Sarcoidosis-Associated Pulmonary Hypertension: Diagnosis and Treatment

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Sarcoidosis-associated pulmonary hypertension (SAPH) has been reported in 10% of all sarcoidosis patients. In the United States, the prevalence is similar to that reported for scleroderma. There are several possible mechanisms for SAPH, including vascular compression, granulomatous angiitis, left ventricular (LV) dysfunction, and fibrosis of lung tissue. The prognosis of those with LV dysfunction is significantly better than those with precapillary pulmonary hypertension. Screening for SAPH includes evaluation of dyspnea by 6-minute walk test, echocardiography, and measurement of pulmonary artery diameter on computer tomographic scan. Right heart catheterization remains the definitive test for characterizing SAPH. Treatment for precapillary hypertension has been shown to improve pulmonary hemodynamics. However, it is still unclear whether such treatments will change the natural course of the disease, especially in those with severe fibrosis.

The World Health Organization (WHO) has divided pulmonary hypertension (PH) into 5 groups.[1] Group 5 includes a variety of conditions with multifactorial pathogenesis of PH, which share one common feature: ie, they do not easily fit into the other 4 categories. Sarcoidosis-associated pulmonary hypertension (SAPH) has been combined with other systemic diseases and placed in Group 5. While one might debate the appropriateness of this classification, it has been endorsed by the fifth World Symposium on Pulmonary Hypertension. The major challenge with SAPH is that it can have features of any of the other 4 WHO diagnostic groups, and more than one may coexist in the same patient.

Despite the limitations of classifying SAPH, it is important to consider in a known sarcoidosis patient with persistent dyspnea. It is also a central cause of PH and should be considered as part of the initial evaluation of any PH patient.

CAUSES OF SAPH

Several potential factors can lead to PH in a sarcoidosis patient. Table 1 lists some of these that have been associated with SAPH. Left ventricular (LV) dysfunction can lead to PH. This can be the result of systolic dysfunction from cardiac sarcoidosis.[2,3] In addition, sarcoidosis patients may have LV dysfunction with preserved systolic function. In one study of SAPH,[4] 20 of 70 (29%) patients with PH had elevated left heart filling pressures. Of those 20 patients, only 7 (35%) had documented reduced LV systolic function. Of the remaining cases, diastolic dysfunction may have been due to sarcoidosis infiltration of the heart or comorbidities of sarcoidosis such as diabetes or systemic hypertension.[5]

Direct vascular disease from sarcoidosis can lead to PH. Changes in vascular tone as well as intimal fibrosis and medial hypertrophy have been reported with SAPH.[6,7,9] One can also encounter granulomatous angiitis from sarcoidosis. In one large series, open lung biopsies of 128 sarcoidosis patients were reviewed.[8] A total of 88 (69%) had some form of angiitis. Of these cases, venous disease was seen in more than 90%, with a third having both arterial and venous involvement. Less than 10% of the angiitis cases had arterial involvement alone. A similar finding was reported in examining explants from sarcoidosis patients undergoing lung transplant.[9] In addition, pulmonary veno-occlusive disease (PVOD) can be found.[9] Since patients with PVOD may develop pulmonary edema when treated with some pulmonary vasodilators such as prostanoids,[10] this is an important consideration in evaluating SAPH. To date, there are no published pathologic studies specifically dealing with SAPH.

Direct compression of the pulmonary vasculature can also lead to PH. The cause may be hilar adenopathy, but more often, it appears in association with mediastinal fibrosis.[11,12] While usually felt to be a rare complication,[11-13] one prospective series found 8 of 72 (11%) sarcoidosis patients had severe proximal pulmonary artery (PA) stenosis.[14] In that series, patients were evaluated with echocardiography and computer tomographic pulmonary angiography. All SAPH cases were confirmed by right heart catheterization. Nonetheless, not all cases of fibrosing mediastinitis are due to sarcoidosis. In one series of PH due to fibrosing mediastinitis, only half were due to sarcoidosis.[12] Other conditions to consider include infections such as histoplasmosis and tuberculosis as well as mediastinal radiation.[12,15]

Pulmonary fibrosis occurs in 10% to 20% of sarcoidosis patients.[16,17] The fibrosis may lead not only to destruction

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Table 1. Causes of PH in Sarcoidosis.

Cardiac
LV dysfunction
Vascular
Granulomatous angiitis (arterial and venous)
Pulmonary veno-occlusive disease
Compression of pulmonary vasculature
Intimal fibrosis and medial hypertrophy
Parenchymal lung disease
Pulmonary fibrosis with obliteration of lung tissue
Hypoxia-induced PH
Systemic disease
Sarcoidosis-associated cirrhosis and portopulmonary hypertension

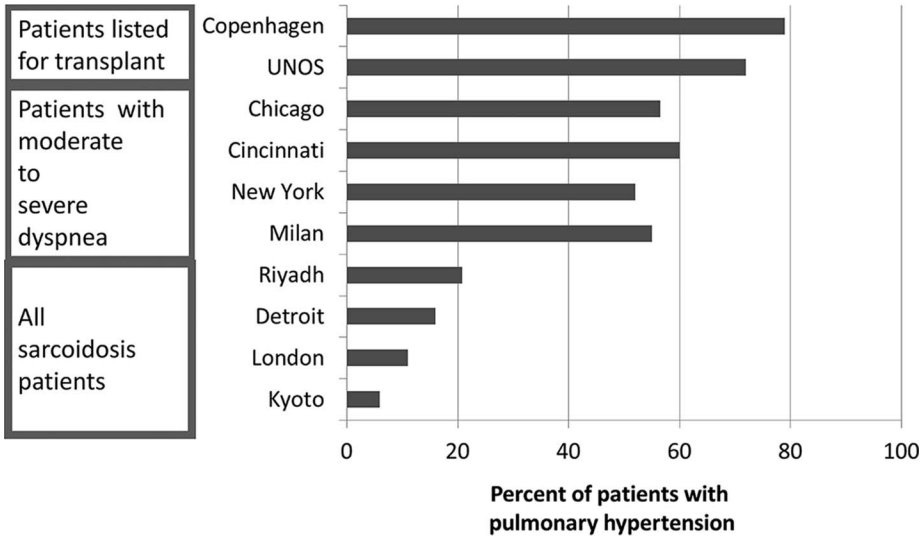

Figure 2: The incidence of PH across the world. Patients were selected for each based on pre-specified criteria: the general sarcoidosis clinic population,[25-28] patients with moderate to severe dyspnea,[4,29-31] or those listed for lung transplant.[32,33]

of lung parenchyma, but may also involve pulmonary vasculature (Figure 1). In addition to fibrosis, airway distortion, traction bronchiectasis, and emphysematous changes may be seen.[18] The destruction of lung tissue can also lead to hypoxia, which further contributes to PH.

Sarcoidosis is a multiorgan disease that affects the liver in at least a quarter of sarcoidosis patients.[19-21] While most cases are mild,[19,20] severe liver involvement with cirrhosis can occur.[19,22] Patients with cirrhosis due to sarcoidosis may rarely develop hepatopulmonary syndrome and PH.[23,24] The varied clinical presentations require expert evaluation to determine the exact cause of the PH in patients with sarcoidosis.

FREQUENCY OF SAPH

The frequency of SAPH depends on which patients are studied. Figure 2 shows the results of several studies looking for sarcoidosis in the general sarcoidosis population,[25-28] patients with moderate to severe dyspnea,[4,29-31] or those listed for lung transplant.[32,33] In some cases, patients underwent right heart catheterization.[4,32,33] Generally, this was performed to confirm PH detected by echocardiography.[25-27,29] Regardless of technique used, the percentage was similar for each of the groups.

Group 1 pulmonary arterial hypertension (PAH) is a rare condition, with an estimated prevalence between 10 and 50 patients per million.[34] In contrast, sarcoidosis is a worldwide disease. In the United States, there are approximately 200,000 sarcoidosis patients.[35] The overall incidence of 5% to 20% of PH in sarcoidosis is similar to that reported for scleroderma.[36] The current data would suggest that there are approximately 20,000 SAPH patients in the United States. Thus, sarcoidosis should be considered as a possible cause of PH. While routine screening with echocardiography for PH is common in scleroderma,[36,37] screening with echocardiography is not routinely performed in sarcoidosis clinics.

Several of the studies shown in Figure 2 examined potential risk factors for SAPH. Features associated with an increased likelihood for SAPH are listed in Table 2. Many of the features were studied in some but not all reports. The typical patient with SAPH will have pulmonary fibrosis, a reduced diffusing capacity of the lung for carbon monoxide (DLCO), and desaturation with exercise. The reduction in DLCO is usually to a larger degree than the reduction in lung volume.[27] This "out-of-proportion"

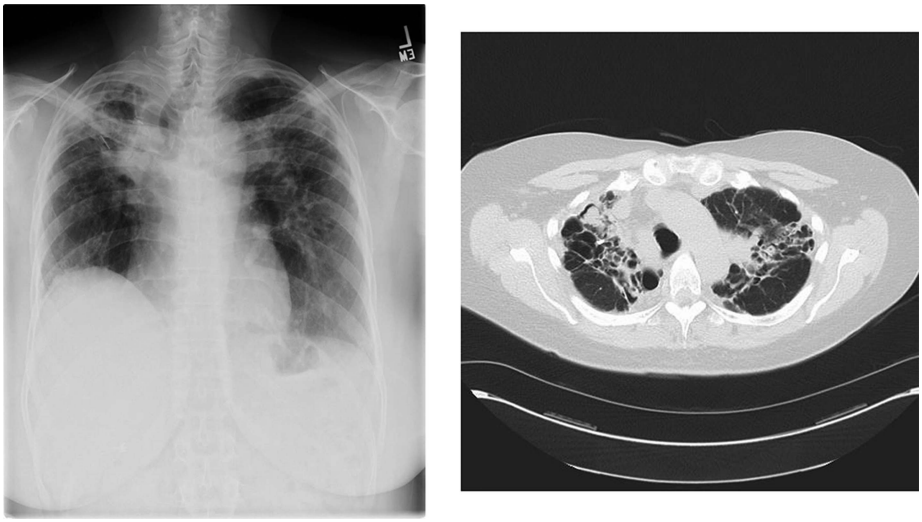

Figure 1: Chest x-ray and CT of sarcoidosis patient with pulmonary fibrosis and SAPH.

Table 2. Features Associated With SAPH.

• Pulmonary fibrosis on chest x-ray[27-30]
• Reduced forced vital capacity[4,26,28,29]
• Reduced DLCO[4,26-29]
• Reduced 6-minute walk distance[26,55,68]
• Hypoxemia, especially after 6MWT[26;68]
• Older age[27]

Table 3. Stepwise Approach to the Diagnosis of SAPH.

● Initial evaluation: Presence of one or more feature
○ Complaint of moderate or greater dyspnea with exertion
○ Hypoxia at rest or with exercise
○ Reduced DLCO out of proportion to reduction of lung volumes
○ Significant pulmonary fibrosis on chest roentgenogram
○ CT scan showing:
▪ Significant pulmonary fibrosis
▪ Main PA-to-aorta ratio of >1 or main PA >29 mm*
● Screening: Presence of one or more feature from initial evaluation leads to
○ Echocardiography showing estimated systolic PA pressure >35 mm Hg
○ Evidence of RV dysfunction
▪ Echocardiography
▪ Magnetic resonance imaging
○ 6-minute walk
▪ Desaturation by more than 5%
● Confirmation and classification of PH if any screening tests positive
○ Right heart catheterization

* Presence of enlarged PA may lead to confirmation with right heart catheterization.

reduction in DLCO has also been noted in SAPH.[38] It is not clear whether this ratio may also be useful in identifying sarcoidosis patients with SAPH.

DIAGNOSIS OF SAPH

The most significant step in detecting SAPH is when the clinician first asks, "Could this patient have PH?" As in many other situations, PH often presents with nonspecific symptoms, usually dyspnea. Sarcoidosis is a multifaceted disease and reduced exercise capacity may be due to multiple causes, such as parenchymal or airway lung disease, direct cardiac dysfunction, skeletal muscle disease, neurologic disease, or even fatigue or depression.[39] The stepwise approach to diagnosis of SAPH is detailed in Table 3.

As part of the initial evaluation, the clinician inquires about dyspnea. There are several standardized questionnaires to stage dyspnea.[40] One commonly used system is the American Thoracic Society/Medical Resource Council questionnaire, which allows one to identify mild, moderate, or severe dyspnea. This

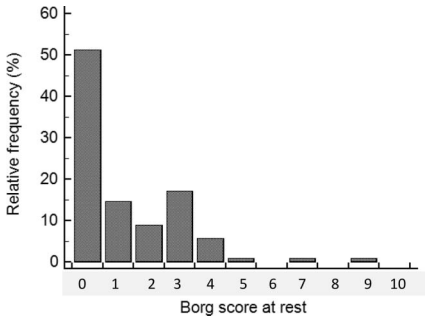

Figure 3A: Borg score at rest in 123 patients with right heart catheterization-confirmed PH.

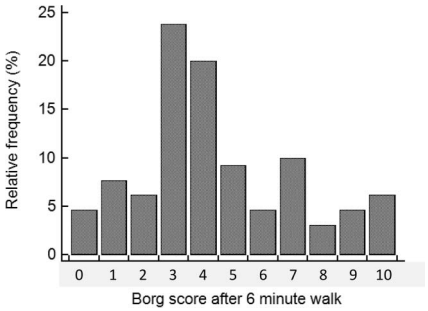

Figure 3B: Borg score after 6-minute walk in 123 patients with right heart catheterization-confirmed PH. (Personal communication, RP Baughman on behalf of ReSAPH investigators.)

questionnaire has been used in sarcoidosis and idiopathic pulmonary fibrosis.[41,42] Another is the Borg score, which is often used in conjunction with the 6-minute walk test (6MWT). The Borg score is a 10-point Likert scale to assess level of dyspnea from none (0) to maximal (10).[43] Figure 3A demonstrates the Borg score reported by more than 120 sarcoidosis patients with confirmed PH before 6MWT. These patients were part of an ongoing registry of sarcoidosis-associated pulmonary hypertension (ReSAPH). As shown in Figure 3A, over half of the patients reported no dyspnea at rest. In contrast, less than 5% reported no dyspnea after 6MWT, with the median score of 4, depicted in Figure 3B.

Hypoxia is encountered in patients with fibrotic sarcoidosis. As noted above, this may lead to PH. However, PH itself can lead to hypoxia. In SAPH, hypoxia, especially with exertion, is a common feature[26] and should lead to further evaluation for SAPH. The hypoxia from PH is often due to shunting, which may be worsened with vasodilator therapy.[7] While this may occur, clinically significant worsening of shunting is relatively rare after vasodilator therapy.[44]

A reduction in the DLCO reflects difficulties with gas exchange. Patients with a DLCO that is reduced more than the reduction of lung volumes, such as the vital capacity, are likely to have PH.[38] A reduced DLCO is a strong predictor of PH, especially in a patient without pulmonary fibrosis.[27] In patients being studied for possible PH, there was a significant negative correlation between the DLCO and the PA pressure.[45]

Patients with SAPH are far more likely to have pulmonary fibrosis on chest x-ray than the general sarcoidosis population.[29,30] The presence of pulmonary fibrosis should raise the question of whether the patient has PH. However, lack of pulmonary fibrosis does not rule out PH.[27,45]

Computed tomography (CT) has been applied more widely to pulmonary sarcoidosis, especially to those with advanced pulmonary disease.[46] The CT scan can provide an estimate of the severity of lung fibrosis, with more than 20% fibrosis of the lung being considered significant.[17] The size of the PA can be readily evaluated by the CT scan. A main PA diameter >29 mm or a PA main-to-aorta ratio >1 has been proposed as highly suggestive of PH.[47] This also has been reported to be useful in patients with interstitial lung disease.[48] In sarcoidosis, the presence of an increased ratio is highly suggestive of PH.[49] However, the ratio does not seem to correlate with the level of PH.[45]

If any of the above features are present, one should screen for PH. The 2 tests most commonly used for screening are echocardiography and 6MWT. As noted above, an enlarged PA and increased ratio of PA to aorta may be another clue to the presence of PH.

The echocardiogram is the most commonly used noninvasive tool for assessing for PH regardless of cause. For patients with interstitial lung disease, the echocardiogram has been shown to have significant limitations, with PA systolic pressure often over- or underestimated.[50,51] However, when estimated PA systolic pressures are more significantly elevated (>50-60 mm Hg), a

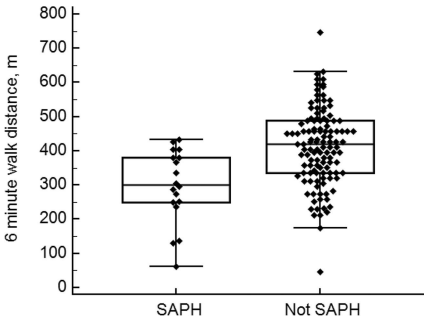

Figure 4: 6-minute walk distance for those with or without SAPH. There was a significant difference in the 6-minute walk distance between the groups ($P<0.001$).[55]

majority of patients will have significant PH by catheterization.[4,51] In sarcoidosis, an elevated PA systolic pressure by echocardiogram of 50 mm Hg or more was associated with increased mortality.[4] However, the echocardiogram is not able to distinguish between precapillary and postcapillary PH.

Right ventricular (RV) function can also be assessed by echocardiography. While this may be difficult to quantitate, the presence of RV dysfunction is suggestive of SAPH.[30] The tricuspid annular plane systolic excursion (TAPSE), a well-described measure of RV performance, has been shown to be abnormal in some cases of SAPH.[52] Magnetic resonance imaging (MRI) has been reported as effective in assessing RV dysfunction.[53] In sarcoidosis, one study evaluated RV function in 50 consecutive patients undergoing cardiac MR for clinical reasons. Using sensitive measures of RV dysfunction, they found abnormal results in more than half of all patients studied. This was most common in patients with parenchymal lung disease, LV dysfunction, and PH, but 4 patients had no cause identified.[54]

The 6MWT is another commonly used assessment for dyspnea and screening for PH. The 6-minute walk distance is shorter in SAPH than other sarcoidosis patients (Figure 4).[55] However, there is considerable overlap. This is in part because of the multiple factors in sarcoidosis that can affect exercise performance.[39] A more reliable screening test for PH is measuring desaturation during the 6MWT.[26] However, not all SAPH patients desaturate,[55] so this test cannot be used to exclude PH.

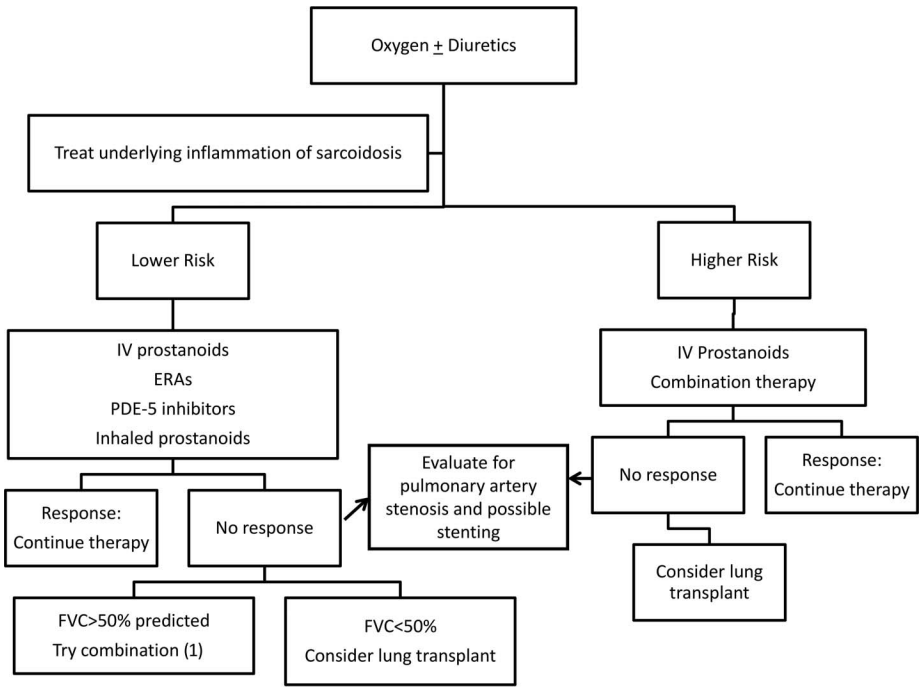

Figure 5: Proposed algorithm for treating precapillary SAPH. IV: intravenous; ERAs: endothelin receptor antagonists; PDE-5: phosphodiesterase 5; FVC: forced vital capacity.

If one or more of the screening tests support PH, one should confirm the diagnosis with right heart catheterization. There are several reasons to perform this particular assessment. It has been shown that the prognosis is significantly different between those with precapillary PH and PH due to diastolic dysfunction.[4] Right heart catheterization also allows one to accurately characterize cardiac output and determine pulmonary vascular resistance. These are important aspects of prognosis and treatment of SAPH.

TREATMENT

While treatment studies for SAPH are far less common than those for idiopathic PAH, there is sufficient information to offer some evidence-based recommendations for the treatment of SAPH. In most cases, these are based on case series and examining the results of treatment trials in other PH conditions. Many of the older agents for idiopathic PH have been studied in SAPH, but there is limited information regarding newer agents. Figure 5 presents a proposed algorithm for treatment. The patient is felt to be at higher risk if there is evidence of RV failure such as a low cardiac output or elevated right atrial pressure.

Prostacyclins

Intravenous epoprostenol was the first drug to be shown to effectively treat precapillary PH.[59] Because of the complexity of drug delivery, this regimen is often reserved for patients with moderate to severe PH.[47] For SAPH, case series have documented the use of intravenous epoprostenol for both short-term[7]and long-term treatment of SAPH.[31,60] In an early series by Fisher et al,[60] 5 of 6 patients tolerated treatment for more than a year. Two patients had severe complications during initiation of therapy: one had a cardiac arrest and the other required mechanical ventilation. The second patient experienced pulmonary edema, possibly due to a component of veno-occlusive disease as part of the SAPH. Nonetheless, that patient was eventually able to tolerate long-term therapy with epoprostenol. A recent retrospective study by Bonham et al reviewed their experience with treating SAPH.[31] They treated 13 patients with prostaglandins, 7 with epoprostenol, and 6 with trepostinil. Their results were similar to those reported by Fisher et al, with 9 of 13 still alive after a year of therapy. Repeat catheterizations were performed on 10 of 13 patients. There was significant improvement in cardiac

output and pulmonary vascular resistance, but not in mean PA pressure. The authors did not comment on changes in 6-minute walk distance.

Prostanoids given by inhalation have also been studied in SAPH. In a prospective study of 22 patients treated with inhaled iloprost,[57] only 15 completed the full 16 weeks of therapy. Repeat right heart catheterization demonstrated improved hemodynamics in only 6 of these patients. Only 3 patients improved their 6-minute walk distance by more than 30 meters. Most patients reported an improvement in quality of life in this open-label trial. Use of iloprost in SAPH has been limited because of the high rate of complications (mostly cough) and low rate of significant improvement in pulmonary hemodynamics and 6-minute walk distance. To date, there are no published randomized controlled trials regarding use of oral prostanoids for SAPH.

Endothelin Receptor Antagonists

Two endothelin receptor antagonists (ERAs) have been studied for treatment of SAPH. Bosentan has been the most widely reported ERA in treatment for SAPH. This includes retrospective cases series as a single agent[45,61,62] or in combination with other agents.[45,52,62] Bosentan was also studied in a double-blind, placebo-controlled trial of SAPH.[44] That study demonstrated a significant improvement in mean PA pressure as well as pulmonary vascular resistance, while there was no change for the placebo group. There was no significant difference in the 6-minute walk distance. This study did not find a significant change in quality of life after treatment with bosentan compared to the placebo-treated group.

Ambrisentan has also been reported as treatment for SAPH.[52] In a prospective, open-label trial of ambrisentan for SAPH, Judson et al found no change in 6-minute walk distance after 24 weeks of therapy.[58] However, there was an improvement in reported quality of life in this open-label study. It should be noted that randomized clinical trials of ambrisentan in SAPH are lacking, and that ambrisentan was associated with worse outcome compared to placebo when used to treat patients with idiopathic pulmonary fibrosis.[63]

Table 4. Outcomes Improved by Pharmacologic Treatment of SAPH.

Outcome	Improvement	No improvement
PA pressure	Barnett[62] Baughman 2014[44] Baughman 2009[57] Milman[32]	Bonham[31] Dobarro[64]
Pulmonary vascular resistance	Barnett[62] Baughman 2014[44] Baughman 2009[57] Bonham[31] Milman[32]	
6-minute walk distance	Barnett[62] Dobarro[64] Keir[52]	Baughman 2014[44] Baughman 2009[57] Judson[58] Milman[32]
Quality of life	Baughman 2009[57] Judson[58]	Baughman 2014[44]
TAPSE	Keir[52]	
N-terminal pro-brain natriuretic peptide	Bonham[31] Dobarro[64] Keir[52]	

Phosphodiesterase Type 5 Inhibitors

The use of sildenafil and tadalafil has been reported in some case series in SAPH.[52,62] In one retrospective series, sarcoidosis patients listed for lung transplant who were found to have SAPH were treated with sildenafil.[32] The authors found a significant improvement in mean PA pressure with treatment. However, there was no change in the 6-minute walk distance. On the other hand, 2 groups have reported on the use of sildenafil alone or in combination with other agents.[52,62] While not reporting on the outcome of treatment with sildenafil explicitly, the authors found that their "real-world" use of this drug was associated with an overall improvement in various parameters including pulmonary hemodynamics,[62] 6-minute walk distance,[52,62] and TAPSE.[52]

Overall Outcome of Pharmacologic Treatment of SAPH

To date, there is no clear-cut PAH-specific therapy with proven efficacy or approval for treatment of SAPH. Nonetheless, a meta-analysis found that pharmacologic treatment of SAPH was associated with improvement in pulmonary hemodynamics and quality of life.[64] Table 4 lists various potential markers of response to therapy that have been reported. It should be noted that only a few of the studies highlighted in the table used only one therapy retrospectively[65] or prospectively.[44,57,58] Other studies used single or combination treatments as commonly employed in a PH center.[52,62,64]

Most studies demonstrated an improvement in pulmonary vascular hemodynamics, either mean PA pressure or pulmonary vascular resistance. In addition, measures of RV dysfunction such as TAPSE and N-terminal pro-brain natriuretic peptide were reported as improved.

Quality-of-life instruments may be useful in assessing the impact of therapy. There is no agreement on a single quality-of-life instrument specific for PAH.[66] In the reported studies of treatment for SAPH, improvement in quality of life using the general instruments Short Form 36 and St George's Respiratory Questionnaire has been reported in 2 open-label prospective trials.[57,58] However, there was no significant improvement in quality of life compared to placebo in the only double-blind trial reported to date in SAPH using these instruments.[44] Future trials using questionnaires that are more specific may provide additional information.

Changes in pulmonary hemodynamics have not always led to improvement in 6-minute walk distance. The 3 studies that reported an improvement in 6-minute walk distance were all retrospective studies in which the clinicians changed therapy based on initial response.[31,52,62] The treatment used in these studies is consistent with recommendations for treatment of Group 1 PAH.[47]

There are 2 important considerations in evaluating the response to pharmacologic therapy in SAPH. The first is the possible presence of PA stenosis. As noted above, mediastinal fibrosis can lead to PH in some cases of sarcoidosis. In a few cases, there may be some response to anti-inflammatory therapy such as glucocorticoids.[11,13] However, anti-inflammatory therapy may not improve the vascular narrowing.[11,12] These patients may respond to PA stenting and/or steroids.[67] A recent series from China investigated 32 patients with SAPH identified by echocardiography.[14] The authors found that 8 (25%) had large vessel narrowing that they treated interventionally and with corticosteroids. All patients were doing well at least 3 months after interventional treatment.

Another important issue is the amount of parenchymal lung destruction. A reduced forced vital capacity (FVC) is a risk factor for lung transplant or death in SAPH.[31,52] There are limited data about the cutoff value at which the impact of lung destruction outweighs effect of treatment. In one study, Barnett et al noted that patients with an FVC percentage predicted above the median, 51% (in that study) were much more likely to improve their 6-minute walk distance with treatment of PH.[62]

CONCLUSION

In summary, SAPH is an important complication of advanced pulmonary sarcoidosis. It is unlikely to respond to conventional anti-inflammatory therapy such as glucocorticoids. Recognition of SAPH requires that one think of the diagnosis. Since LV dysfunction is an important cause of PH in sarcoidosis patients, a right heart catheterization should be considered in all cases of potential SAPH. Treatment of SAPH should follow a stepwise approach and should contemplate issues such as PA narrowing and severely reduced lung tissue. When possible, the treatment of SAPH should be undertaken within PH centers, preferably those conducting clinical trials of the condition.

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