



WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension

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Sarcoidosis-associated pulmonary hypertension is a significant cause of morbidity and mortality. A guide to screening, diagnosis and treatment has been developed by a team of experts.

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Abstract

Sarcoidosis-associated pulmonary hypertension (SAPH) is an important complication of advanced sarcoidosis. Over the past few years, there have been several studies dealing with screening, diagnosis and treatment of SAPH. This includes the results of two large SAPH-specific registries. A task force was established by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) to summarise the current level of knowledge in the area and provide guidance for the management of patients. A group of sarcoidosis and pulmonary hypertension experts participated in this task force. The committee developed a consensus regarding initial screening including who should undergo more specific testing with echocardiogram. Based on the results, the committee agreed upon who should undergo right-heart catheterisation and how to interpret the results. The committee felt there was no specific phenotype of a SAPH patient in whom pulmonary hypertension-specific therapy could be definitively recommended. They recommended that treatment decisions be made jointly with a sarcoidosis and pulmonary hypertension expert. The committee recognised that there were significant defects in the current knowledge regarding SAPH, but felt the statement would be useful in directing future studies.

Introduction

Pulmonary hypertension (PH) is haemodynamically defined by right-heart catheterisation (RHC) by a mean pulmonary artery pressure (mPAP) above 20 mmHg. Post-capillary PH is characterised by a pulmonary artery wedge pressure (PAWP) above 15 mmHg while pre-capillary PH is defined by PAWP \leq 15 mmHg and pulmonary vascular resistance (PVR) $>$ 3 Wood's units (WU). Right ventricle (RV) remodelling and dysfunction induced by increased afterload results in exercise limitation and death. The purpose of the recently updated PH 6th World Symposium clinical classification was to categorise clinical conditions associated with PH based on similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management. Sarcoidosis-associated pulmonary hypertension (SAPH) can be caused by different and sometimes overlapping mechanisms and it has remained in Group 5 of the clinical classification of PH. SAPH is a significant cause of morbidity and mortality in patients



with advanced sarcoidosis [1, 2]. The reported incidence of SAPH has been around 5% in studies from across the world. Higher incidences were reported in patients who had persistent dyspnoea or who were being evaluated for lung transplantation (figure 1) [3–16]. Over the past few years, there has been increasing recognition of the prevalence of this major complication of sarcoidosis, as well as studies regarding screening/early detection, diagnosis and treatment.

Based on the increasing evidence and the need for better awareness of SAPH, a task force was established by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) and the Foundation for Sarcoidosis Research (FSR). This global task force was chaired by three international experts: two of sarcoidosis (RP Baughman, AU Wells) and one of PH (M Humbert). The committee met physically and virtually over 3 years (2019–2021). The committee acknowledges that the present recommendations were for the most part based on limited information available for SAPH. Many organisations such as the European Respiratory Society use the GRADE method and PICO questions (patient, intervention, comparison, outcomes) [17] for clinical practice guidelines. We decided not to use this approach because there were too few well-designed large multicentre SAPH registries and randomised clinical trials. The committee therefore focused on specific areas regarding screening, diagnosis and treatment and made specific comments (table 1). The comments were based on a literature review and a series of polls of the committee members to provide answers where there was consensus among the committee members. Consensus was defined as >70% of voting members agreeing on an individual statement. This Statement is narrative and pragmatic rather than systematic and is further complemented by a description of usual clinical practice and the experience of the panel members [18]. This Statement summarises the current state of knowledge and it does not make formal recommendations for clinical practice.

SAPH clinical outcomes

Is SAPH associated with increased morbidity?

The presence of PH in sarcoidosis is associated with greater supplemental oxygen requirements [10, 12, 15, 19, 20] as exemplified by an analysis of 363 patients with sarcoidosis listed for lung transplantation, in which subjects with SAPH required more supplemental oxygen (2.7 ± 1.8 versus 1.6 ± 1.4 L·min⁻¹) compared with those without PH [15]. In the ReSAPH registry analysis of 176 patients, most desaturated during the 6-min walk test (6MWT), with a median degree of desaturation of 5% [20]. Similarly, in the French Registry cohort of 126 patients with moderate-to-severe SAPH followed over a 10-year period, 54% were on long-term oxygen [21]. Presence of SAPH also increases the burden on functional capacity [10, 22–24], employment status and need for caregiver assistance [19]. In the French Registry, 83% of the patients with SAPH reported World Health Organization (WHO) functional class (FC) III–IV symptoms

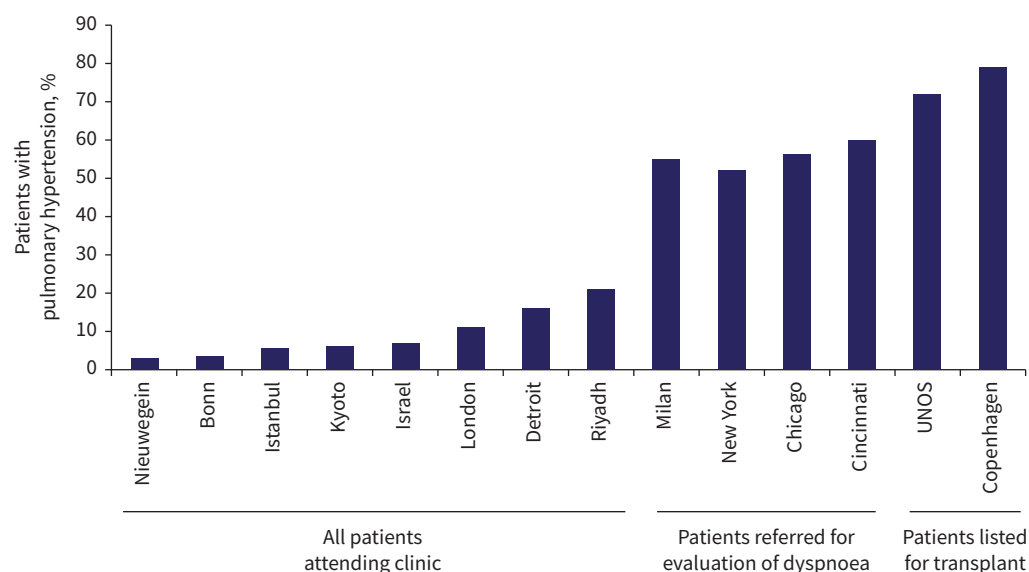


FIGURE 1 The reported incidence of SAPH from various centres across the world. The city or country of origin of the study is indicated. A higher incidence of SAPH was found for patients being evaluated for persistent dyspnoea or lung transplantation [3–16]. SAPH: sarcoidosis-associated pulmonary hypertension; UNOS: United Network Organ Sharing.

TABLE 1 Summary of Task Force comments.

1. Presence of SAPH is associated with significant symptomatology and morbidity, as evidenced by increased WHO FC, decreased 6MWD or desaturation and increased oxygen use.
2. Pulmonary hypertension is an independent predictor of mortality in patients with sarcoidosis.
3. Since the cause of SAPH is multifactorial, the committee commented that the current recommendation to keep SAPH in Group 5 was reasonable. The committee considered that patients with left ventricular disease either due to sarcoidosis or other conditions should be treated as WHO Group 2. The committee felt it was important to identify a dominant cause for SAPH on an individual basis, as it is likely to have treatment implications.
4. The suggestions of who should undergo transthoracic echocardiogram are summarised in figure 3.
5. The committee's suggestions regarding who should undergo RHC are summarised in figure 5.
6. The committee suggested that the right-heart catheterisation results should be interpreted by a multidisciplinary team with at least a sarcoidosis and PH expert and decisions should be made as summarised in figure 6.
7. Evaluate for pulmonary artery stenosis or mediastinal compression by chest imaging.
8. In SAPH, treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert. Off-label use of PAH medical therapy may be considered for symptomatic patients on a case-by-case basis (figure 7).
9. Patients who have failed to respond to treatment for PH should be referred for lung transplant evaluation, if they are deemed otherwise to be appropriate candidates.

SAPH: sarcoidosis-associated pulmonary hypertension; WHO FC: World Health Organization Functional Class; 6MWD: 6-min walk distance; RHC: right-heart catheterisation; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension.

[21]. In the Duke cohort of 95 patients followed for 11 years, almost all patients (99%) were symptomatic with activity (WHO FC II–IV symptoms) and 77% of the cohort reported WHO FC III/IV symptoms [22]. In a small British cohort of 24 patients, 48% had WHO FC III symptoms, while 42% had WHO FC IV symptoms [23]. Moreover, objective assessment of functional capacity supports subjectively reported decreased exercise tolerance in patients with SAPH. The 6-min walk distance (6MWD) was consistently found to be reduced in several studies, with mean values ranging between 305 and 320 metres [20, 21, 24]. The French Registry analysis which captured dyspnoea assessed by the Borg scale found it to be elevated at 4.0 ± 2.3 [21] during the performance of the 6MWT.

Summary

Presence of SAPH is associated with significant symptomatology and morbidity, as evidenced by increased WHO FC, decreased 6MWD or desaturation and increased oxygen use.

Is SAPH an independent predictor of mortality?

Several studies have assessed the presence of RV dysfunction in patients with SAPH. In the Duke cohort, the median N-terminal pro-brain natriuretic peptide (NT-proBNP) level at the time of initial evaluation was $910 \text{ pg}\cdot\text{mL}^{-1}$ (Q1–Q3: 225–2807). On transthoracic echocardiogram, the majority (59%) of patients had either moderate or severe RV enlargement and 55% had moderate or severe RV dysfunction [22]. Interestingly, in this cohort, neither baseline echocardiographic nor haemodynamic characterisation of RV function were associated with outcomes, but follow-up NT-proBNP levels were higher in those who died or were hospitalised (1258.0 versus $262.0 \text{ pg}\cdot\text{mL}^{-1}$, $p=0.007$).

The mortality implications of any PH, both pre- and post-capillary, in the context of sarcoidosis are also profound, with a 10-fold increase in mortality and an estimated 5-year survival of only 59% [1, 14, 25]. Figure 2 shows the 1-, 3-, and 5-year survival reported from several centres across the world [7, 13, 21, 23, 24]. In the Duke cohort, the median time from diagnosis of SAPH to either death or hospitalisation was 6 months (Q1–Q3: 3.0–12.0 months) [22]. Patients with SAPH are more likely to be listed for lung transplant and also have a greater likelihood of succumbing while on the waiting list [15, 26]. In the British cohort, the rate of mortality or transplantation was 41.2% with the median survival without transplantation being 5.3 years. In that study, more patients who died or underwent transplantation during follow-up had baseline RV dysfunction (80%) [23]. The ReSAPH registry analysis of 159 patients with pre-capillary SAPH demonstrated the 1-, 3- and 5-year transplant-free survival to be 83.7%, 70.6% and 58.5%, respectively. Severe gas transfer impairment (diffusing lung capacity for carbon monoxide (D_{LCO}) <35% predicted) and 6MWD <300 m were strong predictors of decreased survival ($p=0.0151$ and $p<0.0001$, respectively) [24]. These results were similar to the French Registry, which demonstrated 3- and 5-year survival rates of 74% and 55%, respectively [21].

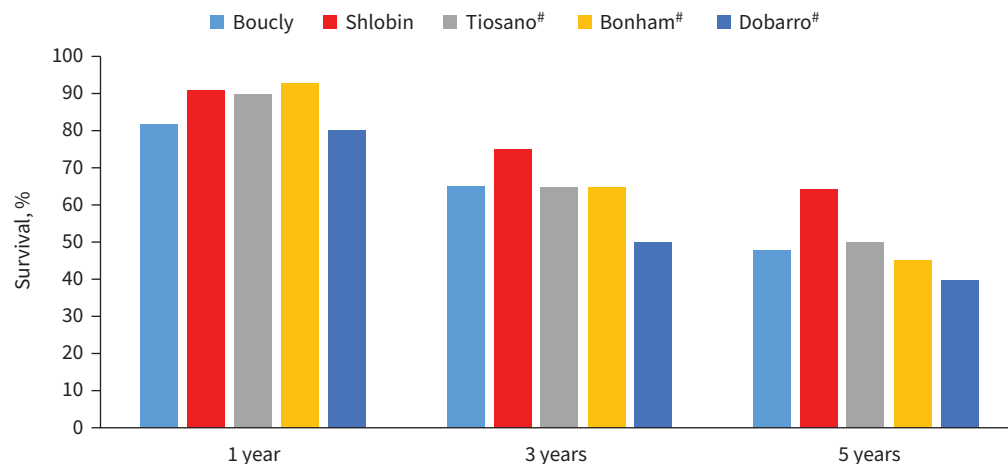


FIGURE 2 The 1-, 3- and 5-year survival from sarcoidosis-associated pulmonary hypertension [7, 13, 21, 23, 24]. #: For three of the studies [7, 13, 23], the survival was estimated based on the Kaplan-Meier survival curves presented in the papers.

In patients with SAPH from the French Registry, univariate analysis showed that WHO FC IV, 6MWD and reduced forced vital capacity (FVC) or D_{LCO} were associated with a poor survival [21]. In multivariate analysis, only 6MWD remained independently associated with mortality [21]. It is still not clear if patients with SAPH are succumbing because of PH or in the presence of PH. In one study, which demonstrated that SAPH was associated with mortality, the only haemodynamic factor that remained predictive of mortality after multivariable analysis was the right arterial pressure [26]. In another study of a small cohort of 24 patients, presence of right ventricular dysfunction on echocardiography was the most powerful predictor of death or transplantation (OR 83.1, 95% CI 2.2–31.02, $p=0.017$) [23]. This evidence of right-sided heart failure implies that patients with SAPH are indeed dying from their PH, rather than the PH being an epiphenomenon.

In two multi-regression analyses PH has been found to be an independent risk factor for mortality [1, 2]. In evaluating patients awaiting lung transplant the final prediction model for mortality included mPAP [19]. In an analysis of fibrotic sarcoidosis patients, presence of PH by echocardiography had a hazard ratio for mortality of 3.42. In the study by KIRKIL *et al.* [1], haemodynamically confirmed pre-capillary SAPH had a hazard ratio of 8.96 and, along with fibrosis >20% by high-resolution computed tomography (HRCT) and age, remained an independent predictor of mortality by Cox modelling.

Summary

PH is an independent predictor of mortality in patients with sarcoidosis.

Classification/cause of SAPH

Should SAPH be divided into various subclasses

SAPH can be caused by a variety of mechanisms (table 2). Due to the predilection of granulomas for the lymphatics, which are found in the bronchovascular bundles and the interlobular septae, pulmonary vascular granulomatous involvement typically occurs on both the arterial and venous sides of the circulation. In one study of organ explants from patients with sarcoidosis undergoing lung transplantation, features of venous involvement were identified in addition to arterial disease [25]. An increased incidence of pulmonary emboli is frequently encountered in sarcoidosis patients [27–29], and chronic thromboembolism can potentially lead to Group 4 PH [30]. Interstitial changes are also highly associated with the development of PH [20, 21]. Although more than half of patients with SAPH have clinical fibrotic lung disease, most studies confirm that up to 20% of patients with SAPH have no radiographic evidence of parenchymal lung disease [12, 20, 31]. Alveolar hypoxia, most frequently in the setting of parenchymal involvement, may also contribute to the development of PH. Hilar adenopathy compressing the pulmonary arteries and veins can also lead to PH. However, compression usually has to be of multiple vessels to lead to significant PH. In a study of 156 patients with SAPH, significant compressive hilar adenopathy leading to PH was identified in only two patients [21]. Fibrosing mediastinitis due to sarcoidosis can also contribute to PH [32–34]. In the French Registry, 3 of 156 patients with SAPH had fibrosing mediastinitis as the identified cause [21]. In a prospective study of 72 patients with SAPH from a

TABLE 2 Causes of pulmonary hypertension in sarcoidosis patients

Condition	Potential treatments
Vascular disease	
Vasculitis	Glucocorticoids and other anti-inflammatory treatments Pulmonary vasodilators
Granulomatous vascular involvement	Glucocorticoids and other anti-inflammatory treatments Pulmonary vasodilators
Veno-occlusive disease	
Pulmonary embolism (CTEPH)	Glucocorticoids and other anti-inflammatory treatments Careful use of pulmonary vasodilators Anticoagulation Balloon pulmonary angioplasty Pulmonary endarterectomy Pulmonary vasodilators
Interstitial lung disease	
Parenchymal lung disease due to granulomas	Glucocorticoids and other anti-inflammatory treatments
Parenchymal lung disease due to fibrosis	Anti-fibrotic agents
Hilar and mediastinal distortion	
Pulmonary artery/vein extrinsic compression	Glucocorticoids and other anti-inflammatory treatments Dilation and/or stenting of compressed vessels
Fibrosing mediastinitis	Dilation and/or stenting of compressed vessels
Extrapulmonary disease	
Left ventricular systolic dysfunction	Glucocorticoids and other anti-inflammatory treatments Diuretics, afterload reduction
Left ventricular diastolic dysfunction	Diuretics
Sleep apnoea	CPAP, oxygen and other measures
Liver disease	Glucocorticoids and other anti-inflammatory treatments

CTEPH: chronic thromboembolic pulmonary hypertension; CPAP: continuous positive airway pressure.

single institution, eight patients were found to have vascular compression/distortion. In all eight patients, stenting was successful in reducing pulmonary artery pressure [35].

Left ventricular disease can lead to development of post-capillary PH. In one study, approximately 20% of patients with SAPH demonstrated elevated PAWP, consistent with left ventricular failure [14]. Sarcoidosis patients may have comorbid coronary artery disease. This can be a cause of significant morbidity in sarcoidosis [36]. Evaluation of patients with elevated pulmonary artery pressure should exclude left ventricular disease as the basis of either ischaemic or nonischaemic heart disease. Granulomatous inflammation can also cause an infiltrative cardiomyopathy often leading to left heart failure [37]. However, in some cases, the left ventricular ejection fraction may be normal or only mildly impaired but still have a less compliant left ventricle [38, 39].

Sleep-related breathing disorders can contribute to PH [40, 41], and patients with sarcoidosis have an increased incidence of obstructive sleep apnoea syndrome (OSAS) [42–44]. Of note, chronic use of corticosteroids increases the risk for OSAS in sarcoidosis patients, regardless of gender of patient [44]. If OSAS is diagnosed, treatment with continuous positive airway pressure (CPAP) should be initiated. Although the liver is one of the most commonly affected organs in sarcoidosis [45, 46], severe liver disease is relatively uncommon [47, 48] and portopulmonary hypertension is rarely seen.

Summary

Since the cause of SAPH is multifactorial, the committee commented that the current recommendation to keep SAPH in Group 5 was reasonable. The committee considered that patients with left ventricular disease either due to sarcoidosis or other conditions should be treated as WHO Group 2. The committee felt it was important to identify a dominant cause for SAPH on an individual basis, as it is likely to have treatment implications.

Screening and diagnosis of SAPH

Who should get a transthoracic echocardiogram?

Screening is defined as the systematic use of a test, or tests, in at-risk individuals to identify disease before symptom onset. Previous studies have shown that screening allows earlier management and better clinical outcome in patients with systemic sclerosis-associated pulmonary arterial hypertension (PAH) [49]. While

the consequences of SAPH screening remains unknown, the task force felt that it is desirable to improve awareness of this severe complication of sarcoidosis in an attempt to diagnose it earlier when functional impairment and haemodynamics are less severely compromised. Therefore, screening (in asymptomatic patients) and early diagnosis (when symptoms and functional impairment are present) have the potential to identify SAPH at an early stage. It has been previously recommended using GRADE methodology that a transthoracic echocardiogram should be performed in those patients with sarcoidosis in whom PH is suspected (conditional recommendation) [50].

The task force evaluated what factors would lead to the decision to perform a transthoracic echocardiogram in patients with sarcoidosis and identified several features which were likely to be associated with SAPH (figure 3). The task force felt the presence of one or more of these features should lead to echocardiography. RHC should be performed when echocardiography gives a high or intermediate probability of PH (according to the ESC/ERS PH guidelines) (figure 4) [51] and for all patients being considered for lung transplant. For those patients, the RHC should be followed by left catheterisation and coronarography because of the potential implication of the results for the patient's management and on future lung transplantation in eligible cases (timing of transplantation, lung or heart-lung transplantation, need of extracorporeal circulation). Over 70% of sarcoidosis patients undergoing lung transplant will have SAPH and presence of SAPH increases the indication for transplant [16, 19]. However, SAPH was not associated with higher mortality after transplant [52]. While a recent study did not find that SAPH was associated with increased mortality for patients on the lung transplant list [53], patients with SAPH still had significant morbidity.

Other features, ranging from chest imaging to serum biomarkers, have been associated with the presence of SAPH and therefore could be considered as part of the screening process. In three large studies, approximately half of sarcoidosis patients with persistent dyspnoea despite anti-inflammatory therapy were noted to have SAPH [11, 12, 14]. These studies did not identify which specific complaint or level of dyspnoea led to further evaluation. However, all three studies found that the rate of SAPH was up to ten

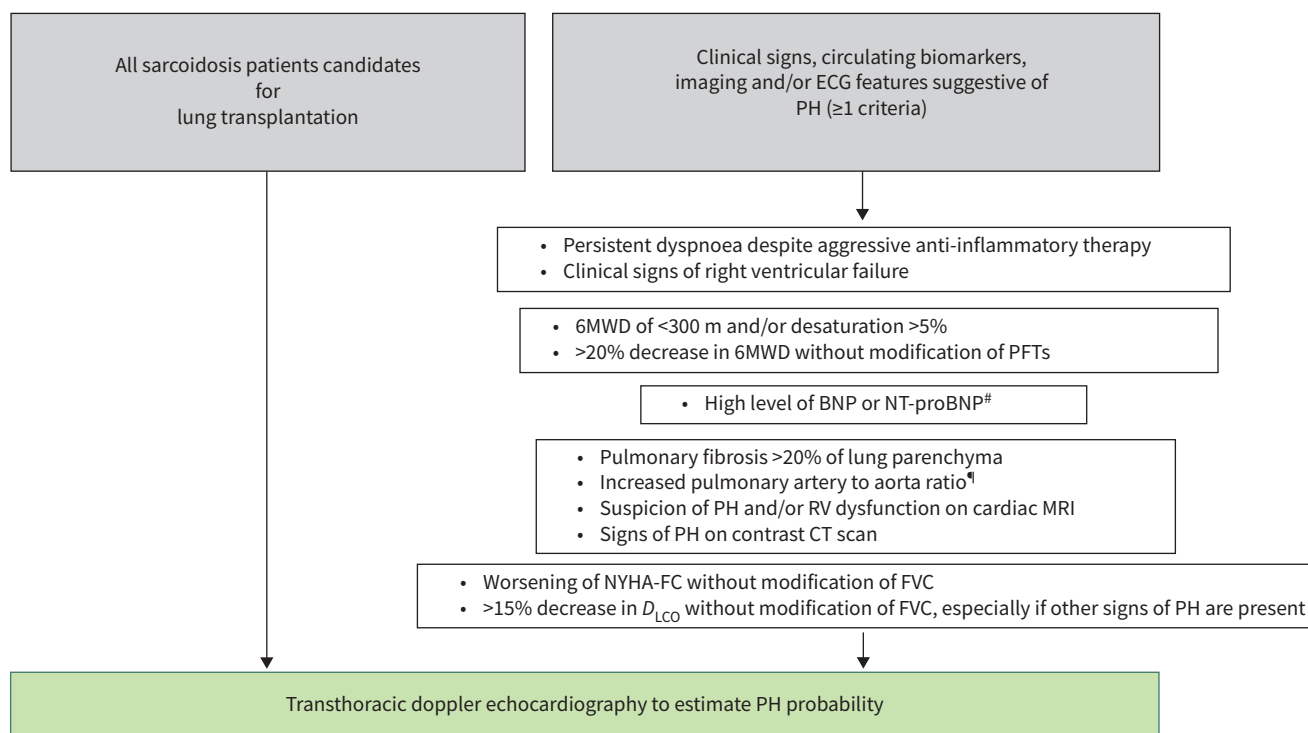


FIGURE 3 Algorithm for who should undergo transthoracic echocardiogram to evaluate for SAPH. 6MWD: 6-min walk distance; BNP: B-type natriuretic peptide; BSA: body surface area; CT: computed tomography; D_{LCO} : diffusing capacity of the lung for carbon monoxide; ECG: electrocardiogram; FVC: forced vital capacity; MRI: magnetic resonance imaging; NT-proBNP: N-terminal (NT)-pro hormone BNP; NYHA-FC: New York Heart Association functional class; PFT: pulmonary function test; PH: pulmonary hypertension; RV: right ventricle; SAPH: sarcoidosis-associated pulmonary hypertension. #: Transthoracic echocardiogram recommended to assess for SAPH and left ventricular dysfunction. ¶: May be more accurate if corrected for BSA.

Echo suggestive of PH	Peak tricuspid regurgitant velocity, m·s ⁻¹	Presence of other echo PH signs (see below)
Low	≤2.8 or not measurable	No
Intermediate	≤2.8 or not measurable	Yes
Intermediate	2.9–3.4	No
High	2.9–3.4	Yes
High	>3.4	Not required
Presence of other echo PH signs:		
The ventricles	Pulmonary artery	Inferior vena cava and right atrium
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or mid systolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m·s ⁻¹	Right atrial area (end-systole) >18 cm ²
	PA diameter >25 mm	

FIGURE 4 Probability of pulmonary hypertension from echocardiography findings of direct estimate of right ventricular systolic pressure and indirect evidence of right ventricular strain. Reproduced from GALIE *et al.* [51]. PA: pulmonary artery; PH: pulmonary hypertension.

times higher than the general sarcoidosis population. Patients with SAPH generally have a median 6MWD of <350 m [9, 20, 21, 54]. Most patients also desaturate >5% during the test [9]. It has also been noted that some patients with SAPH have elevated serum B-type natriuretic peptide (BNP) and NT-proBNP levels [8, 22, 55]. Chest imaging has also been shown to be abnormal in SAPH patients. Patients with SAPH are more likely to have pulmonary fibrosis than a comparable symptomatic group [11, 12]. This has led to the recommendation that all sarcoidosis patients with fibrosis be screened for SAPH [56]. However, there was the concern among the committee about the variable interpretation of presence of pulmonary fibrosis on chest radiograph [57]. The presence of greater than 20% fibrosis on HRCT has proved a more reproducible assessment of fibrosis with good agreement between radiologists and clinicians [58, 59]. The presence of >20% fibrosis on HRCT has been found to be associated with increased mortality in pulmonary sarcoidosis [1, 2, 58]. The presence of an increased pulmonary artery diameter, corrected for by either aorta diameter or body surface area [2, 60, 61], is associated with SAPH. The group also reached consensus regarding an enlarged right ventricle on a contrast computed tomography (CT) scan as an indicator for the patient to have a transthoracic echocardiogram. Cardiac MRI findings of RV dysfunction or PH have been reported in SAPH [62, 63]. Cardiac MRI is useful in identifying cardiac sarcoidosis and as a result any potential treatment implications. Several studies in patients with SAPH have shown that patients with SAPH have a degree of pulmonary restriction (FVC <60% pred) and at least moderate gas transfer impairment (D_{LCO} <50% pred) [11, 12, 24]. Patients with sarcoidosis such lung function parameters would be considered for SAPH screening. Using the paradigm of systemic sclerosis-associated PH, a K_{CO} (transfer coefficient of the lung for carbon monoxide) <60% pred or an FVC/ D_{LCO} ratio >1.6 may be parameters predicting SAPH [49].

There was consensus that the presence of one or more of these factors should lead to echocardiography to determine the probability of PH. In addition, other features were identified by the group and consensus for screening echocardiography was achieved if there is a worsening of New York Heart Association (NYHA) functional class, a decrease >20% in the 6MWD, or a decrease >15% of the D_{LCO} when there was no significant change in lung volumes.

Summary

The suggestions of who should undergo transthoracic echocardiogram are summarised in figure 3.

Who should get right-heart catheterisation?

RHC is the gold standard for diagnosing PH. It has been recognised for several years that echocardiography may over or underestimate pulmonary arterial pressure (PAP), especially in those with

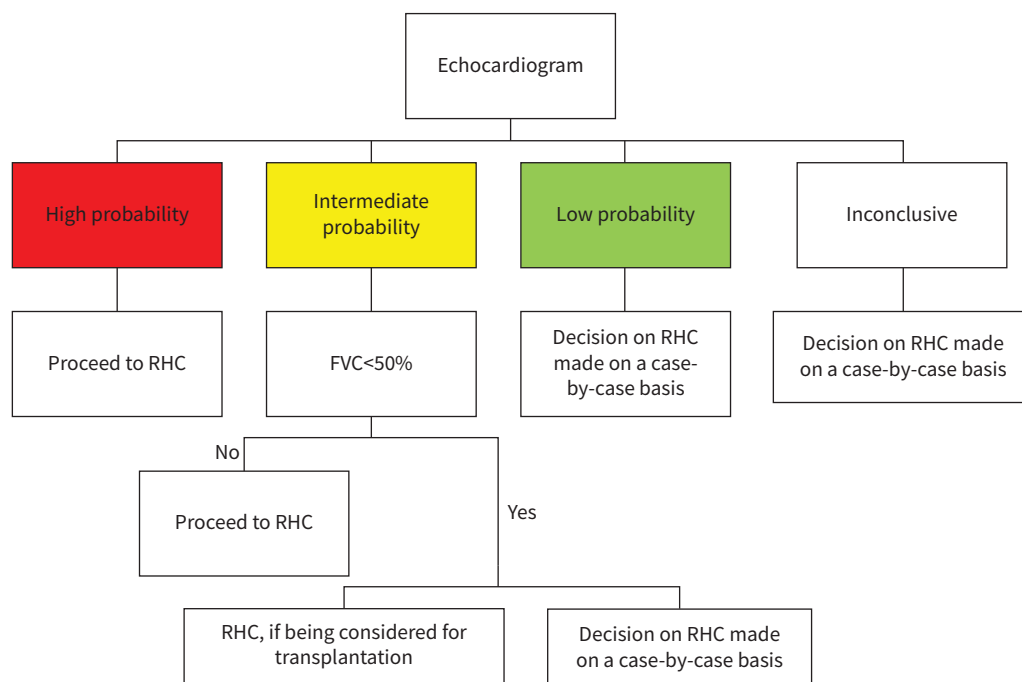


FIGURE 5 Algorithm for who should undergo RHC based on echocardiography. FVC: forced vital capacity; RHC: right-heart catheterisation.

interstitial lung disease [64, 65]. In sarcoidosis, RHC can be particularly helpful in separating pre- and post-capillary PH [14]. A transthoracic echocardiogram can estimate the probability of PH and raise suspicion, but it cannot define SAPH. The echocardiogram can provide information regarding RV function and evaluate left ventricular function may suggest post-capillary PH. However, a RHC remains the definitive test to distinguish between pre- and post-capillary PH [14]. Therefore, the committee felt the results of echocardiography should be used to determine who should undergo RHC.

The estimated RV systolic pressure based on tricuspid regurgitation velocity (TRV) is the most validated echocardiographic parameter to screen for PH. However, the echo may not be a well visualised tricuspid regurgitation (TR) jet seen on transthoracic echocardiogram. Also, other signs suggestive of PH may be seen on transthoracic echocardiogram when analysing the ventricles, the pulmonary arteries, the inferior vena cava and right atrium. The ESC/ERS PH guidelines [51] have proposed a simple algorithm which allows one to incorporate both the TRV and other indirect measures (figure 4) leading to a scoring of patients as having high, intermediate or low probability for PH. For SAPH, for those with low probability, the decision to proceed with a right catheterisation should be made on a case-by-case basis. For those in whom the results were inconclusive, the patient should be considered on a case-by-case basis (figure 5) with a joint decision between a PH and a sarcoidosis expert. Factors which may influence the decision to perform a RHC include echocardiographic evidence for RV dysfunction (figure 4), pulmonary function tests, 6MWT, BNP or NT-proBNP and imaging results. For members of the committee, there was not agreement regarding systematically performing a RHC in those with an intermediate probability of PH associated with severe interstitial lung disease. The presence of right ventricular dysfunction on echocardiogram adds further support to the decision to proceed with RHC, but there was insufficient evidence in sarcoidosis to make this a formal recommendation. Some felt this was not needed unless in the context of a lung transplant evaluation. Others felt that the decision for RHC should be made on a case-by-case basis. This ambivalence is predicated by the current literature that suggests this group may not be responsive to PAH therapies.

Summary

The committee's suggestions regarding who should undergo RHC are summarised in figure 5.

How should one interpret RHC in SAPH?

The committee felt that the RHC should be performed in a PH expert centre and its results (and consequences) should be interpreted by a multidisciplinary team with expertise in PH, sarcoidosis, imaging

and transplantation, if available and appropriate. In some cases, the sarcoidosis and PH expert may be the same person. A cardiologist's input is needed for those with post-capillary PH to distinguish sarcoidosis-related causes from left-sided heart failure. Review of the RHC tracings may be useful in order to precisely define the pre- or post-capillary mechanisms of PH.

Figure 6 summarises the suggestions of the committee on assessing the RHC. For patients with an elevated mPAP (>20 mm Hg), the results of the PAWP measurement will determine whether this is pre- or post-capillary PH (WHO Group 2). As noted in the figure, a PAWP >15 mm Hg confirms a post-capillary PH. If there is any uncertainty about the validity of the PAWP measurement, then direct measurement of the left ventricular end-diastolic pressure measurement should be considered. The distinction is important for both treatment decisions as well as prognosis [14]. The committee recognised that patients might have combined pre- and post-capillary PH which can be either due to pre-capillary vascular changes due to left heart disease or due to sarcoidosis-related factors. Therefore, careful follow-up evaluation after the initial treatment decision should be undertaken for these patients in particular to ensure that the chosen treatment course is accompanied by a salutary and not a deleterious response. Pre-capillary PH due to pulmonary vascular disease is robustly defined when the PVR is ≥ 3 WU but remains likely when the PVR is between 2 and 3.

For patients with a mean PAP of <20 mm Hg, the clinician should look elsewhere for the cause of symptoms and offer regular follow-up.

In patients with a PAWP 13–15 mmHg, left-sided cardiac involvement can still be contributory to PH. However, a RHC occasionally with the need for provocative manoeuvres, such as fluid challenge or exercise, remains the definitive test to distinguish between pre and post-capillary PH.

The cardiac MRI may provide additional information in these cases. It may indicate cardiac involvement as the cause of increased pressures, especially for those WHO Group 2 patients. These patients should still be considered for a multidisciplinary discussion [37]. In addition, the presence of right ventricular abnormalities were prognostic factors in a population of sarcoidosis patients with suspected cardiac sarcoidosis [66]. No study has been conducted to the correlation between right ventricular sarcoidosis and the presence of PH.

Summary

The committee indicated that the RHC results should be interpreted by a multidisciplinary team with at least a sarcoidosis and PH expert and decisions should be made as summarised in figure 6.

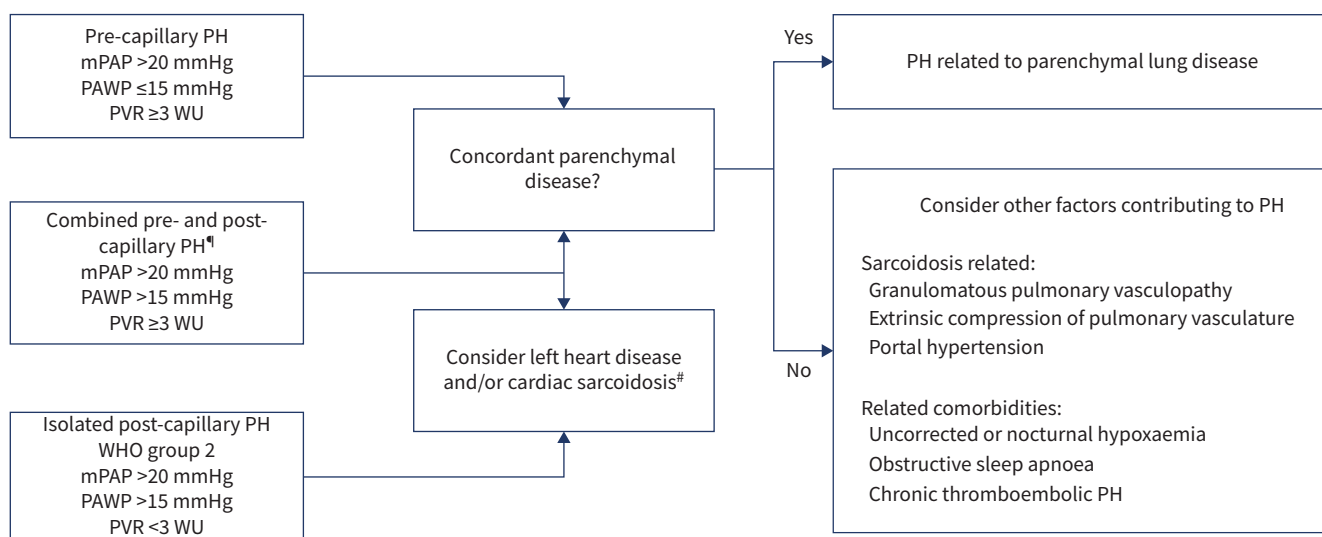


FIGURE 6 Interpretation of right-heart catheterisation and subsequent treatment recommendations are made in the figure. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WHO: World Health Organization; WU: Wood's unit. [#]: Cardiac sarcoidosis may be evident in pre-capillary PH without changing haemodynamics. [‡]: Careful evaluation should be performed by a cardiologist/PH specialist to distinguish PH due to left heart disease with subsequent pre-capillary vascular changes and sarcoidosis-associated PH.

TABLE 3 Treatment of pre-capillary SAPH

	Highest level of evidence study in patients with SAPH	Total number of patients with SAPH treated	Results in sarcoidosis
Prostenooids			
Epoprostenol	Retrospective OL positive [78, 79]	12	Haemodynamics improved [78, 79]
Iloprost	Prospective, OL [72]	15 of 22 enrolled completed 16 weeks' therapy	In sarcoidosis, haemodynamics and QoL improved [72]
Endothelin receptor antagonists			
Bosentan	DBPC [71]	23	Haemodynamics improved, no change in 6MWD [71]
Ambrisentan	Prospective OL [73]	21	Nonsignificant improved QoL, no change 6MWD [73]
Macitentan	Retrospective OL [82]	6	WHO FC improved in 4/6 treated patients [82]
Phosphodiesterase 5 inhibitors			
Sildenafil	Retrospective OL [16]	12	Haemodynamics improved, 6MWD no changes
Tadalafil	Prospective OL [74]	12	No significant changes in 6MWD and QoL
Others			
Riociguat	DBPC [70]	16	TCW and 6MWD significantly better compared with placebo
Combination therapy	Retrospective OL positive [8, 21, 77]	29	Haemodynamics and 6MWD improved in some

SAPH: sarcoidosis-associated pulmonary hypertension; OL: open-label; QoL: quality of life; DBPC: double-blind, placebo-controlled; 6MWD: 6-min walk distance; WHO FC: World Health Organization functional class; TCW: time to clinical worsening.

Treatment

Should pulmonary vasculature be visualised to rule in/out narrowing

SAPH may be caused by direct compression of the pulmonary artery by either mediastinal adenopathy or fibrosis. For patients with adenopathy compressing the pulmonary arteries, anti-inflammatory therapy may lead to reduction of the size of the nodes and relief of the compression. BOUCLY *et al.* [21] identified this situation in five of their 126 (4%) patients with severe SAPH. The authors performed positron emission tomography (PET) scanning to detect this situation. Distortion of the vasculature due to mediastinal fibrosis can also lead to SAPH. In some cases, stenting of the vasculature may reduce PAP [35, 67]. In a prospective study, all patients with SAPH underwent computer tomographic pulmonary angiography. Eight of 72 (11%) were found to have significant pulmonary artery stenosis and underwent successful stenting to relieve pressure [35]. A recent meta-analysis of the literature found that pulmonary artery angioplasty with or without stenting was successful in improving 6MWD [68].

Summary

Evaluate for pulmonary artery stenosis and mediastinal compression chest imaging.

Should pre-capillary SAPH be treated?

The committee focused on treatment of pre-capillary PH. The World Symposium on Pulmonary Hypertension concluded in 2019 that there was insufficient information to make routine recommendations for therapy in SAPH [69]. The results of treatment of SAPH for individual PAH drugs are summarised in table 3 [70–82], with results from the studies with the highest level of evidence for each treatment presented. To date, there have been only two double-blind, placebo controlled (DBPC) trials for SAPH [70, 71]. Three studies reported the results of prospective open label trials [72–74]. The remaining studies were retrospective case series. Initial or sequential combination therapy has been shown to be effective in treating PAH [75, 76]. Three series have reported the outcome of treatment with various treatment regimens in SAPH [8, 21, 77]. In those studies, measuring haemodynamics before and after therapy, the majority of patients showed improvement [8, 16, 21, 71, 72, 77–79]. There was only one study evaluating haemodynamics for placebo-treated patients demonstrating no significant change in pressures after 16 weeks [71]. Other end-points, including 6MWD and quality of life measures, had more mixed results. As summarised in table 3, not all studies found a positive response to treatment in SAPH. To date, only

one study has evaluated time to clinical worsening (TCW) with therapy [70]. That study has been published online and did find a significant improvement in TCW for riociguat compared with placebo.

Because of the limited number of randomised trials, the committee did not feel any specific recommendation could be made regarding one or other agent to treat pre-capillary PH. The committee felt that off-label use of PAH drugs may be considered on a case-by-case basis [21, 22]. While not specifically studied in any of the trials, the committee felt that specific PAH therapies should be considered after taking into account the mechanisms involved in the development of PH, the severity of PH and the severity of the underlying parenchymal lung disease. Table 2 points out the various factors which can lead to SAPH. Therapy for pre-capillary hypertension is directed to vascular disease. Care must be taken when using these treatments in patients with veno-occlusive disease. For those with moderate-to-severe parenchymal lung disease (FVC <50% pred), treatment of SAPH may not be as effective. However, if there is evidence for RV dysfunction, treatment of SAPH may still be indicated. For patients with milder SAPH, other factors may be the major cause of patient’s symptoms. A recently published study did demonstrate that treatment of mild PH in idiopathic interstitial lung disease was associated with a positive response [80]. However, that study did not include sarcoidosis patients. Worsening of ventilation/perfusion mismatch may occur with pulmonary vasodilator therapy, but in one 16 week study the frequency was similar to that seen with placebo-treated patients [71]. Another potential limitation is uncovering pulmonary veno-occlusive disease (PVOD) [79]. Treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert.

Summary

In SAPH, treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert. Off-label use of PAH therapy may be considered for symptomatic patients on a case-by-case basis (figure 7). As noted above, nearly three-quarters of sarcoidosis patients listed for lung transplant have SAPH [16, 19]. It has been observed that post-transplant survival in patients with pulmonary sarcoidosis was similar to that in patients with other indications for lung transplantation [52, 81].

Summary

Patients who have failed to respond to treatment for PH should be referred for lung transplant evaluation, if they are deemed otherwise to be appropriate candidates.

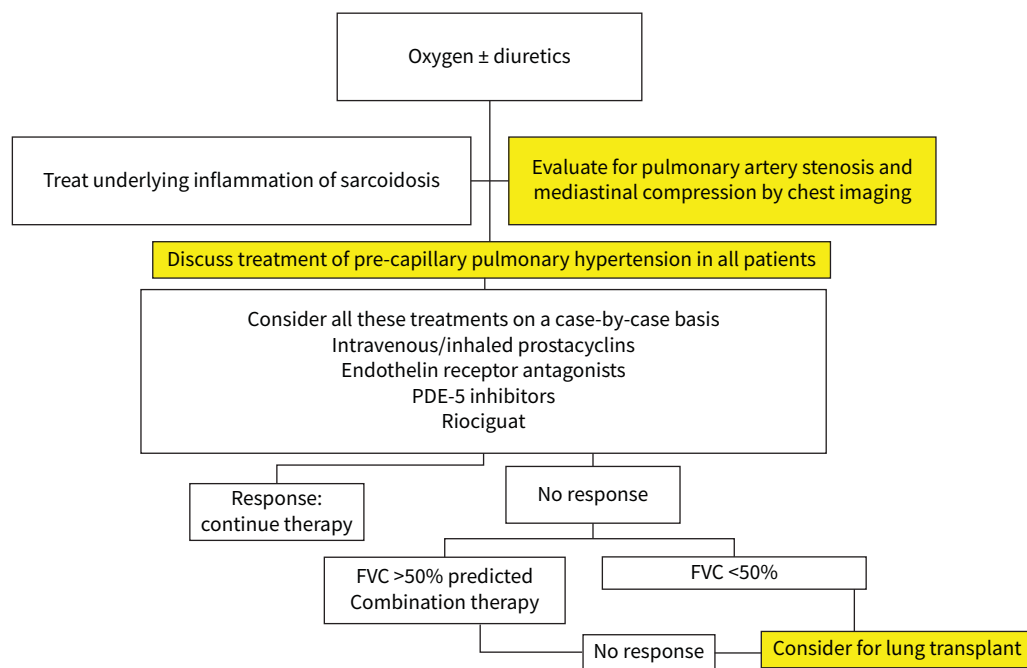


FIGURE 7 Proposed algorithm for treating pre-capillary sarcoidosis-associated pulmonary hypertension. FVC: forced vital capacity; PDE-5: phosphodiesterase 5.

Future research and next steps

Screening

The development of noninvasive screening tools, including serum biomarkers and MRI, need to be further evaluated in SAPH. In addition, the indications for when to repeat screening for SAPH need to be better defined.

Treatment trials

The first priority is the need to develop therapy for SAPH based on well-designed placebo controlled trials. The data summarised in this statement provide ample support for the likelihood that highly efficacious therapies will emerge and the existence of a large multinational SAPH registry indicates that the sarcoidosis community is now geared for definitive studies. The recent treprostinil data in nonsarcoid interstitial lung disease (ILD)-PH [80], suggesting major efficacy in the short-term, is an additional spur: based on past data, there has been more basis for optimism in SAPH than in nonsarcoid ILD-PH. However, SAPH poses unique challenges in two respects.

Treatment trial phenotypes

The definition of optimal patient phenotypes for treatment trials must take into account the multiple mechanisms driving SAPH. Ideally, based on research into haemodynamic profiles, individual phenotypes will be integrated into combined phenotype trials or selectively excluded. Core phenotypes include pre-capillary vasculopathy (whether due to direct granulomatous involvement or to pathways associated with pulmonary fibrosis), vascular compression, and post-capillary pulmonary pathways (veno-occlusive processes). When SAPH coexists with cardiac disease (including cardiac sarcoidosis and comorbidities), robust algorithms will need to be developed to optimise inclusion and exclusion criteria. The distinction between SAPH resulting from end-stage lung disease and other forms of SAPH needs to be considered further, based on the definition of realistic treatment goals, short-term haemodynamic data in these patient subgroups and accumulating data on the specific effects of individual candidate therapies. Imaging assessment of the extent and distribution of parenchymal lung involvement in relation to the haemodynamic profile will also be integral to any phenotyping.

Trial end-points

Because sarcoidosis is multidimensional in its nature, with variably severe co-existent pulmonary and systemic disease, end-point selection is likely to be heavily influenced by the distinction between: 1) short-term trials designed to establish safety and proof of concept; and 2) phase 3 studies evaluating major clinical benefit. Pivotal end-point selection is not confined to the selection of the primary end-point but includes the choice of key secondary end-points. There is a need to cover the spectrum of haemodynamic effects, major clinical end-points (mortality, TCW), multidimensional functionality (6MWT data and actigraphy) and measures of quality of life, crucially including patient-reported outcomes. In short-term trials, haemodynamic effects may continue to be the primary focus but pivotal secondary end-points should cover the domains listed above. In phase 3 trials, with clinical end-points likely to have primacy, possible strategies include the use of co-primary end-points (*e.g.* TCW, 6MWT data) to capture both major adverse outcomes and average cohort treatment effects. Composite end-points should be constituted by relevant clinical outcomes including but not necessarily limited to cardiopulmonary hospitalisation, mortality and categorical changes in 6MWT. In summary, whether the end-point focus is haemodynamic or primarily clinical, depending upon trial duration, all domains should be represented by pivotal secondary end-points, including the individual components of composite indices. Ongoing clinical research, defining the optimal end-point and its performance characteristics, is pivotal. Continued efforts are ongoing to identify biomarkers especially those that might identify longer-term efficacy based on short-term change.

Optimal prognostic evaluation

Clinicians now have easy access to markers of PH, in SAPH and in ILD-PH alike. Noninvasive PH markers in various forms of PH are listed in table 4. More clinical research is required in SAPH to validate the prognostic significance of individual variables, with comparisons between variables of prognostic values in large well-phenotyped cohorts. These should ideally include patients with SAPH and those with less advanced disease, in order to identify earlier markers of pulmonary vasculopathy.

Composite noninvasive indices

Whether combinations of noninvasive indices, covering the multiple vasculopathic domains listed in the previous section, may enhance prognostic evaluation is ripe for further investigation. Studies are ongoing to determine optimal weighting of composite indices, defined by multivariable evaluation against key

TABLE 4 Noninvasive PH markers

Cardiac functional impairment
Echocardiography
Cardiac magnetic resonance
PH severity evaluation
Echocardiography
Cardiac stress
BNP
Morphologic consequences
PA dilatation on CT
Global functional consequences
6MWD
Oxygen desaturation during 6MWD
Heart rate recovery
Pulmonary function vasculopathy profiles
Severe reduction in D_{LCO}
D_{LCO} reduction that is disproportionate to reductions in lung volumes – K_{CO} , the D_{LCO}/FVC ratio
PH: pulmonary hypertension; BNP: B-type natriuretic peptide; PA: pulmonary artery; CT: computed tomography; 6MWD: 6-min walk distance; D_{LCO} : diffusing capacity of the lung for carbon monoxide; K_{CO} : transfer coefficient of the lung for carbon monoxide; FVC: forced vital capacity.

clinical outcomes and by the presence of PH at RHC. In this way, the utility of noninvasive composite indices in the selection of patients for RHC and their inclusion as end-points in pivotal trials can be established.

Harnessing of technological advances

Recent advances in PH and in ILD have included deep phenotyping data (CT vascular morphometry, SPECT/CT, PET metabolomics, four-dimensional MRI, machine learning) and in ILD, automated quantification of pulmonary vascular volume using CALIPER, with major added value in prognostic evaluation. In particular, it appears increasingly likely that machine learning, applied both to individual modalities and to combinations of techniques, will enhance prognostic evaluation. This is likely to be particularly relevant to powering trials by selecting patients more likely to have adverse outcomes.

Summary and conclusion

SAPH is a significant cause of morbidity and mortality in advanced pulmonary disease. An approach to detection of SAPH was developed by the committee. This approach relies on information from patient history, physical examination, pulmonary function testing, chest imaging and serum biomarkers. The echocardiogram remains the most commonly used next step in the patient with risk factors for SAPH. However, RHC is needed to confirm the diagnosis and properly categorise the type of PH. Potential treatments for SAPH are available. The committee felt that the interpretation of the RHC and the use of specific treatments should be made by a multidisciplinary team including both a specialist in sarcoidosis and PH.

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