical vascular obstruction should be pursued when these concurrent illnesses are present.

The results of the studies investigating treatment of SAPH with PVs demonstrate improvements in hemodynamics and functional status. The PV treatment in SAPH was not associated with harm in patients carefully selected by expert centers, though none were able to clearly demonstrate a mortality benefit. Many studies are limited by small populations of patients and a high dropout rate. Table 2 summarizes major findings.

Endothelin Receptor Antagonists

Bosentan, ambrisentan, and macitentan are endothelin receptor antagonists, which block the activity of endothelin on pulmonary vascular smooth muscle. Endothelin is a potent endogenous vasoactive molecule implicated in the pathophysiology of PAH via its ability to increase pulmonary vascular tone and impact long-term effects of pulmonary vascular remodeling[58]. Bosentan and ambrisentan are among the first line therapies in the treatment of PAH, while macitentan has not been studied in SAPH.

Bosentan is approved for PAH and also has shown hemodynamic benefit in PH secondary to congenital heart disease and CTEPH[59,60]. The sole randomized clinical trial for SAPH examined the use of bosentan. This study randomized patients with SAPH diagnosed by RHC to bosentan versus placebo and measured hemodynamic and functional outcomes after 16 weeks of therapy[54]. It demonstrated an improvement in hemodynamics with the use of bosentan, but no significant improvement in pulmonary function tests or 6MWT. Two patients who were treated with bosentan also required oxygen. Liver toxicity, a common side effect of bosentan, was not observed. The trial had a somewhat high dropout rate, with 8 of the 43 enrolled (19%) patients not being observed for the full 16 weeks. The placebo and treatment groups were similar in WHO functional class, sarcoidosis treatment and degree of lung parenchymal involvement of sarcoidosis.

Ambrisentan has a mechanism of action similar to bosentan but boasts less liver toxicity and has also been studied in SAPH[62]. Judson et al performed an open-label prospective study to assess the impact of ambrisentan on SAPH patients. At a follow-up period of 24 weeks, there was improvement in WHO functional class and in quality of life. Hemodynamics were not assessed. The study was limited in large part by the high dropout rate: only 10/21 subjects remained in the study through the full follow-up period. Two patients reported liver toxicity.

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors inhibit the degradation of intracellular cyclic guanylyl monophosphate in vascular smooth muscle, which leads to increased nitric oxide generation and subsequent smooth muscle relaxation. Sildenafil and tadalafil are members of this class, along with vardenafil which is less commonly used. The results of phosphodiesterase inhibitor studies are mixed, with one retrospective study demonstrating improvement in

hemodynamics but not 6MWT[63]. A prospective case series highlighting the use of tadalafil in 12 patients noted no change in 6MWT nor quality of life measures, although like many other studies, the dropout rate was significant. Patients on tadalafil did not worsen clinically[64].

Riociguat, a soluble guanylyl cyclase activator, also serves to increase intracellular cyclic guanylyl monophosphate and is approved in Group I and Group III PH[36]. This medication has not been assessed in SAPH.

Prostacyclins

Prostacyclins, including epoprostenol, treprostinil and iloprost, are mainstays of treatment for PAH patients with WHO functional class III or IV symptoms. Epoprostenol was the first medication approved for the treatment of PAH and has demonstrated mortality benefit[65]. Available formulations for prostacyclin analogs include continuous IV infusion (epoprostenol and treprostinil), subcutaneous (treprostinil), oral (treprostinil), and inhaled (iloprost). More recently, selexipag, a non-prostanoid prostacyclin receptor agonist, demonstrated good tolerance, reduced hospitalization, and slowing of disease progression, but has not been studied in SAPH[66].

Fisher first reported on the use of epoprostenol for SAPH in 2006 in a small study of 8 patients, half of whom had Stage IV radiographic disease[67]. Of the 7 patients who underwent a vasodilator trial, 6 had a >25% reduction in PVR. This was the first report of the long-term use of epoprostenol in SAPH.

Subsequently, inhaled iloprost was studied by Baughman and colleagues in a group of 22 patients and was associated with a decrement in the PVR of >20% and improved quality of life[68]. This study was limited by a significant dropout rate of 31% due mainly to side effects or difficulty adhering to the regimen. Only 15 subjects completed the 16-week study, of which 6 experienced a significant decrease in PVR, and 5/6 demonstrated a reduction in MPAP. A few patients demonstrated an improved 6MWT, although this did not correlate to hemodynamic parameters. This discrepancy points to the fact that MPAP and PVR are only partially correlated with functional status, with factors such as deconditioning and lung disease also contributing to the dyspnea of SAPH. Despite its limitations, as one of the earliest trials of PAH-directed therapy in SAPH, this study served to illustrate the potential efficacy of prostacyclins.

Bonham and colleagues published a retrospective study regarding the efficacy of prostacyclins in the treatment of SAPH[10]. In this cohort of 26 patients prostacyclin use was associated with significant decreases in PVR, decreased MPAP, improved cardiac output and functional class. Both intravenous epoprostenol as well as treprostinil were used, often on a background of other PVs. This study also noted the potential for long-term use of prostacyclins in sarcoidosis, as many of the patients remained on prostacyclin therapy for years.

Conclusion

We suggest a stepwise approach to screening, diagnosis and selection of treatment for sarcoidosis patients suspected of having SAPH (Table 3). We emphasize that any patient with sarcoidosis who has dyspnea should receive chest imaging and full PFTs with 6MWT. Key clues that raise suspicion for SAPH include markedly reduced DLCO below 60% of predicted, oxygen desaturation below 90% on 6MWT, as well as dyspnea that seems refractory to immune suppression. Echocardiography is the key noninvasive test to screen for cardiac dysfunction and pulmonary hypertension.

While a positive initial evaluation should prompt referral for RHC, the question remains about what to do regarding negative screening. We recommend that unexplained dyspnea in a sarcoidosis patient, particularly in light of abnormal 6MWT or indeterminate echocardiography should be referred for RHC.

Because of the heterogeneity of SAPH, future studies must clearly phenotype patients' PH and extent of pulmonary disease if we are to understand which treatments are efficacious for which patients. Figure 2 delineates an algorithm for assessment of the pathophysiology of SAPH based on RHC data. PVs are currently approved for the treatment of PAH, but the majority of patients with SAPH have lung disease, where the role of PVs remains unclear. As discussed above, the literature to date supports a favorable safety profile for the use of PVs in SAPH patients who present with pre-capillary predominant PAH. A clear algorithm for PV initiation is not known. Patient preferences, physician experience and side effect profiles currently drive PV medication selection. In addition, SAPH patients with poor functional class or rapid progression are typically started on combination therapy. This is analogous to the current practice for group 1 PH, which has shown that combination up front therapy gives a longer time to first exacerbation[69]. Referral to an experienced PH center for RHC and treatment planning is advised.

Finally, when presented with severe or refractory disease, guidelines for lung transplantation in patients with PAH may be applied to SAPH. Early lung transplant referral is made for patients with rapidly progressive PH, functional class III or IV symptoms during escalating therapy, use of parenteral targeted PH therapy, or physiology mimicking pulmonary veno-occlusive disease[70]. Sarcoidosis patients who have severe lung disease with FVC less than 50% predicted have been shown to respond less favorably to PH specific therapy and should also be referred early for lung transplant consideration[71].

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Abbreviations

6MWT	six minute walk test
CT	computed tomography

CTEPH	chronic thromboembolic pulmonary hypertension
FVC	forced vital capacity
DLCO	diffusing capacity of the lung for carbon monoxide
MPAP	mean pulmonary artery pressure
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PFT	pulmonary function test
PH	pulmonary hypertension
PV	pulmonary vasodilator
PVR	pulmonary vascular resistance
RHC	right heart catheterization
SAPH	sarcoidosis associated pulmonary hypertension
WHO	World Health Organization

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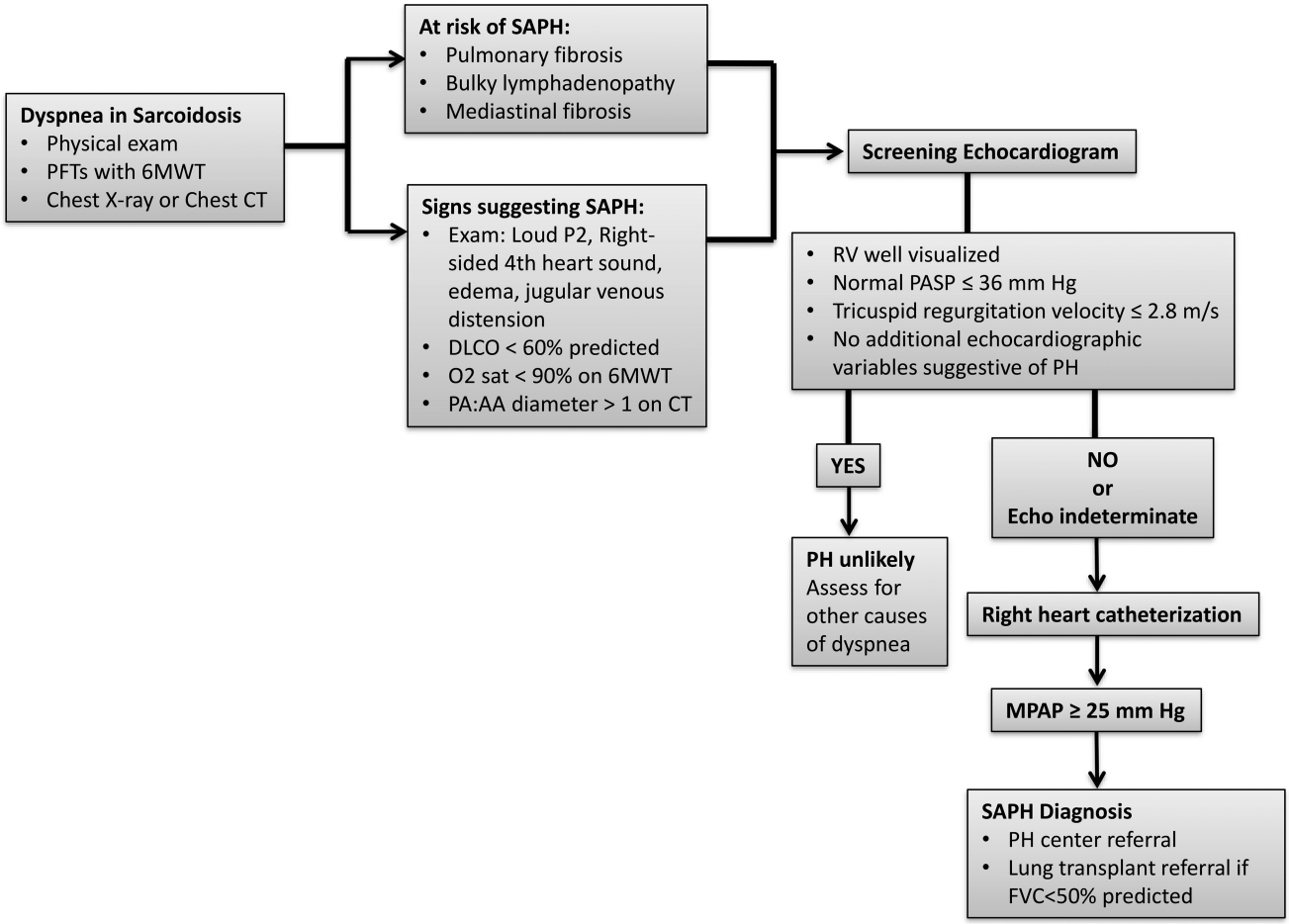

Figure 1. Screening and diagnostic algorithm for SAPH

In dyspneic patients with sarcoidosis at risk of PH or who exhibit signs suggestive of PH, screening echocardiography is performed, followed by right heart catheterization if echocardiography is positive or indeterminate. *6MWT* 6 minute walk test, *CT* computed tomography, *DLCO* diffusing capacity of the lung for carbon monoxide, *PA* pulmonary artery diameter, *AA* Aorta diameter, *FVC* forced vital capacity, *PASP* pulmonary artery systolic pressure, *RV* right ventricle, *SAPH* sarcoidosis associated pulmonary hypertension, *PH* pulmonary hypertension

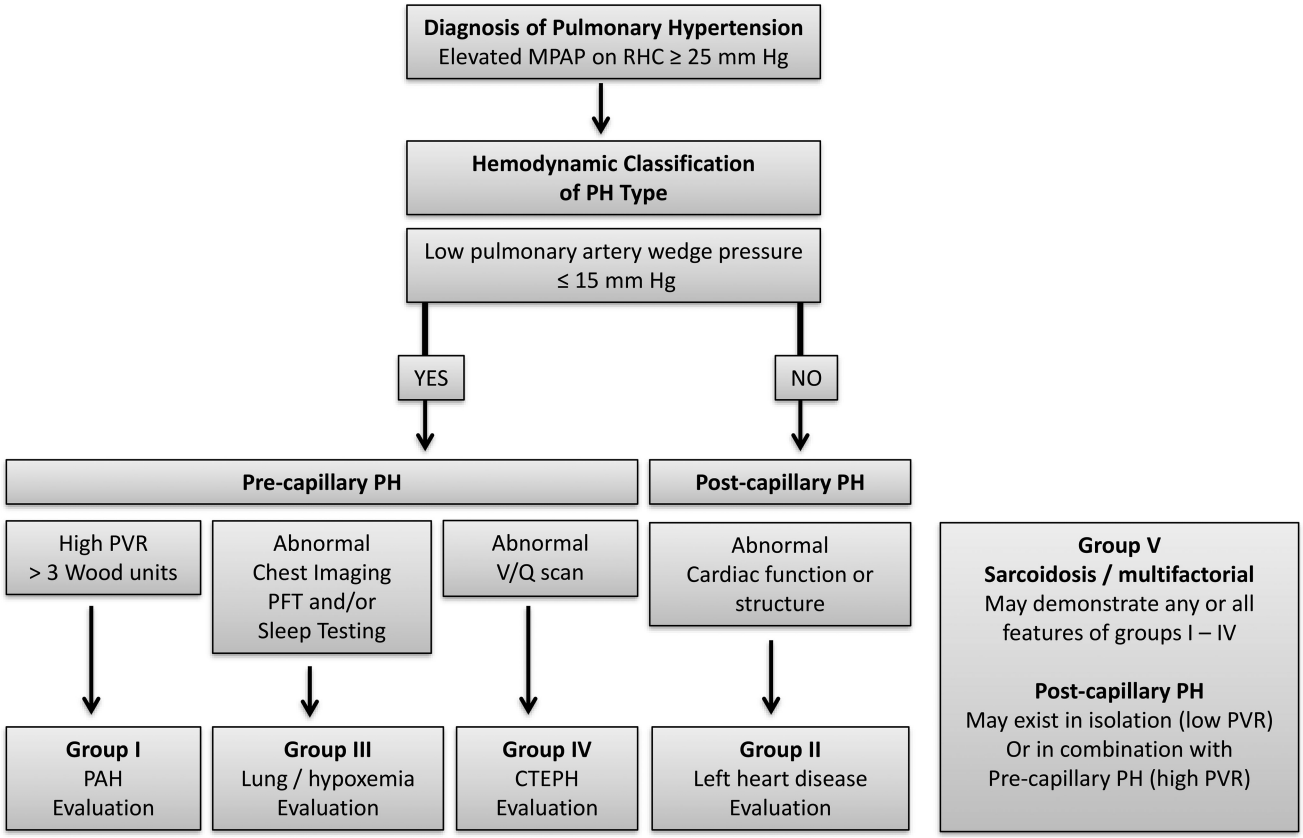

Figure 2. Diagnostic algorithm for pulmonary hypertension phenotype classification

Hemodynamic evaluation via RHC aids in grouping patients into pre- and post-capillary etiologies of PH. Individuals with sarcoidosis are classified as group V, and may have predominating features from any group I to IV. *CTEPH* chronic thromboembolic pulmonary hypertension, *MPAP* mean pulmonary artery pressure, *PAH* pulmonary arterial hypertension, *PFT* pulmonary function test, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RHC* right heart catheterization.

Table 1

World Health Organization Classification of Pulmonary Hypertension[11]

Pulmonary hypertension is defined by the World Health Organization as a mean pulmonary artery pressure ≥ 25 as measured by right heart catheterization. The diagnosis of pulmonary arterial hypertension (Group 1) also requires measured pulmonary vascular resistance of >3 Wood units. Items in bold represent etiologies which have been implicated in SAPH.

1 Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
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
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
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 pulmonary hypertension**

Table 2

Summary of trials of SAPH treatment

These nine studies report the use of PH-specific therapy in select SAPH patients with pre-capillary PH.

Author, year	Study type	Number of patients	Percentage with lung fibrosis	Drug	Percentage of patients completing study or average follow up time	Results
Prostacyclins						
Baughman et al, 2009[68]	Case series, prospective	22	68%	Inhaled iloprost	68% (16 weeks)	Improvement in RHC, 6MWT distance, quality of life
Bonham et al, 2015[10]	Case series, retrospective	26	81%	Epoprostenol, treprostinil	12.7 months	Improvement in hemodynamics, reduced BNP
Fisher et al, 2006[67]	Case series, retrospective	8	50%	Epoprostenol	29 months	Hemodynamic improvement, WHO functional class
Endothelin Receptor Antagonists						
Baughman et al, 2014[54]	Multi-center randomized double-blind controlled trial	35	51%	Bosentan	90% (16 weeks)	Improvement in hemodynamics, no change in quality of life or 6MWT
Judson et al, 2011[62]	Case series, prospective	21	38%	Ambrisentan	48% (24 weeks)	Improvements in quality of life and WHO functional class, poor tolerance of ambrisentan
Phosphodiesterase Inhibitors						
Ford et al, 2016[64]	Case series, prospective	12	33%	Tadalafil	58% (24 weeks)	No clinical worsening, no improvement in 6MWT, primary endpoint not met, no change in quality of life
Milman et al, 2008[63]	Case series, retrospective	24	75%	Sildenafil	14 months	Improvement in hemodynamics but not 6MWT distance
Studies with multiple pharmacologic categories in combined analysis						

Author, year	Study type	Number of patients	Percentage with lung fibrosis	Drug	Percentage of patients completing study or average follow up time	Results
Dobarro et al, 2013[72]	Case series, retrospective	24	63.2%	Sildenafil, bosentan	22.6 months	No difference in mortality, improved 6MWT, reduced BNP
Barnett et al, 2009[71]	Case series, retrospective	22	68.2%	Sildenafil, bosentan, epoprostenol	11 months	Improvement in functional class and hemodynamics
Boucly et al, 2017[57]	Cohort, prospective	126	74%	Bosentan/ambri-sentan, Sildenafil/Tadalafil, Epoprostenol/tre-prostinil/iloprost	28 months	Improvement in hemodynamics, no change in exercise capacity, 4/11 patients treated with only immunosuppression saw improved hemodynamics

RHC Right Heart Catheterization, *BNP* brain natriuretic peptide, *6MWT* 6 minute walk test.

Table 3

Key checkpoints in the evaluation of a dyspneic sarcoidosis patient

1. Establish the suspicion of pulmonary hypertension via physical examination, chest imaging, pulmonary function testing with six-minute walk, and echocardiography
2. Confirm the diagnosis via right heart catheterization
3. Classify the predominant type(s) of pulmonary hypertension present
4. Determine disease severity
5. Select appropriate treatment