Pulmonary hypertension complicating sarcoidosis

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Summary

Pulmonary hypertension is a challenging complication of sarcoidosis, which reported rates of prevalence largely depend on the advancement of pulmonary disease. About 6% of unselected sarcoidosis patients suffer from PH. Although destruction of the distal capillary bed and resultant hypoxemia are important, the mechanisms of sarcoidosis-PH are multifactorial, including specific vasculopathy, local increased vasoreactivity, extrinsic compression of pulmonary vessels and portal hypertension. As a result, a proportion of patients exhibit “out of proportion” PH, i.e. more severe than expected from functional impairment (mean PAP > 35–40 mmHg). The sarcoidosis vasculopathy prevails in the venous side, reflecting the spreading of granulomatous process, and can cause pulmonary veno-occlusive disease. The responsibility of left-heart dysfunction is probably underestimated by echocardiography. There is no validated screening algorithm for the detection of sarcoidosis-PH but recent studies have underlined the role of right heart catheterisation to exclude post-capillary PH. PH carries a poor prognosis in sarcoidosis patients, with a significantly increased morbidity and mortality. Management of sarcoidosis-PH mainly relies on supportive therapy (supplemental oxygen and diuretics as needed) and lung transplantation in otherwise eligible patients. Rare cases of sarcoidosis-PH with nonfibrotic pulmonary disease respond to corticosteroids. Data on the efficacy and safety of PAH agents are scarce and discrepant. Further controlled trials are warranted and should integrate the concept of disproportionate PH in their design.
Sarcoidosis is a multisystemic disorder of unknown etiology characterized by the formation of immune granulomas in affected tissues, particularly the lung and the lymphatic system. The disease has an estimated annual incidence of 1 to 40/100,000 and mainly affects 25–40 years old people with a predilection for women and Blacks. Multiple phenotypes are seen according to presentation, involved organs, disease duration and severity [1]. Sarcoidosis resolves spontaneously within 2 years in half cases and 5 years in many others. After 5 years, remission is much less probable. This different outcome has led to classify patients into acute (≤ 2 years) and chronic (≥ 3–5 years) course. A major concern with chronic sarcoidosis is the development of pulmonary fibrosis [1]. Pulmonary hypertension (PH) is a serious complication of sarcoidosis (sarcoidosis-associated PH), which frequency largely depends on the severity of pulmonary involvement. However, PH can occur at all stages of disease advancement and its underlying mechanisms are various. PH results in substantial morbidity and adversely impacts on the survival of affected patients. Over the last years, there has been a dramatic resurgence of interest for sarcoidosis-associated PH, improving our understanding of its pathogenesis and providing a better estimation of its prevalence and prognosis. In parallel, several studies have burgeoned with the new agents approved for pulmonary arterial hypertension (PAH). This review examines the current literature regarding sarcoidosis-associated PH, with an accent on the most recent insights, including therapeutical management.

**Classification of pulmonary hypertension and concept of “out of proportion” pulmonary hypertension**

PH is defined by an increased mean pulmonary arterial pressure (mPAP) greater or equal to 25 mmHg at rest on right heart catheterisation (RHC). In an attempt to assist physicians on their clinical practice, an updated clinical classification of PH derived from the Dana Point meeting has been published in 2009 (box 1) [2]. Group 3 refers to “PH due to lung diseases and/or hypoxia”, including interstitial lung diseases (ILDs). Group 5 has been created for “PH with unclear and/or multifactorial mechanisms” where sarcoidosis has been placed. This distinction from group 3 is justified by the pathogenesis of sarcoidosis-associated PH which is much more complex than just parenchymal disease and resultant hypoxia. Another important point of the new classification is that pulmonary veno-occlusive disease (PVOD) has been individualized from PAH in group 1’ [2]. However, several authors continue to consider PVOD as a syndrome rather than a disease entity.

In patients suffering from ILDs, PH has long been believed to be due to the loss of capillaries in fibrotic zones and hypoxic vasoconstriction, with mPAP rarely exceeding 35–40 mmHg [2,3]. However, the concept of “out of proportion” PH has been the matter of growing attention in ILDs, particularly in sarcoidosis. Actually, a proportion of patients with ILDs-PH sometimes exhibit “out of proportion” PH, i.e. with a mPAP greater than 40 mmHg, which seems insufficiently explained by lung mechanical disturbances and corroborates the possible role of other underlying mechanisms, including intrinsic vasculopathy.

**Frequency of sarcoidosis-associated PH**

The exact prevalence of PH complicating sarcoidosis remains to establish. The wide distribution in published rates is most likely due to the use of different measurement techniques, selection of diverse patient populations or various stages of disease (table I). Overall, PH affects 1% to 6% patients with sarcoidosis [4–8] but it is much more frequent in advanced lung disease [9] or in symptomatic patients [10].

The only available prospective study conducted by Handa et al. has evaluated 212 consecutive outpatients with sarcoidosis by trans-thoracic Doppler-echocardiography (TTE). An estimated systolic PAP (sPAP) greater than 40 mm Hg was found in 5.7%. Regrettably, RHC was not performed to confirm the diagnosis of PH [6]. Shorr et al. reviewed retrospectively the USA cohort of 363 sarcoidosis patients listed for lung transplantation who had completed RHC. PH was identified in 73.8% of cases and mPAP was greater than 40 mmHg in 36.1% [9]. In the retrospective study by Baughman et al., 130 patients with persistent dyspnoea despite systemic therapy for their sarcoidosis were systematically explored with RHC, 38.5% had evidence of PH [11].

No difference is observed in terms of sarcoidosis phenotype or demographic characteristics between patients with or without PH, except for higher frequency of stage IV on chest radiography [6,11–14] and possible male gender predominance [6].

**Pathogenesis of sarcoidosis-associated PH**

As already indicated above, sarcoidosis is classified in the group 5 of PH classification but essentially, the mechanisms of sarcoidosis-associated PH may fit into all five categories [2,3].

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**Glossary**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CCB</td>
<td>Calcium channel blockers</td>
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<td>ILDs</td>
<td>Interstitial lung diseases</td>
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<td>IPF</td>
<td>Idiopathic pulmonary fibrosis</td>
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<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
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<td>PH</td>
<td>Pulmonary hypertension</td>
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<td>PVOD</td>
<td>Pulmonary veno-occlusive disease</td>
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<td>PWP</td>
<td>Pulmonary wedge pressure</td>
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<td>RHC</td>
<td>Right heart catheterisation</td>
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</table>
**Box 1**

**Updated clinical classification of pulmonary hypertension (Dana Point, 2008)**[2]

1 Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable
   1.2.1 BMPR2
   1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
   1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn

2 Pulmonary hypertension owing to left-heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3 Pulmonary hypertension owing to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental abnormalities

4 Chronic thrombo-embolic pulmonary hypertension

5 Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor type 2; ALK1: activin receptor-like kinase type 1; HIV: human immunodeficiency virus.

**Pre-capillary pulmonary hypertension**

**Destruction of the distal capillary bed and resultant hypoxemia**

The majority of sarcoidosis patients with PH have evidence of advanced disease [6,11–14]. However, 31.8 to 50% of patients with sarcoidosis-associated PH develop this complication in the absence of patent pulmonary fibrosis [11,13,14] and a small subset of cases have apparently no underlying lung disease (radiographic stage 0 and I) [6,11,13–15]. Moreover, hemodynamic measurements do not correlate well with spirometric parameters and PaO₂ [6,10,13,16] and mPAP is 9 mmHg higher in sarcoidosis than in idiopathic pulmonary fibrosis (IPF) for equivalent respiratory impairment (34.4 versus 25.6 mmHg, \( P < 0.0001 \)) [17]. Last, the degree of PH is sometimes disproportionate to functional abnormalities [9,11,13,18] and PH may even be more severe when it occurs in patients without fibrotic disease [13]. Taken together, these findings support the idea that other mechanisms may play a role in the development of sarcoidosis-associated PH. These include specific vasculopathy, local increased vasoreactivity, extrinsic compression of pulmonary vessels, left-heart dysfunction and portal hypertension. Co-morbidities associated with sarcoidosis can also cause PH.

**Specific vasculopathy**

Vascular involvement is very common in pulmonary sarcoidosis, reaching 69 to 100% of cases according to pathological studies [19,20]. Changes consist of occlusive or destructive lesions due to the invasion of vessel walls by granulomas or to the perivascular fibrosis [19,20]. Vascular involvement can be observed at all levels, from large branches of PA to small veins but it prevails in the venous side, reflecting the lymphatic spreading of granulomatous process (figures 1 and 2) [19–21]. Despite frequent granulomatous vascular involvement, clinically significant PH is rare. In the autopsy study of Takemura et al., significant PH was noted in only four out of 40 patients with vascular involvement [19,20]. The reasons why some individuals will develop PH are incompletely understood. A type of PVOD-like disease is now a well-recognised cause of sarcoidosis-associated PH [13,22,23]. The occlusive narrowing of interlobular veins by granuloma can mimic PVOD and result in PH. This mechanical granulomatous PVOD has been pathologically authenticated in a handful of cases with nonfibrotic sarcoidosis [22,23]. Besides, Nunes et al. described an intrinsic occlusive venopathy in explanted lungs from five sarcoidosis patients with PH and pulmonary fibrosis. This venopathy was characterized by marked intimal fibrosis and recanalisation of the interlobular septal veins associated with chronic haemosiderosis. Conversely, arterial changes were minor with no evidence of plexiform or thrombotic lesions. Scattered granuloma were present in veins in four out of five cases whereas arterial granulomas were seen in only two cases and neither venous nor arterial granuloma could be found in one patient.
Interestingly, a similar venopathy has also been described in another “granulomatous” disorder, pulmonary Langerhans cell histiocytosis [24].

**Local increased vasoreactivity**

The potential role of heightened reactivity of the pulmonary vasculature to vasoactive mediators has been raised because a number of patients with sarcoidosis-associated PH are responders to acute vasodilator challenge with inhaled NO or prostacyclin [18,25,26]. Among the various contenders, ET-1 is the most attractive. ET-1 is a potent vasoconstrictive cytokine, which also possesses proinflammatory and mitogenic properties, in particular for smooth muscle cells and fibroblasts, inducing vascular remodelling. Yet, despite emerging results, data are currently limited and none has compared ET-1 measurements with the presence of PH.

Sofia et al. demonstrated that urine but not plasma levels of ET-1 were significantly higher in sarcoidosis than in IPF. Urine ET-1 decreased significantly in sarcoidosis patients under corticosteroids, and the decrease concurred with clinical improvement. Urine ET-1 was significantly correlated with the intensity of lymphocytic alveolitis [27]. Conversely, plasma ET-1 was increased in sarcoidosis patients compared with healthy controls in the study of Letizia et al., [28]. In those who went into remission following successful corticosteroid therapy, ET-1 levels normalized in parallel with other parameters of disease activity [28]. Reichenberger et al. examined ET-1 concentrations in BAL specimens from patients with various pulmonary disorders and healthy controls [29,30]. Raised ET-1 levels were observed in sarcoidosis patients, comparably to those seen in scleroderma and IPF patients [29,30]. BAL ET-1 was also compared between 22 nonsmoking sarcoidosis patients and 12 nonsmoking healthy controls in the study of Teraslita et al. [30]. Levels were significantly higher in sarcoidosis and they were correlated with the number of alveolar macrophages harvested in BAL. Similarly, ET-1-immunoreactivity was localized mainly in alveolar macrophages. Last, BAL fluid from the sarcoidosis patients stimulated fibroblast proliferation, compared with control BALF, and fibroblast proliferation was blocked in the presence of an ET-1 inhibitor [30]. Consistently, earlier work had demonstrated that alveolar macrophages from sarcoidosis patients were a primary source of ET-1, and that the supernatant from these alveolar macrophages incited the growth of fibroblasts [31].

**Extrinsic compression of pulmonary vessels**

Sarcoidosis-associated PH may be caused by extrinsic compression of the proximal PA by enlarged lymph nodes or fibrosing mediastinitis (figure 3) [13,32,33]. Compression of the large pulmonary veins is much rarer and can provoke localized oedema. Although occasionally described in early stages of sarcoidosis, PA compression is much more frequent in patients with long-standing disease when lymph nodes become fibrotic and calcify. This mechanism was demonstrated in 21.4% of patients with PH and radiographic stage IV in the study of Nunes et al. [13].

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**Table 1**

Main studies on the prevalence of pulmonary hypertension in patients with sarcoidosis.

<table>
<thead>
<tr>
<th>Population</th>
<th>Method</th>
<th>Definition</th>
<th>Prevalence</th>
<th>Reference</th>
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<tbody>
<tr>
<td>n = 50</td>
<td>RHC at rest: n = 50</td>
<td>Resting mPAP &gt; 25 mmHg</td>
<td>3/50 = 6%</td>
<td>[8]</td>
</tr>
<tr>
<td>Methods of selection not available</td>
<td>RHC at exercise: n = 34</td>
<td>Exercise mPAP &gt; 30 mmHg</td>
<td>9/34 = 26.5%</td>
<td></td>
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<tr>
<td>Stage 0: n = 5, I: n = 5, II: n = 16, III: n = 24</td>
<td>mPAP &gt; 25 mmHg</td>
<td>mPAP ≥ 40 mmHg</td>
<td>73.8%</td>
<td>73.8%</td>
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<tr>
<td>Stage 0: n = 96, I: n = 52, II: n = 26, III: n = 31, IV: n = 7</td>
<td>TTE</td>
<td>sPAP ≥ 40 mmHg</td>
<td>5.7%</td>
<td>[6]</td>
</tr>
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</table>

RHC: right heart catheterisation; mPA: mean pulmonary artery; OLT: orthotopic lung transplantation; TTE: trans-thoracic Doppler-echocardiography; VTR: peak velocity of tricuspid regurgitation jet; sPAP: systolic pulmonary artery pressure; PWP: pulmonary wedge pressure.

1 In this study, stage III included patients with or without fibrosis.
Pulmonary hypertension complicating sarcoidosis

**Figure 1**

**Patient with sarcoidosis-associated PH**
The scan shows multiple lymph nodes with an extrinsic compression of the right pulmonary artery and a significantly increased calibre of the main pulmonary artery as compared with aorta (Panel A). There is no associated parenchymal disease (Panel B).

**Portal hypertension**
PH may also be the consequence of hepatic sarcoidosis, which can rarely lead to cirrhosis and portal hypertension [34].

**Post-capillary pulmonary hypertension**
Clinical myocardial involvement is seen in about 5% of sarcoidosis patients and can generate left ventricular systolic or diastolic impairment. Noteworthy, unsuspected occult involvement is much more frequent at pathology [35]. Several Doppler echocardiographic studies have pointed to a high prevalence of diastolic dysfunction (14–50%) in patients without clinical evidence of cardiomyopathy, possibly mirroring early cardiac disease [36,37]. Similarly, in sarcoidosis patients awaiting for lung transplantation, although within normal values for the vast majority of patients, pulmonary wedge pressure (PWP) is, on average, significantly higher in the presence of PH and it is also independently associated with PH, which indicates that subtle impairment in cardiac diastolic performance may nonetheless exist [9].

Although newer techniques have improved the detection of left ventricular dysfunction in sarcoidosis [35], the reliability of routine TTE is weak in such a context. The study of Baughman et al. cited beyond is extremely interesting in this regard. Hundred and thirty sarcoidosis patients with persistent dyspnoea were thoroughly investigated by RHC [11]. Left ventricular dysfunction as defined by an elevated PWP was revealed in 20 (15.4%) [11], which represented 28.6% of all cases with PH. Only seven of them (35%) had a reduced left ventricular ejection fraction on TTE [11].

**Co-morbidities**
A potential link between sarcoidosis and thrombo-embolic events has been newly emphasized [38,39]. Crawshaw et al. have performed a retrospective cohort analysis using a well-established epidemiological data set, covering the period between 1963 and 1998, which recorded all hospital admissions to National Health Service hospitals and all deaths within Oxfordshire region [38]. A significant association was demonstrated between sarcoidosis and pulmonary embolism, in comparison with a matched reference population (OR: 1.92, 95% CI: 1.05–3.23, P = 0.01), but not deep vein thrombosis [38]. Using United States death certificates from 1988 to 2007, Swigis et al. have shown that pulmonary embolism was declared in 2.54% of decedents with sarcoidosis, compared

**Figure 2**

**Pulmonary arterial involvement of sarcoidosis**
The figure shows an intralobular artery with its adjacent bronchiole. The artery is surrounded by coalescent and fibrotic granulomas, which narrow the vascular lumen (HES × 50).
with only 1.13% of the background population (OR: 2.3, 95% CI: 2.1–2.5, \( P < 0.0001 \)) \[39\]. The risk was significantly greater than for decedents with COPD \[39\]. However, to the best of our knowledge, post-embolic \( \text{PH} \) has been described in a unique patient with sarcoidosis showing exuberant granulomas inside the thrombi at pathology \[40\].

The reasons why sarcoidosis confers an increased risk for pulmonary embolism remain to be elucidated. The rate of either IgG or IgM antiphospholipid serum antibodies reached 38% of sarcoidosis patients in the study of Ina et al., which was significantly upper than in healthy controls \[41\]. Several observations have described antiphospholipid syndrome occurring in sarcoidosis patients with \[42\] or without concentric lupus \[43,44\]. Also, sarcoidosis can co-exist with various auto-immune disorders known to facilitate thrombo-embolic disease and/or \( \text{PAH} \), including Takayasu arteritis \[45\] and systemic scleroderma \[46\].

Last, a higher than expected prevalence of obstructive sleep apnea has been mentioned in sarcoidosis \[47,48\], attaining 17% in one study \[47\].

**Diagnosis of sarcoidosis-associated PH**

The clinical picture of underlying respiratory disorder can mask \( \text{PH} \) and delay its recognition. Several symptoms should, yet, prompt diagnostic intervention: dyspnoea more severe than one would expect from functional impairment, chest pain,
palpitations, near syncope on exertion. Physical signs include a loud P2 component to the second heart sound, a fixed, split S2, a holosystolic murmur of tricuspid regurgitation (TR) and a diastolic murmur of pulmonic regurgitation. About one quarter of patients with sarcoidosis-associated PH present with signs of right-sided heart failure [13,14]. Raynaud’s phenomenon is occasionally noted as in idiopathic PAH [13]. ECG may show signs of right ventricle strain and chest radiography may show right cardiomegaly and PA enlargement.

**Trans-thoracic Doppler-echocardiography**

It is admitted that TTE is imperfect but remains the most appropriate modality for the noninvasive assessment of PH. In ILDs, the peak velocity of TR jet is measurable in only 44–54% of patients, and even if available, estimation of the sPAP is often inaccurate [49–51]. Arcasoy et al. examined the performance of TTE in 106 patients with diverse forms of ILDs referred for lung transplantation, using RHC as the gold standard [49]. Despite the significantly higher likelihood of achieving an estimation of sPAP in ILDs, the accuracy of TTE was much worse than in COPD. There was a good correlation between sPAP estimated on TTE and measured on RHC but the values were within 10 mmHg in only 37% of patients with ILDs. When considering estimated sPAP in excess of 45 mm Hg as a determinant of PH, the sensitivity, specificity, and positive and negative predictive values of TTE were 85%, 17%, 60% and 44%, respectively. When right ventricular abnormalities were used as a surrogate diagnostic marker of PH, the values of TTE were 76%, 53%, 57% and 74% respectively [49]. Unfortunately, there is little specific information for sarcoidosis [11,12]. In the study of Baughman et al., 80 patients underwent both echocardiographic and hemodynamic assessments. Of these, only 70% had sufficient TR jet identified so that sPAP could be estimated. For these cases, there was a significant correlation between estimated and measured sPAS (r = 0.62, P < 0.0001). Sensitivity and specificity of TTE were not provided in this study [11].

Hence, the absence of an increased sPAP appears to be sub-optimal to exclude significant PH and does not obviate the need for RHC in selected patients. Right ventricular abnormalities are valuable additional parameters to reinforce suspicion of PH, irrespective of TR velocity.

**Right heart catheterisation**

Although definite diagnosis relies on invasive measurements, not all patients with ILDs and suspected PH should undergo confirmatory RHC. The Task Force statement assert following reasonable indications for RHC in group 3 PH: proper diagnosis of PH in candidates for transplantation; suspected “out of proportion” PH potentially amenable to be enrolled in a clinical trial with specific PAH drug therapy; frequent episodes of right heart failure; and inconclusive echocardiographic study in cases with a high index of clinical suspicion [3]. In sarcoidosis, a wider adoption of RHC has however gained credit following the published experience of Baughman et al. [10,11]. As discussed previously, left-heart dysfunction is not uncommon in sarcoidosis and probably underreported by TTE [11]. Furthermore, RHC also provides per se important information on prognosis [11,52,53]. In the one hand, it allows assessment of severity of hemodynamic impairment. In the other, the pre or post-capillary nature of PH has not only therapeutic but also prognosis implications [11]. The hemodynamic severity of sarcoidosis-associated PH is extremely variable. In the study of Baughman et al. on 50 patients with pre-capillary PH, median mPAP was 33 mmHg [range: 25–75] and median PVR was 4.3 Wood units [range: 0.9–21.2]. These patients displayed a similar mPAP but a significantly higher PVR than those with PH due to left ventricular dysfunction. mPAP was over 35 mmHg and 40 mmHg in 46% and 28% of patients with pre-capillary PH, respectively [11]. “Out of proportion” PH seems more frequent in patients without than with pulmonary fibrosis [9,13]. As therapy with high doses of calcium channel blockers (CCB) has no role in group 3 PH, acute vasodilator challenge is not recommended in the majority of patients with ILDs but may still be useful for some with sarcoidosis. The rate of patients with a positive short-term response varies between 0% and 87.5% in three series [13,18,25,26], depending on the agent used and the definition of response.

**Pulmonary function tests and 6-minute walk test**

Most of studies have shown statistically lower FVC, FEV1, TLC [6,11–14] and DLCO [6,11–14] values in sarcoidosis patients with PH. These patients are also more hypoxemic and/or require more frequently supplemental oxygen than those without PH [6,9,11–14]. Nonetheless, the contribution of PFTs alone for the identification of patients with PH is modest. In multivariate analysis, the need for oxygen remained the only predictor of PH in the transplant cohort of Shorr et al. (OR: 8.39, 95% CI: 3.44–20.47 for any O2), with a sensitivity and specificity of 91.8% and 32.6%, respectively. In other words, relying on oxygen requirement would lead to the misclassification of nearly one third of patients in this population [9]. Handa et al. demonstrated that only decreased TLC was independently associated with echocardiographic PH in consecutive outpatients with sarcoidosis (OR: 0.69, 95% CI: 0.48–0.99, P < 0.05) but its predictive power was mild [6]. Because the reduction of DLCO can be related to both interstitial and vascular involvement, several authors have postulated that a high FVC%/DLCO% ratio (with a cut-off of 1.4–1.5), reflecting a disproportionately reduced DLCO for the degree of restriction, may be a better tool for gauging PH in ILDs, alone or together with SaO2 [54–58]. The ability of FVC%/DLCO% ratio in screening for PH has never been tested in sarcoidosis, although
findings are significantly higher in patients with increased echocardiographic sPAP (1.6 ± 0.7 versus 1.2 ± 0.4, P < 0.01) [14]. No study has focused on the predictive value of the measure of membrane and blood components of DLCO for the detection of PH in sarcoidosis.

Baughman et al. evaluated prospectively six-minute walk test (6MWT) in 142 sarcoidosis patients [59]. The 14 patients with documented PH accomplished a significantly shorter distance, with a median of 280 m against 411 m for all other patients [59]. Similar results were found in the retrospective study of Bourbonsais et al. on 162 patients, which aimed to determine the clinical predictors of PH in sarcoidosis [12]. The 22 patients with PH walked less (343 ± 116 m versus 426 ± 105 m, P < 0.004) and had a greater desaturation (8.85 ± 4.22% versus 2.99 ± 2.14%, P < 0.001) and Borg score at 6 minutes [12]. After adjusting for BMI and age, multivariate analyses showed that the significant predictors of PH on TTE were SaO2 less than 90% on 6MWT (OR: 12.1, 95% CI: 3.66–19.73) and DLCO less than 60% predicted (OR: 7.3, 95% CI: 1.98–24.82). DLCO did no longer retain significance when PH was defined on RHC. These cut-off values for SaO2 and DLCO were obtained from the ROC curves. The other variables tested, including marched distance, and all other PFTs parameters failed to predict the presence of PH. Interestingly, all seven patients being misdiagnosed as having no PH on TTE desaturated to less than 90% during 6MWT, suggesting that a composite model combining the results of SaO2 on 6MWT with those of TTE would improve the pre-test probability before performing RHC [12]. Although not clearly evaluated, exercise testing may be interesting to identify PH in patients with ILDs, in particular sarcoidosis.

**Imaging**

Contrast-enhanced high resolution computed tomography (CT) can show a raised calibre of PA (widest diameter of the main PA greater than 29 mm or superior to that of the ascending aorta). Even so, the PA diameter and PA/aorta ratio are not reliable to predict the presence of PH in ILDs [60,61], possibly because the restrictive lung physiology may result in a traction effect on the mediastinal vascular structures, distending the PA independently of the underlying PAP. In sarcoidosis, contrast-enhanced HRCT helps delineating the mechanisms of PH. First, it allows the diagnosis of extrinsic vascular compression. Second, several findings may hint to PVOD such as extensive ground-glass opacities and/or thickened interlobular septa. Although these features may be related solely to sarcoidosis, Nunes et al. demonstrated that patients with sarcoidosis-associated PH showed a significantly higher frequency of ground-glass attenuation and septal lines as compared to sarcoidosis controls without PH [13]. The differentiation between extrinsic vascular compression and pulmonary embolism is sometimes tricky and occasionally requires pulmonary angiography. Hepatic ultrasound is necessary to exclude porto-pulmonary hypertension.

**Natriuretic peptides**

Plasma Brain Natriuretic Peptide (BNP) or N-terminal proBNP (NT-proBNP) may be helpful biomarkers for the detection of PH in patients with ILDs. In the study by Leuchte et al. on patients with diverse ILDs, elevated plasma BNP levels were predictive of moderate to severe PH, as defined by mPAP greater than 35 mmHg on RHC, with 100% sensitivity and 89% specificity [62]. BNP is also independently associated with a higher risk of mortality in ILDs [63–65]. Handa et al. performed a prospective study on 150 consecutive sarcoidosis patients to investigate the utility of plasma NT-proBNP in the assessment of PH and cardiac involvement [66]. Among the 130 subjects evaluable for PH status at TTE, 21 were diagnosed with PH, as defined by a sPAP greater than 35 mmHg. Patients with PH had significantly higher levels of NT-proBNP compared with those without but the increase was milder than in patients with cardiac involvement. Moreover, NT-proBNP had a poor discriminative capacity for PH, even when patients with cardiac sarcoidosis were excluded. The sensitivity and specificity were 75.0% and 60.9%, respectively, the optimal cut-off value being 103 pg/ml based on ROC curves [66].

**Screening of sarcoidosis-associated PH**

As PH bears a severe prognosis in sarcoidosis, early diagnosis and consideration of treatment options may be keys to improve patients’ outcome. Nonetheless, there is no consistent single clinical criteria that can be used to adequately segregate sarcoidosis patients with a high or low risk for PH. Owing the limited accuracy of TTE, this should not serve as the only guide to determine who requires further invasive intervention. In light of recent data, RHC seems particularly important in patients with persistent uncertainty regarding left ventricular dysfunction and/or who endure dyspnea despite systemic therapy. However, the balance benefit/risk/costs of such a procedure has been questioned [67]. Once PH is confirmed, a comprehensive workup is intended to scrupulously rule out the other classical causes of PH, chiefly pulmonary embolism. In cases with suspected heart sarcoidosis, several cardiac tests complement RHC. A screening algorithm for sarcoidosis-associated PH is proposed in figure 4.

**Clinical impact and prognosis of sarcoidosis-associated PH**

PH is a debilitating condition in sarcoidosis patients, which accounts for refractory dyspnoea [10] and reduced exercise capacity [12,59]. Additionally, the burden of PH on functional status and employment status is substantial [9]. Transplantation candidates with PH are more likely to need some or total assistance with their activities of daily living (nearly 70% of...
those with mPAP ≥ 40 mmHg) and PH increases the risk of being unemployed due to disease [9]. Furthermore, PH is well known to portend a pejorative outcome [11,13,15,17,68,69]. In sarcoidosis subjects waiting for lung transplantation, mPAP is an independent predictor of death together with oxygen requirement [68,69]. In the cohort of Nardi et al. on 142 stage IV patients originating from a non-transplant center, the occurrence of PH was the most robust correlate of mortality, with an 8.1-fold increase in risk of death (95% CI: 2.1–31.6, P = 0.002), and intractable right heart failure was the first cause of mortality (31.2%) [70].

In the retrospective series by Nunes et al. on 22 patients with sarcoidosis-associated PH, 2- and 5-year survival rates were 73.5% and 59%, respectively, which was significantly worse than for matched controls without PH [13]. Baughman et al. demonstrated that the relative risk of death in the presence of PH without left ventricular dysfunction versus no PH was 10.39 (95% CI: 2.99–31.6, P < 0.0001) and 3.14 (95% CI: 1.01–5.62, P < 0.05) when comparing PH without or with left ventricular dysfunction [11]. The median survival was 4.2 years for patients with pre-capillary PH. There was a significant difference in survival curves according to the level of
### Table II
Main studies on long-term PAH-targeted therapy for sarcoidosis-associated PH.¹

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Agent</th>
<th>Effect</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n</em> = 7</td>
<td></td>
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<tr>
<td>Stage III: <em>n</em> = 1 and IV: <em>n</em> = 6</td>
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<tr>
<td>Baseline mPAP = 55 ± 4 mmHg</td>
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<tr>
<td>Baseline PVR = 896 ± 200 dyne.s.cm⁻¹</td>
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<td></td>
<td>Inhaled NO: <em>n</em> = 4</td>
<td>Patients treated with INO: improvement in 6MWTD for 5/5 and in NYHA for 3/5; worsening in hemodynamics in 3/3 tested patients</td>
<td>6 patients died</td>
<td>[18]</td>
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<tr>
<td></td>
<td>Inhaled NO + EPO: <em>n</em> = 1</td>
<td></td>
<td>2 patients alive under INO for 1.5 and 2 years awaiting for transplantation</td>
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<tr>
<td></td>
<td>CCB: <em>n</em> = 2</td>
<td>Patients treated with CCB: worsening in 2/2</td>
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<tr>
<td><em>n</em> = 15/22 (7 patients could not complete 16 weeks therapy for several reasons)</td>
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<tr>
<td>Stage 0: <em>n</em> = 1, I: <em>n</em> = 1, II: <em>n</em> = 1, III: <em>n</em> = 1 and IV: <em>n</em> = 11</td>
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<tr>
<td>Baseline mPAP = 36 (20–62) mmHg and PVR = 488 (157–1304) dyne.s.cm⁻¹</td>
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<td></td>
<td>Inhaled Iloprost</td>
<td>Patients were followed prospectively</td>
<td>NA</td>
<td>[81]</td>
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<tr>
<td></td>
<td></td>
<td>At 16 weeks therapy, 8/15 patients were considered responders as defined as either an increase in 6MWTD ≥ 30 m or a decrease in the PVR ≥ 20%. Globally, SGRQ activity score decreased significantly</td>
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<td><em>n</em> = 5</td>
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<tr>
<td>Stage I: <em>n</em> = 1, III: <em>n</em> = 1 and IV: <em>n</em> = 3</td>
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<tr>
<td>Baseline mPAP = 58 ± 7 mmHg</td>
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<tr>
<td>Baseline PVR = 1142 ± 568 dyne.s.cm⁻¹</td>
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<tr>
<td></td>
<td>IV EPO: <em>n</em> = 3</td>
<td>Improvement in NYHA for all patients</td>
<td>4 patients alive and 1 transplanted after an average of 29 months therapy</td>
<td>[26]</td>
</tr>
<tr>
<td><em>n</em> = 6</td>
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<tr>
<td>IV EPO: <em>n</em> = 3</td>
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<tr>
<td>Bosentan: <em>n</em> = 3</td>
<td>4 initial responders (increase in 6MWD &gt; 50 m at 3–6 months therapy): 2 with EPO and 2 with Bosentan</td>
<td>NA</td>
<td>[82]</td>
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</tr>
<tr>
<td>Bosentan + EPO: <em>n</em> = 1</td>
<td>Only 1 responder at 12 months therapy</td>
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<tr>
<td>EPO: <em>n</em> = 1</td>
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<tr>
<td>CCB: <em>n</em> = 1</td>
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<td><em>n</em> = 7</td>
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<tr>
<td>Baseline mPAP = 53.4 ± 13.4 mmHg</td>
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<tr>
<td>Bosentan: <em>n</em> = 4</td>
<td>Significant improvement in hemodynamics in 4/5 tested patients (bosentan: <em>n</em> = 2, EPO: <em>n</em> = 1, CCB: <em>n</em> = 1) and stability in 1/5 (CCB)</td>
<td>Follow-up between 4 and 8 months</td>
<td>[10]</td>
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</tr>
<tr>
<td>Bosentan + EPO: <em>n</em> = 1</td>
<td></td>
<td></td>
<td>2 patients died</td>
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</tr>
<tr>
<td>EPO: <em>n</em> = 1</td>
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<tr>
<td>CCB: <em>n</em> = 1</td>
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<td></td>
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<tr>
<td><em>n</em> = 12</td>
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<tr>
<td>Patients with end-stage disease referred for lung transplantation</td>
<td></td>
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<tr>
<td>Baseline mPAP = 48 ± 15 mmHg and PVR: 856 ± 384 dyne.s.cm⁻¹</td>
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<tr>
<td>Sildenafil</td>
<td>Treatment was given for a median duration of 4 (1–12) months</td>
<td>Significant improvement in hemodynamics in 9 tested patients (mPAP: ~8 mmHg, PVR: ~392 dyne.s.cm⁻¹) with a decrease in PVR ≥ 20% in 6/9. No significant change in 6MWTD</td>
<td>NA</td>
<td>[83]</td>
</tr>
</tbody>
</table>
Patients who completed therapy, improvement but not significant, in WHO functional class and SGRQ. 1 All studies were retrospective, except two prospective open-label uncontrolled studies [81,85].

**Table II (Continued)**

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Agent</th>
<th>Effect</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 22</td>
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<tr>
<td>Stage 0: n = 3, I: n = 3, II: n = 1 and IV: n = 15</td>
<td>Initial monotherapy</td>
<td>Improvement in NYHA in 9 patients, significant increase in 6MWT in 18 tested patients (+59 m), significant improvement in hemodynamics in 12 tested patients (mPAP: −9.1 mmHg, PVR: −350 dyne.s.cm⁻²⁻¹)</td>
<td>Median of 11 months of follow-up</td>
<td>[15]</td>
</tr>
<tr>
<td>Baseline mPAP = 46.1 ± 2.7 mmHg</td>
<td>Bosentan: n = 12</td>
<td>Patients with a higher FVC had a greater increment in exercise capacity</td>
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<tr>
<td>Baseline PVR = 8.10 ± 8.91 dyne.s.cm⁻²</td>
<td>Sildenafil: n = 9</td>
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<td></td>
<td>Various combination therapy (inadequate response to initial monotherapy): n = 8</td>
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<td></td>
<td>Ambrisentan</td>
<td>Patients were followed prospectively</td>
<td>NA</td>
<td>[85]</td>
</tr>
<tr>
<td>n = 21 (11 patients could not complete 24 weeks therapy for several reasons)</td>
<td></td>
<td>Overall, at 24 weeks therapy, no significant change in 6MWT, Borg scale, serum BNP and QOL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0: n = 2, I: n = 0, II: n = 8, III: n = 2 and IV: n = 8</td>
<td></td>
<td>For patients who completed therapy, improvement but not significant, in WHO functional class and SGRQ</td>
<td></td>
<td></td>
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<tr>
<td>Baseline mPAP = 32.7 ± 7.3 mmHg</td>
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<tr>
<td>Baseline PVR = 5.9 ± 2.3 Woods units</td>
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</tbody>
</table>

mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; NO: nitric oxide; IV: intravenous; EO: intravenous epoprostenol; CCB: calcium channel blockers; 6MWT: six-minute walk test distance; SGRQ: St Georges respiratory questionnaire; BNP: brain naturetic peptide; QOL: quality of life; NA: not available.

In sarcoidosis-associated PH, the intrinsic vasculopathy that exists in a subset of patients makes the use of PAH specific receptors A and B antagonists [80]. In sarcoidosis, A and B antagonist [80].

There are four classes of PAH specific agents: (1) CCB, which are usually reserved for a small subgroup of patients with a passive pulmonary vasculopathy. (2) Prostacyclin analogues (3) PI-1 receptor antagonists and (4) phosphodiesterase-5 inhibitors. The use of PAH therapies in the management of sarcoidosis-associated PH is advocated for patients who have failed conventional therapy and are not surgical candidates [71].

**Treatment of sarcoidosis-associated PAH**

In view of the published evidence, no recommendation can be made on the optimal therapeutic strategy for sarcoidosis-associated PH. However, a potential role for P-glycoprotein inhibitors is suggested by the observed improvement in sarcoidosis-associated PH, which may be due to a reduction in the metabolism of PAH-specific agents. However, the optimal therapeutic strategy for sarcoidosis-associated PH requires further investigation. P-glycoprotein inhibitors may be useful in the management of sarcoidosis-associated PH in patients who have failed conventional therapy and are not surgical candidates [71].
agents appealing. Unfortunately though, available data are scarce and results are variable. The main studies on long-term responses to PAH therapy are summarized in table II [10,15,18,26,81–85]. These comprise only two prospective uncontrolled trials [81,85], others being retrospective small series or case observations.

These conflicting results are confusing for clinicians and spark the need for prospective randomized, placebo-controlled trials. A more rational approach is critical to define which patients to treat (on the basis of radiographic stage and/or lung function and/or the levels of mPAP?), which drug to prescribe and whether it should be used after immunosuppressive therapy or in association. Anyway, these drugs should be used with caution in patients with suspected PVOD. One case of sudden death and one case of acute pulmonary oedema have been described following intravenous Epoprostenol [26]. Clinical trials are underway to determine the efficacy and safety of PAH therapy in sarcoidosis-associated PH (www.clinicaltrials.gov).

Given the high mortality rate of patients with sarcoidosis-associated PH, evaluation for lung transplantation, when otherwise appropriate, should be considered early. Interestingly, angioplasty and stenting of the PA with sustained hemody-
namic and functional improvement has been reported in two sarcoid patients with extrinsic compression from mediastinal fibrosis [32].

Conclusion

PH is a challenging complication of sarcoidosis both in terms of diagnosis and management. There are recent shreds of evidence suggesting that sarcoidosis-associated PH may be more complex than just the result of parenchymal lung disease and hypoxemia. Intrinsic vasculopathy may play an important role. The presence of PH signifies a grave prognosis in patients with sarcoidosis. PAH-targeted therapy is tempting in sarcoidosis-associated PH but the lack of conclusive data leaves many uncertainties in this area. Although difficult to conduct in such a rare condition, prospective, randomized-controlled trials are warranted. At least, a great effort should be put in the constitution of international registries to obtain data from patients with sarcoidosis-associated PH.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

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