Sarcoidosis-Associated Pulmonary Hypertension: An Updated Review and Discussion of the Clinical Conundrum

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ABSTRACT: Pulmonary hypertension (PH) is a life-threatening disease with complex pathophysiology. The World Health Organization has classified PH in 5 groups according to etiology, the fifth of which corresponds to PH due to unknown or multiple mechanisms; including sarcoidosis-associated PH (SAPH). Although this system has been used to guide treatment recommendations according to each group, it does not provide much insight into the heterogeneous group 5. Furthermore, pulmonary vasodilators have been contraindicated for patients in this cluster which represents a challenge for the management of SAPH which can sometimes improve with these PH-directed drugs. In this review, we discuss the classification of SAPH; as well as the evidence behind the use of pulmonary vasodilator, invasive procedures, and lung transplantation for treating SAPH; and the little that is known about his disease in the setting of cardiac sarcoidosis. (Curr Probl Cardiol 2021;46:100506.)

Introduction

Treatment of sarcoidosis-associated pulmonary hypertension (SAPH) is challenging and is best accomplished with multidisciplinary collaboration between cardiologists, pulmonologists, rheumatologists, and radiologists with experience in the management of

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pulmonary hypertension (PH) and sarcoidosis.[1] Because the etiology of PH in sarcoidosis is multifactorial, treatment options target the underlying pathogenic mechanisms of PH and include both sarcoidosis-directed and PH-directed therapies; the latter consisting of pulmonary vasodilators (PVD) which are indicated to treat only pulmonary arterial hypertension (PAH; World Health Organization [WHO] group 1 PH) and chronic thromboembolic PH (WHO group 4 PH). There are no current specific treatment recommendations for SAPH and each patient must be considered on an individual basis.

Classification of SAPH

SAPH is a term that covers a heterogeneous group of patients with PH in whom the culprit is thought to be their underlying sarcoidosis. Given the granulomatous and inflammatory nature of this disease, and its wide distribution throughout the pulmonary, lymphoid, and cardiovascular structures, sarcoidosis can lead to PH through a wide variety of mechanisms. These can be classified into precapillary (pulmonary wedge pressure [PWP] $\leq$ 15 mmHg) and postcapillary (PWP $>$ 15 mmHg); according to the hemodynamic profile (see Table 1).[1]

Although the WHO classifies SAPH as group 5 (unknown and multifactorial mechanisms), SAPH has been hypothesized; and in some cases evidenced, to be caused by a diversity of pathways that correspond to each of the other groups of the WHO classification.[1] Rather than preventing the use of PH-directed pharmacologic or interventional therapies in SAPH as in current treatment guidelines for PH, this highlights the need

TABLE 1. Mechanisms of sarcoidosis-associated pulmonary hypertension*

Vascular location	PWP	Mechanism
Precapillary PH	≤15 mmHg	Destruction of distal capillary bed leading to hypoxemia Specific vasculopathy (granulomatous vasculopathy) Local increase in vasoreactivity Extrinsic compression of pulmonary arteries by lymph nodes or fibrosing mediastinitis Portal hypertension (due to hepatic sarcoidosis with cirrhosis)
Postcapillary PH	≤15 mmHg	Pulmonary veno-occlusive disease Extrinsic compression of pulmonary veins by lymph nodes or fibrosing mediastinitis
	>15 mmHg	Cardiac sarcoidosis with left ventricular failure

*Only includes mechanisms attributed to sarcoidosis, patients may also have other causes of PH unrelated or indirectly associated to their sarcoidosis.

to analyze cases individually, and to consider the use of PVD in addition to immunosuppression.[1]

The complexity of the histologic and macroscopic pathophysiologic mechanisms of SAPH represents a major challenge for translational and clinical researchers who are seeking to conduct randomized clinical trials with a homogeneous subgroup of patients. Furthermore, in some individuals, several processes falling in different WHO groups may simultaneously lead to the development of PH; such as would be the case of a patient with pulmonary veno-occlusive disease and left ventricular dysfunction (LVD) due to sarcoidosis. Additionally, the overall profile of the SAPH in a certain patient may change during flares, remissions, and progression of the disease in each organ involved; such as heart, lungs, thoracic vessels, liver, and lymph nodes.

Sarcoidosis-directed Therapies

Corticosteroids

When active granulomatous inflammation is present, PH may dramatically improve with corticosteroid treatment. In a study by Nunes et al,[2] 3-6 months of treatment with high-dose corticosteroids resulted in >20% reduction in systolic pulmonary arterial pressure (PAP) in 3 out of 5 patients with grade 0 and grade II sarcoidosis. These patients were maintained on low-dose corticosteroids following the study, with further reductions in PAP reported.

However, this result has not been demonstrated consistently, and long-term use of corticosteroids is not without consequence.[3-5] In addition, no significant improvement in hemodynamics was seen after treatment of stage IV sarcoidosis; the most common stage at presentation, with corticosteroids in this or any other study.[2,6,7] This suggests that patients with fibrocystic sarcoidosis are not likely to respond to corticosteroids and this treatment option should only be considered for those with active granulomatous inflammation or compression of the pulmonary arteries (PAs) by lymphadenopathy.

Anti-inflammatory and Immunomodulatory Therapies

Following corticosteroids, second line treatment of granulomatous sarcoidosis includes the antimetabolites methotrexate and azathioprine.[1] These agents may have a potential therapeutic role if the etiology of the PH is active sarcoidosis.[7] Third-line treatment includes antitumor necrosis

factor (TNF) monoclonal antibodies or rituximab.[1,8] While it is known that antitumor necrosis factor -α plays a role in both the pathogenesis of sarcoidosis and the inflammation associated with PAH, there is no data to suggest the use of these agents has any therapeutic benefit to treat SAPH.[7]

Supportive Therapies

Supportive measures including supplemental oxygen in the setting of resting hypoxemia, diuretics, and anticoagulation in the presence of thromboembolic disease should be used when appropriate.[1,7] Comorbid conditions including obstructive sleep apnea and cardiac dysfunction should also be treated.

PH-directed Therapies

Studies investigating the use of PH-targeted therapies or PVD in patients with SAPH predominantly consist of small cohorts or single arm clinical trials rather than randomized placebo-controlled clinical trials, and there is some heterogeneity of outcomes among studies (see Table 2). As such, use of these medications in SAPH is off label. While there may be potential benefit to some patients with improvement in functional capacity, quality of life (QOL) and hemodynamics, they are often ineffective in others, and in some may cause harm.[1]

For example, in patients with fibrocavitary disease, PVD may worsen oxygenation by inhibition of hypoxic pulmonary vasoconstriction in affected regions with a resultant increase in blood flow to areas with poor ventilation leading to shunting.[6] For this reason, PAH-directed therapies are contraindicated in patients with significant hypoxia.[1] In addition, because of the high incidence of pulmonary venous involvement, clinicians should watch for pulmonary edema and discontinue the use of PH-directed therapies should it occur.

What limited data exist on the use of approved PH-directed therapies in patients with SAPH is discussed below, with outcomes of monotherapy, and combination therapy summarized in Tables 2 and 3; respectively. Unless otherwise stated, the sample size for each study discussed below refers to those patients who actually received PH-directed therapies.

Calcium Channel Blockers

The role of Calcium Channel Blockers (CCBs) in SAPH has not been investigated in depth. Preston et al demonstrated a high rate of pulmonary vasoreactivity in patients with SAPH by challenging patients undergoing

TABLE 2. Studies evaluating pulmonary hypertension-specific monotherapies in patients with sarcoidosis-associated pulmonary hypertension*

Study	Year of publication	Study type	Drug	Primary outcome	N†	Follow-up (mean/median [range]; weeks)‡	Acutely vasoreactive	Hemodynamic outcomes	Other outcomes/notes
Preston[9]	2001	Prospective cohort	Inhaled Nitric oxide	≥20% ↓ in PVR	8	(9-26; for 6MWD)	7/8	In 7/8 pts: ↓ PVR (≥20%) In 4/8 pts: ↓ mPAP (≥20%) ↑CO (12%; from 4.7 to 5.2)	4 pts received long-term iNO only. 1 pt was on iNO/epoprostenol. All of them improved in 6MWD. 3/5 pts improved in NYHA class; from IV to III.
			Epoprostenol		6		4/6	4/6 pts: ↓ PVR (≥20%) ↑CO (25%; from 5.2 to 6.4)	
			Calcium Channel Blockers		5		2/5	2/5 pts: ↓ PVR (≥20%), ↓ SVR No change in CO	1 pt received verapamil only and died 4 months after lung transplant. 1 pt received diltiazem only, had intractable heart failure and died 4 months afterwards.
Fisher[11]	2006	Retrospective cohort	Epoprostenol, treprostinil	≥25% ↓ in PVR	7	29 (15-49)	6/7	↓ PVR (45%) ↓ mPAP (11%) ↑CO (44%) ↑CI (66%)	5 pts survived, 1 pt died after initiation of epoprostenil. 1 pt did not tolerate treprostinil (access site pain) and died after discontinuation. 5 pts alive improved one to two NYHA classes. 1 pt received lung transplantation.
Milman[18]	2008	Retrospective cohort	Sildenafil	-	9	17 (4-52)	-	In 9 pts: ↓ mPAP (18.8%) In 8/8 pts: ↓ PVR (47.7%) In 6/8 pts: ↓ PVR (≥20%) ↑CO (35.7%)	All pts tolerated sildenafil well. No change in 6MWD. This cohort consisted of patients with end-stage pulmonary sarcoidosis referred for lung transplantation.

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TABLE 2. (*continued*)

Study	Year of publication	Study type	Drug	Primary outcome	N[†]	Follow-up (mean/ median [range]; weeks)[‡]	Acutely vasoreactive	Hemodynamic outcomes	Other outcomes/notes
								↑CI (26.0%) No change in PWP	
Baughman[14]	2009	Open-label, nonrandomized, single arm, clinical trial with per protocol analysis	Iloprost	Mean change in 6MWD	15	16	-	In 6/15 pts: ↓ PVR (≥20%) ↑mPAP (3.3%) ↓ PVR (2.0%) In 8/15 pts: ↑PVR ≥20% and/or ↑6MWD (≥30 m)	3/12 pts had an increase in the 6MWD (≥30 m) at 16 weeks. There was major variability in the changes of 6MWD during follow up. 7/15 pts had improvement of QOL. 4/15 pts improved in NYHA class; from III to II. Another pt worsened. Among the 22 pts recruted: 1 pt withdrew before initiation, 2 pts did not comply with frequency of treatment, 3 pts did not tolerate side effects (cough), and 1 pt developed urosepsis.
Judson[17]	2011	Open-label, non-randomized, single arm, clinical trial	Ambrisentan	Mean change in 6MWD	21	24	-	-	Most of the patients were black women. 11/21 pts withdrew, 8 pts due to dyspnea or edema, and 3 due to social reasons. No change in 6MWD, Borg dyspnea score, serum BNP, diffusion capacity, or QOL. 10/10 pts followed for 24 weeks had no change in NYHA class. None of the patients developed hepatotoxicity.
Baughman[15]	2014	Double-blind, placebo-controlled, randomized clinical trial with per protocol analysis	Bosentan	Mean change in mPAP	23	16	-	↓ mPAP (11.1%) ↓ PVR (25.4%)	No change in 6MWD. 1 pt could not repeat 6MWT due to above-knee amputation. Half of patients on each group had Scadding stage IV.
Ford[19]	2016		Tadalafil	Mean change in 6MWD	12	24	-	-	No change in 6MWD, QOL or Borg dyspnea score. 6/12 pts completed the study.

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TABLE 2. (*continued*)

Study	Year of publication	Study type	Drug	Primary outcome	N[†]	Follow-up (mean/median [range]; weeks)[‡]	Acutely vasoreactive	Hemodynamic outcomes	Other outcomes/notes
		Open-label, non-randomized, single arm, clinical trial							3/12 pts withdrew due to side-effects, and 2/12 due to social factors. 3/6 pts who completed the trial had Scadding stage III and decreased in 6MWD. 1/7 pts improved NYHA class by one.
Hon[12]	2018	Retrospective cohort	Epoprostenol	-	9	107 (±60)	-	↓ PVR (50.8%) ↓ RAP (47.1%) ↑CO (48.6%)	Follow-up hemodynamic parameters were measured after acute titration of epoprostenol. All patients survived 10-month follow-up. NYHA class improved by almost one class.

All changes were statistically significant ($P < 0.05$) unless otherwise stated. Arrows indicate increase (↑) or decrease (↓). 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CI, cardiac index; CO, cardiac output; iNO, inhaled nitric oxide; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal-proBNP; NYHA, New York Heart Association; pt(s), patient(s); PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; QOL, quality of life; RAP, right atrial pressure.

*Only studies evaluating monotherapy (pulmonary hypertension-specific therapies) were included.

†Only patients on the intervention arm for the specific vasodilator were counted. Those with PH-specific polytherapies were excluded; except for Preston et al. which was the only one to detail results for iNO and included only one patient on iNO/epoprostenol.

‡Follow-up listed is for hemodynamic outcomes unless otherwise stated. Fractions "/" represent the "number of patients that had a certain outcome/all those evaluated for such outcome."

TABLE 3. Studies evaluating combination regimens of pulmonary hypertension-specific therapies in patients with sarcoidosis-associated pulmonary hypertension

Study	Year of publication	Study type	Drug	Primary outcome	N*	Follow-up (mean/ median [±SD or IQR])†	Hemodynamic outcomes	Other outcomes/Notes
Palmero[21]	2011	Retrospective cohort	Bosentan, PDE-5is, PCAs	-	38	38.7 (14-62) months	↓ mPAP (10.7%) ↓ PVR (27.5%)	This cohort seems to overlap with the one reported by Qua et al. Follow-up hemodynamics were measured at 15 (±8.8) months on monotherapy with bosentan. 3 pts had liver function abnormalities. No major adverse effect reported. At 1 year, 6MWD increased by 74.6 m, and dyspnea improved (according to Borg score). At 3 years, 21/40 pts were still alive (52.5%), and 8/35 pts required additional PH-therapy (PDE-5is and/or PCAs) Main cause of death was right ventricular failure, followed by respiratory failure. There was no deterioration in O2 sat at rest or exercise.
Qua[23]	2012	Retrospective cohort	Bosentan, PDE-5is, PCAs		45	36 months	↓ mPAP (17.3%) ↓ PVR (28.6%)	This cohort seems to overlap with the one reported by Palmero et al. Bosentan was discontinued in 5 pts due to liver function abnormalities. 45% of patients required additional PH-directed therapy. 29 pts remained on bosentan for 3 years with increase in 6MWD. 1- and 3-year survival rates were 73% and 48%.
Dobarro[20]	2013	Retrospective cohort	-	-	11 (only 8 had F/U RHC)	22.6 months 5.3 months for RHC	No change in RAP, mPAP, PWP, CO, or CI	The rate of mortality or lung transplantation was 41.2%. 6MWD increased by 35.3%. NT-ProBNP decreased by 62.9%. Baseline predictors of death or transplantation: right ventricular failure (strongest predictor), moderate or severe lung fibrosis, and NYHA class IV.
Bhandari[24]	2014	Retrospective cohort	PDE-5is, ERAs	6MWD	7	11 (±4.9) months	-	6MWD increased by 20 m. 5 pts were on long-term oxygen therapy 1 pt was intolerant to ERAs and was on PDE-5is only. At baseline, mPAP 38.9 mmHg, PCWP 8.7 mmHg, PVR 7.2 Wood Units. At baseline, FEV1 53%, FVC 56%, FEV1/FVC ratio 88%, TLC 63.16, DLCO 35%.

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TABLE 3. (*continued*)

Study	Year of publication	Study type	Drug	Primary outcome	N*	Follow-up (mean/median [±SD or IQR])†	Hemodynamic outcomes	Other outcomes/Notes
Keir[26]	2014	Retrospective cohort	Sildenafil, bosentan	-	33	6 months 13.5 (3-37) months for mortality	-	29 pts were started on sildenafil, 4 pts on bosentan. 3/29 pts on sildenafil required combination with bosentan. In 29 pts, BNP decreased from 35 to 26 pml/L. In 19 pts, 6MWD increased from 226 to 240 m. On F/U TTE, RVSP did not change but TAPSE increased by 2.5 mm. NYHA class decreased in 14 pts but increased in 8 pts. 10 (30.3%) pts died and 1 received lung transplantation. FVC, DLCO, and CO were significantly higher; and PVR lower, among survivors.
Bonham[19]	2015	Retrospective cohort	Epoprostenol, treprostinil, ERAs, PDE-5is, CCBs	-	13	5 years 12.7 months for RHC	↓ PVR (49%) ↑ CO (56%) ↑ CI (71%)	5/13 pts survived at 5-year follow-up. 4/13 pts died at 1-year follow-up. 1 pt died within 24 hours of emergently starting PCA for right heart failure. 8/8 pts improved in NYHA class at 1-year follow-up. 3/3 pts improved in 6MWD (32.6 m). NT-proBNP decreased from 2,207 pg/mL to 354 pg/mL (1-year follow-up) and 49 pg/mL (3-year follow-up).
Boucly[27]	2017	Retrospective and prospective cohort	ERAs, PDE-5is, epoprostenol, iloprost	-	97	28 (11-56) months 4.5 months (IQR 4-6.7) for RHC	↓ RAP (14.3%) ↓ mPAP (12.5%) ↑ CI (11.5%) ↓ PVR (28.9%)	Number of pts on monotherapies: ERAs (60), PDE-5is (20), epoprostenol (2), iloprost (1). Number of pts on combination therapies: ERAs + PDE-5is (12), ERAs + PCAs (2) Survival was 93% at 1 year, 74% at 3 years, and 55% at 5 years. 6MWD did not change at median of 4.5 months (first follow-up visit). NYHA class improved significantly. There was no discontinuation due to side effects. 39 pts needed escalation of PH-directed therapy. At baseline, 72% of pts had Scadding stage IV, 24% had FVC <50%, and 83%, NYHA classes III/IV, and 54% were on long-term oxygen therapy. At the time of PH diagnosis, 40% were on steroids. 5 pts had extrinsic compression of pulmonary arteries by lymph nodes or fibrosing mediastinitis.

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TABLE 3. (*continued*)

Study	Year of publication	Study type	Drug	Primary outcome	N*	Follow-up (mean/median [±SD or IQR])†	Hemodynamic outcomes	Other outcomes/Notes
Albujoq[25]	2018	Retrospective cohort	PDE-5is, ERAs, PCAs	-	22	334 days (IQR 140-499) for TTE	-	6MWD increased by 19.2%. BNP decreased by 25.5%. mPAP decreased by 34% on TTE.
Parikh[22]	2019	Retrospective cohort	-	6MWD, NT-proBNP	74	Up to 11 years	-	74/95 (78%) pts in the cohort received PH-directed therapies. Initial regimen: oral monotherapy (37.9%, parenteral monotherapy (24.2%), inhaled monotherapy (4.2%), combined therapy (11.6%), no PH-directed therapy (22.1%). 6MWD did not change significantly. NT-proBNP decreased by 387 pg/mL (51.2%). Mortality at a median of 3 years was 32%. 33 pts continued on their initial therapy through follow-up. Those receiving parenteral monotherapy had the highest prevalence of moderate/severe right ventricular dysfunction while those on no PH-directed therapy had the lowest. At baseline, 77% had NYHA classes III/IV. At baseline, RAP 8 mmHg, mPAP 49.1 mmHg, CI 2.3 L/min/m^2, PVR 8.6 Wood Units.

All changes were statistically significant ($P < 0.05$) unless otherwise stated. Arrows indicate increase (↑) or decrease (↓). 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CCB, calcium-channel blockers; CI, cardiac index; CO, cardiac output; ERA(s), endothelin-receptor antagonist(s); DLCO, diffusion capacity of the lung for carbon monoxide; ERA(s), endothelin-receptor antagonist(s); FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal-proBNP; NYHA, New York Heart Association; PCA(s), prostacyclin agonist(s); PDE-5i(s), phosphodiesterase-5 inhibitor(s); PH, pulmonary hypertension; pt(s), patient(s); PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SD, standard deviation.

*Only patients on the intervention arm for vasodilators were included.

†Follow-up listed is for hemodynamic outcomes, or the only follow-up provided on the reference, unless otherwise stated. Fractions "/" represent the "number of patients that had a certain outcome/all those evaluated for such outcome."

right heart catheterization (RHC) with intravenous (IV) epoprostenol, inhaled nitric oxide (iNO), or CCBs.[9] Two of five patients who received the latter had ≥20% reduction in pulmonary vascular resistance (PVR) and were continued on CCBs long term. However, a reduction in systemic vascular resistance was the only significant response to treatment with CCBs and both patients died 4 months afterwards.[9]

Prostacyclin Analogues

Prostacyclin is a potent PVD that inhibits platelet aggregation, causes relaxation of smooth muscle and vasodilation of the PA. Prostacyclin analogues (PCAs) may be given via continuous IV infusion (epoprostenol and treprostinil), subcutaneously (treprostinil), or inhaled (iloprost and treprostinil).

In 1985, Barst et al first described a case of a patient with severe SAPH who responded to short-term IV epoprostenol.[10] Almost 20 years later, Fisher et al published a retrospective cohort in which 7 patients with moderate to severe SAPH and New York Heart Association (NYHA) functional class III or IV symptoms, underwent PVD challenge with IV epoprostenol.[11] Six of seven patients had a significant hemodynamic response defined as >25% reduction in PVR, and 5 of them were continued on therapy with IV epoprostenol. Mean follow-up was 29 months, at which time average clinical improvement was a decrease of 1-2 levels of NYHA functional class. Only one patient developed pulmonary edema (PWP 30 mmHg) requiring mechanical ventilation, diuresis, and temporary reduction of the dose of epoprostenol.

Preston et al demonstrated a significant response to IV epoprostenol with a decrease of ≥20% in PVR in 4 of 6 patients, with a mean increase of 25% in cardiac output (CO).[9]

In a retrospective study of 9 patients, Hon et al observed decrease in PVR and right atrial pressure (RAP) to about half with an increase in CO of 48.6%.[12] All patients survived a 10-month follow-up. There was also an average improvement of approximately one NYHA class.

loprost was used in 21 patients with SAPH and NYHA class II and III symptoms in an open label, single-arm clinical trial conducted by Baughman et al.[13] Fifteen patients completed 16 weeks of therapy and were analyzed as per protocol. In this group, there was a ≥20% decrease in PVR from baseline in 6 patients, 5 of who also had a ≥5 mmHg reduction in mean PA Pressure (mPAP). In addition, 6-minute walk distance (6MWD) improved by at least 30 m in 3 patients, and in 7, QOL as assessed by the Saint George Respiratory Questionnaire (SGRQ) was significantly improved. NYHA class improved in four and worsened in 1 patient. The study was not powered or long enough to evaluate effect on survival.

Endothelin Receptor Antagonists

Endothelin is arguably the most potent vasoconstrictive mediator in the body and is found in higher levels in both patients with sarcoidosis and idiopathic PAH.[7] The endothelin receptor antagonist (ERAs) bosentan, ambrisentan, and macitentan, are approved therapy for the treatment of WHO group 1 PAH.

Baughman et al conducted a 16-week randomized, double-blind, placebo-controlled trial of bosentan in 35 patients with SAPH.[14] There was a significant reduction in mPAP (11.1%) and PVR (25.4%) in the 23 patients randomized to bosentan and no significant change in those treated with placebo. There was no significant difference in 6MWD in either group. Two of the patients who received bosentan had a >2 L increase in oxygen requirement after 16 weeks of treatment.

Barnett et al also demonstrated improved mPAP, PVR, NYHA class, and 6MWD in 22 patients with SAPH, 12 of whom were receiving bosentan in a 2-center retrospective cohort.[15] The control arm consisted of patients who were either on sildenafil, PCA, or combination therapy. This improvement was particularly evident in those with lower Scadding stage (radiographic staging system of pulmonary sarcoidosis) and higher FVC (>51%). This study showed no association between diffusion capacity of the lungs for carbon monoxide and change in 6MWD.

Judson et al performed a prospective, open-label trial using ambrisentan in 21 patients with SAPH for 24 weeks.[16] There was no significant change in 6MWD, Borg dyspnea score, serum brain natriuretic peptide (BNP), diffusing capacity, or QOL as measured by the Short-Form-36 (SF-36). There was a 52% drop out rate, due to social or medical reasons, dyspnea, and/or edema. There was a trend toward improvement in NYHA class and QOL measured by the SGRQ, but these results did not reach statistical significance.

There are no studies evaluating the use of macitentan in SAPH.

Inhaled Nitric Oxide and Phosphodiesterase-5 Inhibitors

iNO is a potent PVD that is commonly used in catheterization laboratories for PVD challenge during RHC. Preston et al used iNO both for acute vasoreactivity testing and for long-term treatment in 8 patients with moderate to severe SAPH.[9] Seven out of eight patients had a ≥20% reduction in PVR and mPAP during PVD challenge with iNO. Five patients received long-term treatment with iNO; one in combination with epoprostenol, with improvement in 6MWD. Three patients had improvement in NYHA class. Three of the 5 demonstrated sustained

improvements in hemodynamics on repeat RHC. At the time of publication, 3 of the 5 patients treated long term with iNO had died; 1 at 5 months (due to right heart failure), the second at one and a half years (due to catheter-related sepsis), and the third at 1 year (sudden death). Two were still on therapy awaiting lung transplantation, one at one-and-a-half year and the second at 2-year follow-up.

The phosphodiesterase-5 inhibitors (PDE-5s) sildenafil and tadalafil increase local nitric oxide in arterial smooth muscle cells leading to both short- and long-term vasodilation and potentially a reduction in the proliferation of vascular smooth muscle cells.[7] Barnett et al reported the aforementioned cohort with patients that received bosentan, sildenafil, other agents, and/or combination therapies with significant reductions in mPAP and PVR without significant difference of outcomes among patients according to their index therapy.[15]

In another single-center retrospective case series by Milman et al, 12 patients with endstage pulmonary sarcoidosis referred for pulmonary transplantation were treated with sildenafil for an average of 4 months.[17] In this study, there were significant reductions in mPAP and PVR, and a significant increase in CO and cardiac index (CI) with treatment. There were, however, no significant changes in 6MWD.

Ford et al performed an open-label trial of tadalafil in 12 patients with SAPH in 2 academic medical centers.[18] At 24 weeks, there was no significant improvement in 6MWD, QOL by SF36 or SGRQ, or Borg dyspnea score. Five of the 12 patients dropped out of the study early (for social or medical reasons). Three of six patients who completed the trial had Scadding stage III and experienced a decrease in 6MWD.

PH-directed Combination Therapies

Data available for outcomes on regimens that include combination of PH-directed medications is based mostly on retrospective cohort studies,[19-26] with only one partially prospective study.[27]

Although, these reports provide evidence from “real-world” experiences; adding the value of external validity or generalizability of their outcomes, they do pose major challenges for interpretation and maybe some threat to their internal validity. Some of these studies had different proportions of patients on a wide variety of regimens; mono- and combination therapies at different times of follow-up. Furthermore, outcomes are not provided for each regimen but as an overall for the whole sample and most do not include a control arm. Nevertheless, they do have their strengths, as some consist of a larger sample size and represent the

outcomes of complex "real-world" management of these patients during significantly longer follow-up.

Seven of the 9 studies that investigated the outcomes of combined PVD-directed therapies in patients with SAPH reported the class of PVD used. In these 7 cohorts, ERAs and PDE-5s were used (see Table 3).

In most of these studies reporting hemodynamics through RHC, there was a significant decrease in the PVR, except for the cohort of Dobarro et al in which 8 patients that underwent RHC before and after initiation of PVD, showed hemodynamic changes in RAP, mPAP, PWP, PVR, CO, and CI that did not reach statistical significance.[20] However, they did evidence a statistically significant increase on 6MWD of 20 m (35.3%) as well as a significant decrease in N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) of 62.9%. In this study, right ventricular failure at baseline was the strongest predictor of mortality or lung transplantation.

Palmero et al and Qua et al each reported results of patients at the same center with probable sample overlap.[21,23] Palmero et al reported in 2011 a cohort of 38 patients that received bosentan for SAPH with a survival of over 50% at 3 years, and significant improvements in 6MWD and dyspnea. There was no deterioration of blood oxygen saturation after initiation of PVDs.[21] Qua et al included 45 patients in their cohort 1 year later.[23] Bosentan was discontinued in 5 patients due to liver disfunction, 45% of the patients required additional PH-directed therapy, and 29 patients remained on bosentan for 3 years with a significant increase in 6MWD.

Bhandari et al described results of 7 patients; 6 received PDE-5s and ERAs, and 1 PDE-5s only.[24] Five patients were on supplemental oxygen therapy prior to initiation of therapy. There was a significant increase in 6MWD of 20 m.

The cohort of Keir et al included 33 patients on sildenafil and/or bosentan.[26] Twenty-nine were initially on sildenafil monotherapy but three required combination with bosentan during follow-up. Six-minute walk distance was measured at baseline and follow-up in 19 patients with an increase from 226 to 240 m. There were also improvements in BNP and tricuspid annular plane systolic excursion on transthoracic echocardiography (TTE). Only 2 patients had side effects with sildenafil or bosentan that required changing to different PVDs.

The largest cohort of patients with SAPH was published by Boucly et al in 2017.[27] It included 97 patients from the French Pulmonary Hypertension Registry. Most (61.9%) of the patients were on ERA-monotherapy, and 14.4% were on a combination of ERAs and either PDE-5s or PCAs. There was a significant improvement in hemodynamics on follow-up at 4.5 months including a 28.9% decrease in PVR. Although 6MWD

did not significantly change by first follow-up visit after initiation on PVDs, survival at 1 year was 93% and there was a significant improvement in NYHA class. Remarkably, this series seems to include a high proportion of patients with very advanced pulmonary sarcoidosis, since 72% had Scadding stage IV, 24% had FVC < 50%, 83% were NYHA class III/IV, and 54% were on chronic supplemental oxygen therapy.

The second largest cohort of patients receiving PVDs for SAPH was published by Parikh et al in 2019.[22] From a total of 126 patients, combined PH-directed therapies were given to 11.6%, while 22.1% did not receive PVDs for their PH. A total of 74 patients received PVD, of whom 74.3% were Scadding IV, and the mean FVC was 56.5%. NYHA class was III/IV in 78.4% of the patients on PVDs. The authors investigated clinical events in the whole cohort and found that the median time to hospitalization or death was 6 months. Interestingly, there was no association between clinical events (death or hospitalization) and treatment with PH-directed therapies or immunosuppressants.

One study of Albujoq et al evaluated hemodynamic changes on TTE and 6MWD after initiation of PH-directed therapies in 22 patients.[25] They found significant reductions in mPAP and BNP, and a significant increase in 6MWD.

Bonham et al published a larger series, in which 26 of 46 patients with sarcoidosis had PH.[19] Thirteen of these patients were treated with PCA (7 with epoprostenol and 6 with treprostinil) either as monotherapy or in combination with oral PVDs. There was no significant difference in survival between patients on PCA and those receiving other PVD. Nine of the 13 patients treated were alive at 1 year, and in this group, there was a significant improvement in hemodynamics, NYHA class, and NT-proBNP.

Invasive (Procedural) Therapies

Current knowledge of outcomes of invasive therapies for SAPH due to mediastinal fibrosis with extrinsic compression of the pulmonary vessels is limited, with most information being provided by case reports and small cohorts (Table 4).[28-35] To our knowledge, the highest level of evidence comes from a prospective cohort of Liu et al that reported the outcomes of 8 patients with SAPH; due to extrinsic compression that failed treatment with steroids and underwent balloon angioplasty with or without stenting of the pulmonary vasculature.[33] They observed a reduction of the mPAP to less than half of baseline, a reduction of the PVR to a third, and significant increases in CI and 6MWD. Although, some patients had procedural complications, all 8 survived at 3-month follow-up.

Condado et al. published a small retrospective series of five patients with external compression of the pulmonary vasculature due to external compression attributed to sarcoidosis.[32] In that series, three underwent stenting of the PAs, two of who also had balloon angioplasty to the pulmonary veins. One of them had restenosis of the veins and required repeat balloon angioplasty in two following encounters. The patient who only received PA stenting, had in-stent thrombosis, which was treated with aspiration thrombectomy, and local thrombolysis. They managed to decrease or even discontinue immunotherapy in all three patients afterwards.

Labyk et al reported the successful use of "kissing stent" technique in a patient with chronic thromboembolic PH and advanced sarcoid affecting 2 adjacent arterial branches of the right middle lobe artery.[31]

For more details about each report of invasive therapies for SAPH, see Table 4.

Lung Transplantation

As with all forms of advanced lung disease, lung transplantation remains the treatment option of last resort for patients with advanced fibrocystic sarcoidosis when all other possible therapies have failed.[7] Univariate analysis has identified mPAP $\geq$ 35 mmHg as risk factor for increased mortality on the transplant waitlist, and mPAP has been shown to be 35% higher in endstaged sarcoidosis patients compared with idiopathic pulmonary fibrosis.[36,37] Conversely, those with lower mPAP have been shown to be more likely to survive on the transplant waitlist than those with higher mPAP.[37]

The 2006 International Society of Heart and Lung Transplantation consensus guidelines recognize that there is little data regarding the optimal timing of referral of patients and prediction of outcomes for patients with sarcoidosis.[38] It is recommended that patients with NYHA class III and IV symptoms be referred for transplant consideration and that those with any of the following be listed: hypoxemia at rest, PH, elevated RAP $>$ 15 mmHg. The 2014 updated guidelines for selection of lung transplant candidates list the following factors identified in the US Registry to Evaluate Early and Long-term PAH Disease Management registry and associated with increased mortality in idiopathic PAH: NYHA class IV, male gender with age $>$60 years old, increased PVR, PAH associated with portal hypertension, or family history of PAH.[39] Additional risk factors associated with increased mortality include: NYHA class III, increased mRAP, decreased resting systolic blood pressure or an elevated heart rate, decreased 6MWD, increased BNP, renal insufficiency, PAH

TABLE 4. Reports of invasive therapies for sarcoidosis-associated pulmonary hypertension

Author	Year of publication	Study type	Presentation/ methodology	Preprocedure hemodynamics						Procedure	Postprocedure hemodynamics						Other outcomes/Notes
				RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (wood units)	Miscelaneous		RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (Wood Units)	Miscelaneous	
Hamilton-Craig*,[28]	2009	Case series	Case 1: 71-year-old man with pulmonary sarcoidosis and progressive dyspnea. V/Q scan mismatch perfusion deficits. Angiogram had shown filling defect in the PA. TTE: RV dilatation with reduced systolic function, RVSP of 114 mmHg. CT: Hiliar and mediatinal adenopathy with severe extrinsic compression of the PAs.	8	44	12	2.2	-	-	Balloon angioplasty	-	33	-	-	-	-	6MWD↑ from 210 to 375 m, NYHA class ↓ from III to II. At 6 months: 6MWD↑ to 425 m. TTE: RVSP ↓ from 110 to 35 mmHg.
			Case 2: 48-year-old woman with mediastinal arterial compression due to sarcoidosis.	-	-	-	-	-	-	Stenting	-	-	-	-		"Good angioplastic and hemodynamic results"	Developed in-stent restenosis a year later and was treated successfully with balloon angioplasty.
Ferguson*,[34]	2010	Retrospective cohort	6 pts with fibrosing mediastinitis; 1 due to sarcoidosis, underwent pulmonary arterial catheterization. 4 received percutaneous angioplasty and stenting. The pt with sarcoidosis was a 57-year-old man who received a stent to the lower lobe branches of the RPA as well as sildenafil.	-	-	-	-	-	-	Stenting	-	-	-	-	-	-	Peak systolic gradient ↓ from 51 to 34 mmHg. At 6 weeks: RHC showed moderate-severe PH. Symptoms improved with sildenafil. TTE: RVSP ↓ from 95 to 71 mmHg.

(*continued on next page*)

TABLE 4. (*continued*)

Author	Year of publication	Study type	Presentation/ methodology	Preprocedure hemodynamics						Procedure	Postprocedure hemodynamics						Other outcomes/Notes
				RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (wood units)	Miscelaneous		RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (Wood Units)	Miscelaneous	
Sekiguchi[35]	2013	Case report	60-year-old-woman with sarcoidosis presented with chronic dysnea, cough and wheezing. She had mediastinal and hilar lymphademopathy compressing mediastinal estructures including pulmonary arteries and bronchi.	-	26	-	-	-	-	Balloon angioplasty	-	-	-	-	-	-	Symptoms did not improve despite steroids and angioplasty. Refused second encounter for angioplasty.
Condado*,[32]	2016	Retrospective cohort	Case 1: 63-year-old woman with pulmonary sarcoidosis presented with dyspnea despite prednisone and leflunomide. CTA: high-grade stenosis of left upper, left lower, right middle, and right lower lobe PAs, and total occlusion of the right upper lobe PA. Received balloon angioplasty and stenting in the right main and left lower lobe PAs, as well as left upper PV stenting.	-	50	-	-	-	-	Stenting	-	45	-	-	-	-	2 of initial 5 pts did not receive a procedure due to underlying thromboembolic disease. PFT parameters and 6MWD improved postprocedurally.
			Case 2: 42-year-old woman with sarcoidosis complained of progressive dyspnea and was found to have pulmonary hypertension. CTA: Hilar lymphadenopathy compressing the pulmonary arteries. Underwent balloon angioplasty stenting of the right upper and left lower lobe PAs.	-	90	-	-	-	-	Stenting	-	42	-	-	-	-	Had in-stent thrombosis treated with aspiration thrombectomy and local thrombolytics. Was started on chronic anticoagulation and bosentan. Steroids were weaned off. CTA on follow-up showed patent stents.

(*continued on next page*)

TABLE 4. (*continued*)

Author	Year of publication	Study type	Presentation/ methodology	Preprocedure hemodynamics						Procedure	Postprocedure hemodynamics						Other outcomes/Notes
				RA (mmHg)	mPAP (mmHg)	PW (mmHg)	PCI ($L/min/m^2$)	PVR (wood units)	Miscelaneous		RA (mmHg)	mPAP (mmHg)	PW (mmHg)	PCI ($L/min/m^2$)	PVR (Wood Units)	Miscelaneous	
			Case 3: 60-year-old woman with sarcoidosis had dyspnea despite prednisone. CTA: bilateral superior PA and PV compression. Underwent stenting of 2 right and 2 left upper PVs. 4 months later, had balloon angioplasty of PV stents (for restenosis) and LPA stenting. Required an additional session of PV angioplasty for restenosis.	-	48	-	-	-	-	Balloon angioplasty (PVs), stenting (LPA)	-	29	-	-	-	-	Had clinical improvement at 1-year follow-up.
Bazmpani[29]	2017	Case report	Woman with a diagnosis of CTEPH on riociguat had presented at age 45-year-old (at the time of index procedure). V/Q scan: multiple areas of V/Q mismatch. Angiography: total occlusion of the right superior trunk, linear occlusion of the right lower lobe artery which received balloon angioplasty with stenting 3 weeks later for restenosis. Recent FDG-PET and lymph node biopsy diagnosed sarcoidosis (17 years after index procedure) and she was finally started on steroids.	-	-	-	-	-	-	Stenting	5	53	8	4.3	6.2	-	Had not been treated with steroids during years of false diagnosis of CTEPH. PFT: restrictive pattern. After steroids, RAP 2 mmHg, mPAP 34 mmHg, CO 4 L/min, PVR 8 Wood Units.

(*continued on next page*)

TABLE 4. (*continued*)

Author	Year of publication	Study type	Presentation/ methodology	Preprocedure hemodynamics						Procedure	Postprocedure hemodynamics					Other outcomes/Notes
				RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (wood units)	Miscelaneous		RAP (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (Wood Units)	Miscelaneous	
Liu[33]	2017	Prospective cohort[†]	72 consecutive patients with sarcoidosis in an outpatient clinics had TTE and CT. SAPH was confirmed by RHC. Parameters were compared after 2-month treatment with steroids. Eight patients had SAPH with severe PA stenosis (despite steroids); hence underwent angioplasty ± stenting with follow-up RHC 3 months later.	-	42.5	-	2.1	12.3	-	Balloon angioplasty ± stenting	-	20.5	-	3.2	3.8	All changes in hemodynamic parameters were statistically significant ($p < 0.05$)	6MWD ↑ from 236.8 to 456.4 m. Complications: one thromboembolism during angioplasty, one hemoptysis, one had PA dissection. All survived 3 month follow-up.
Labyk[31]	2018	Case report	65-year-old man with pulmonary sarcoidosis on steroids presented with progressive RV failure. CT (1 year prior): embolus in left supperior lobe artery. He was started on anticoagulation. CT (recent): advanced interstitial pulmonary fibrosis and calcified mediastinal lymph nodes, organized thrombi in RPA and LPA. Angiography: confirmed CTEPH; left upper lobe artery occlusion, intravascular webs in the RPA.	9	54	6	2.1	13.5	PPRs: 0.19 in A9, 0.22 in A10 in the right pulmonary system.	Balloon angioplasty (including "kissing balooning")	1	27	-	3.3	3.7	PPRs: 0.63 in A9 and 0.65 in A10 in the right pulmonary system	At 12 months: 6MWD ↑ from 100 to 405 m, NYHA class ↓ from IV to II.

(*continued on next page*)

TABLE 4. (*continued*)

Author	Year of publication	Study type	Presentation/ methodology	Preprocedure hemodynamics						Procedure	Postprocedure hemodynamics						Other outcomes/Notes
				RA (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (wood units)	Miscelaneous		RA (mmHg)	mPAP (mmHg)	PWP (mmHg)	CI (L/min/m^2)	PVR (Wood Units)	Miscelaneous	
Tramper[30]	2018	Case report	43-year-old woman with progressive dyspnea when steroids were weaned. CT: pleural and pericardial effusions but no pulmonary fibrosis. TTE: PASP of 80 mmHg with no signs of left heart disease. CTA: lymphadenopathy compressing the RPA, acute stop of blood flow bilaterally (lower lobes). MRI: no myocardial dysfunction or sarcoidosis. FDG-PET: hiliar and pulmonary sarcoidosis. She received steroids for >3 months without improvement. Angiography: right middle lobe artery stenosis, complete occlusion of the left lower lobe arteries.	-	44	15	3.5	4.8	-	Balloon angioplasty	-	22	-	-	-	-	6MWD ↑ from 422 to 475 m, NYHA class ↓ from III to II.

6MWD, 6-minute walk distance; CI, cardiac index; CT, computed tomography; CTA, computed tomography angiography; CTEPH, chronic thromboembolic pulmonary hypertension; FDG-PET, fluorodeoxyglucose-positron emission tomography; LPA, left pulmonary artery; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; PA(s), pulmonary artery(ies); PFT, pulmonary pressure ratio; PPR, pulmonary pressure ratio; PV, pulmonary vein; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; RHC, right heart catheterization; RPA, right pulmonary artery; RV, right ventricle; RVSP, right ventricular systolic pressure; SAPH, sarcoidosis-associated pulmonary hypertension; TTE, transthoracic echocardiography.

*Only data for the patient with sarcoidosis was extracted for this table.

†Information about the study type was obtained from contact author.

associated with connective tissue diseases, decreased diffusion capacity of the lungs for carbon monoxide, and the presence of pericardial effusion. The relevance of these factors in the setting of SAPH is unclear as patients with SAPH were not included in the US Registry to Evaluate Early and Long-term PAH Disease Management registry, and SAPH is not specifically mentioned in the updated consensus document.

From a surgical perspective, sarcoidosis makes transplant more challenging with increased likelihood of pleural thickening, adhesions, bulky hilar lymphadenopathy, and perihilar fibrosis.[7] PH and refractory hypoxemia worsen the situation by increasing the likelihood of bleeding. That said, post-transplant survival in patients with sarcoidosis is similar to that of those with other advanced lung diseases.[7] In the International Society of Heart and Lung Transplantation registry, 954 patients with sarcoidosis underwent lung transplantation between January 1995 and June 2012.[40] Sarcoidosis was the indication for transplantation in 2.5% patients transplanted and median survival in these patients was 8.5 years.

SAPH in the Setting of Cardiac Sarcoidosis

Cardiac sarcoidosis (CS) occurs due to inflammation, development of noncaseating granulomas, and fibrosis in the heart. It is most commonly diagnosed in the setting of multiorgan sarcoidosis but can also present as isolated CS. When clinically overt, it usually presents with unspecific signs and symptoms of heart failure, arrhythmias, and conduction abnormalities that easily overlap with those of other conditions or organs affected by sarcoidosis.

It is thought that 25%-27% of patients with sarcoidosis have cardiac involvement, and 35% of them are subclinical.[41] However, most of the information available about the prevalence of CS in patients with sarcoidosis comes from autopsy studies from the 1970s to 1990s.[41-44]

CS is still considered a rare disease, although the prevalence and rates of diagnosis have increased over time. A nationwide study from Finland showed a >20-fold increase in diagnosis from 1988 to 2012.[45] Another study found a 2-fold increase of hospitalizations associated to the diagnosis of CS from 2005 to 2011.[46] This raises concern about previous and likely current underdiagnosis of this severe condition with high morbidity and mortality. Furthermore, most observational studies and clinical trials actively exclude patients with LVD;[9,13,14,18,19] hence limiting their external validity to patients with CS and SAPH, although it would be expected that the coexistence of PH and CS could pose a major therapeutic challenge and worsen prognosis.

Baughman et al performed a study of 130 sarcoid patients undergoing RHC in which the incidence of SAPH with LVD was 15.4%.[47] In a cross-sectional study of 313 patients with biopsy-proven sarcoidosis, Rapti et al showed that 37 (11.8%) patients had PH on TTE with PA systolic pressure >40 mmHg, and 9 of 12 had PH confirmed by RHC.[48] In that series, pulmonary fibrosis and LVD were the etiologies of the SAPH in the majority of patients, and when cardiac MRI was added to comprehensive clinical evaluation, the incidence of PH due to CS associated LVD was as high as 52.2%. In patients with PH associated with CS-LVD, the prognosis is good, and treatment consists of use of corticosteroids and management of the underlying congestive heart failure.[49]

Conclusions

SAPH can result from one or several combinations of pathophysiologic mechanisms; hence should be recognized as a heterogeneous cluster, and management should be adapted to each patient presentation, multiorgan involvement, stage of pulmonary disease, and prognosis.

Underdiagnosis, late diagnosis, and the variable presentation of SAPH have been limitations for the conduction of large studies to evaluate invasive and medical therapies for these patients, and among the available studies evaluating PVDs, results have been inconsistent. However, we suspect that inappropriate patient selection has played a role; since many patients in these studies have been at the terminal stage of the disease and unlikely to respond to therapy. The literature of invasive therapies has shown positive results, but the level of evidence is relatively low as most studies are case reports with only one prospective series.

Lung transplant has provided good outcomes in patients with sarcoidosis and remains an excellent option for SAPH due to pulmonary involvement of this disease.

SAPH due to CS tends to improve with treatment of the underlying cardiomyopathy, which is based on immunosuppression, mostly with corticosteroids, and guideline directed medical therapy for heart failure.

Further research is warranted to better discriminate which patients with SAPH would benefit from treatment with PH-directed therapies and in which patients these treatment options would cause more harm.

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