

Chapter 14

Pulmonary hypertension associated with sarcoidosis



Hilario Nunes*, Yurdagul Uzunhan*, Olivia Freynet*, Marc Humbert^{#,¶}, Pierre-Yves Brillet[†], Marianne Kambouchner[§] and Dominique Valeyre*

SUMMARY: Pulmonary hypertension (PH) affects approximately 6% of unselected patients with sarcoidosis but its prevalence is much higher in advanced pulmonary fibrosis. Although destruction of the distal capillary bed and resultant hypoxaemia are central, the underlying mechanisms are multifactorial: left heart dysfunction, specific pulmonary vasculopathy (which can cause pulmonary veno-occlusive disease), local increased vasoreactivity, extrinsic vascular compression and portal hypertension. As a result, some patients exhibit “disproportionate” PH, *i.e.* more severe than expected from the level of functional impairment. There is no validated screening algorithm for the detection of sarcoidosis-associated PH but recent studies have underlined the role of right heart catheterisation (RHC) to exclude post-capillary PH, which is frequently underestimated by echocardiography. PH is associated with a significantly increased morbidity and mortality in sarcoidosis. The cornerstone of management is supportive therapy and lung transplantation in otherwise eligible patients. Rare cases with nonfibrotic pulmonary disease respond to corticosteroids. Published data on the efficacy and safety of pulmonary arterial hypertension (PAH) agents are scarce and discrepant, requiring further studies.

KEYWORDS: Pulmonary hypertension, pulmonary veno-occlusive disease, sarcoidosis

*Dept of Pneumology, Avicenne Hospital,
†Dept of Radiology, Avicenne Hospital,
‡Dept of Pathology, Avicenne Hospital, University Paris 13, UPRES EA 2363, Assistance Publique Hôpitaux de Paris, Bobigny,
§Dept of Pneumology, Kremlin-Bicêtre Hospital, University Paris Sud, INSERM U999, Assistance Publique Hôpitaux de Paris, Kremlin-Bicêtre.
¶INSERM U999, Hypertension Artérielle Pulmonaire – Physiopathologie et Innovation Thérapeutique, Centre Chirurgical Marie-Lannelongue, Le Piessis-Robinson, France.

Correspondence: H. Nunes, Service de Pneumologie, Hôpital Avicenne, 125 rue de Stalingrad, 93009 Bobigny, France.
Email: hilario.nunes@avc.aphp.fr

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Sarcoidosis is a multisystemic disorder of unknown aetiology characterised by the formation of immune granulomas in affected tissues, particularly the lung and lymphatic system. The disease has an estimated annual incidence of one to 40 cases per 100,000 and mainly affects people aged 25–40 years, with a predilection for female sex and black ethnicity. Multiple phenotypes are seen according to presentation, the organs involved, disease duration and severity [1]. Sarcoidosis resolves spontaneously within 2 years in half of cases and 5 years in many others. After 5 years, remission is much less probable. This difference in outcome has led us to classify patients as acute

(≤ 2 years) or chronic (3–5 years or more). 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), the frequency of which 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 few years, there has been a dramatic resurgence of interest in sarcoidosis-associated PH, improving our understanding of its pathogenesis, and providing a better estimation of its prevalence and prognosis. In parallel, several studies have been conducted with new agents approved for pulmonary arterial hypertension (PAH).

This chapter examines the current literature regarding sarcoidosis-associated PH, with an emphasis on the most recent insights, including therapeutic management.

Classification of PH and the concept of “out-of-proportion” PH

PH is defined as an increased mean pulmonary artery pressure (P_{pa}) of ≥ 25 mmHg at rest on right heart catheterisation (RHC). In an attempt to assist physicians in clinical practice, an updated clinical classification of PH derived from the Dana Point meeting was published in 2009 (see chapter 2 of this issue) [2, 3]. Group 3 of this classification is “PH due to lung diseases and/or hypoxia”, including interstitial lung diseases (ILDs). Group 5 is “PH with unclear and/or multifactorial mechanisms”, including sarcoidosis. This distinction from group 3 is justified by the pathogenesis of sarcoidosis-associated PH, which is much more complex than parenchymal disease and resultant hypoxia. Another important point of the new classification is that pulmonary veno-occlusive disease (PVOD) has been separated from pulmonary arterial hypertension (PAH) and classified in its own group (group 1') [2]. However, several authors continue to consider PVOD 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 mean P_{pa} rarely exceeding 35–40 mmHg [2, 4]. However, the concept of “out-of-proportion” PH has been the subject of growing attention in ILDs, particularly in sarcoidosis. Actually, a proportion of patients with ILD-PH sometimes exhibit out-of-proportion PH, *i.e.* a mean $P_{pa} > 40$ 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 be established. The wide distribution in published rates is most probably due to the use of different measurement techniques, selection of diverse patient populations or different stages of disease (table 1). Overall, PH affects 1–6% of patients with sarcoidosis [5, 7, 9–11] but it is much more frequent in advanced lung disease [6] and symptomatic patients [12].

The only available prospective study, conducted by HANDA *et al.* [7], evaluated 212 consecutive outpatients with sarcoidosis by transthoracic echocardiography (TTE). An estimated systolic $P_{pa} > 40$ mmHg was found in 5.7% of patients. Regrettably, RHC was not performed to confirm the diagnosis of PH [7]. SHORR *et al.* [6] retrospectively reviewed a US cohort of 363 sarcoidosis patients listed for lung transplantation who had completed RHC. PH was identified in 73.8% of cases and mean P_{pa} was > 40 mmHg in 36.1% of patients [10]. In a retrospective study by BAUGHMAN *et al.* [8], 130 patients with persistent dyspnoea despite systemic therapy for their sarcoidosis were systematically explored with RHC; 38.5% had evidence of PH.

Table 1. Main studies on the prevalence of pulmonary hypertension in patients with sarcoidosis

First author [ref.]	Population	Method	Definition	Prevalence
RIZZATO [5]	n=50 Methods of selection not available Stage: 0, n=5; I, n=5; II, n=16; III: n=24 [#]	RHC at rest, n=50 RHC at exercise, n=34	Resting mean $P_{pa} > 25$ mmHg Exercise mean $P_{pa} > 30$ mmHg	3/50 (6%) 9/34 (26.5%)
SHORR [6]	n=363 Retrospective registry of patients listed for OLT	RHC at rest	Mean $P_{pa} > 25$ mmHg Mean $P_{pa} \geq 40$ mmHg	73.8% 36%
HANDA [7]	246 consecutive outpatients Prospective, observational Stage: 0, n=96; I, n=52; II, n=26; III, n=31; IV, n=7	TTE peak TRJV measurable in 212 patients	Systolic $P_{pa} \geq 40$ mmHg	5.7%
BAUGHMAN [8]	130 patients with persistent dyspnoea despite systemic therapy Retrospective	RHC at rest	Mean $P_{pa} > 25$ mmHg with $P_{pcw} < 15$ mmHg Mean $P_{pa} \geq 40$ mmHg $P_{pcw} \geq 15$ mmHg	50/130 (38.5%) 14/130 (10.8%) 20/130 (15.4%)

OLT: orthotopic lung transplantation; RHC: right heart catheterisation; TTE: transthoracic echocardiography; TRJV: tricuspid regurgitation jet velocity; P_{pa} : pulmonary artery pressure; P_{pcw} : pulmonary capillary wedge pressure. #: stage III included patients with or without fibrosis.

No difference has been observed between patients with and without PH in terms of sarcoidosis phenotype or demographic characteristics, except for a higher frequency of stage IV disease on chest radiography [7, 8, 13–15] and possible male predominance [7].

Pathogenesis of sarcoidosis-associated PH

As already indicated, sarcoidosis is classified in group 5 of the Dana Point PH classification but, essentially, the mechanisms of sarcoidosis-associated PH may fit into all five groups [2, 4].

Pre-capillary PH

Destruction of the distal capillary bed and resultant hypoxaemia

The majority of sarcoidosis patients with PH have evidence of advanced disease [7, 8, 13–15]. However, 31.8% to 50% of patients with sarcoidosis-associated PH develop this complication in the absence of patent pulmonary fibrosis [8, 14, 15] and a small subset of cases have no apparent underlying lung disease (radiographic stage 0–I) [7, 8, 14–16]. Moreover, haemodynamic measurements do not correlate well with spirometric parameters and arterial oxygen tension (P_{a,O_2}) [7, 12, 14, 17], and mean P_{pa} is 9 mmHg higher in sarcoidosis than in idiopathic pulmonary fibrosis (IPF) for equivalent levels of respiratory impairment (34.4 *versus* 25.6 mmHg, $p < 0.0001$) [18]. Finally, the degree of PH is sometimes disproportionate to functional abnormalities [6, 8, 14, 19] and PH may even be more severe when it occurs in patients without fibrotic disease [14]. 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, locally increased vasoreactivity, extrinsic compression of pulmonary vessels, left heart dysfunction and portal hypertension. Comorbidities associated with sarcoidosis can also cause PH.

Specific vasculopathy

Vascular involvement is very common in pulmonary sarcoidosis, occurring in 69–100% of cases according to pathological studies [20, 21]. Changes consist of occlusive or destructive lesions due to the invasion of vessel walls by granulomas or to perivascular fibrosis [20, 21]. Vascular involvement can be observed at all levels, from large branches of the pulmonary artery to small veins, but it prevails in the venous side, reflecting the lymphatic spreading of the granulomatous process (figs 1 and 2) [20–22]. Despite frequent granulomatous vascular involvement, clinically significant PH is rare. In the autopsy study by TAKEMURA *et al.* [21], significant PH was noted in only four out of 40 patients with vascular involvement. The reasons why some individuals will develop PH are not completely understood.

PVOD-like disease is now a well-recognised cause of sarcoidosis-associated PH [14, 23, 24]. The occlusive narrowing of interlobular veins by granulomas can mimic PVOD and result in PH. This mechanical granulomatous PVOD has been pathologically authenticated in a handful of cases with nonfibrotic sarcoidosis [23, 24]. In addition, NUNES *et al.* [14] described an intrinsic occlusive venopathy in explanted lungs from five sarcoidosis patients with PH and pulmonary fibrosis. This venopathy was characterised 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 granulomas were present in the veins of four out of five cases whereas arterial granulomas were seen in only two cases and neither venous nor arterial granulomas were found in one patient [14]. Interestingly, a similar venopathy has also been described in another “granulomatous” disorder, pulmonary Langerhans’ cell histiocytosis (PLCH) [25].

Locally 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 nitric oxide or prostacyclin [19, 26, 27]. Among the various contenders, endothelin-1 (ET-1) is the most attractive. ET-1 is a potent vasoconstrictive cytokine, which also possesses pro-inflammatory and mitogenic properties, in particular for smooth muscle cells and fibroblasts, inducing vascular remodelling. Yet, despite emerging results, data are currently limited and no study has compared ET-1 measurements with the presence of PH.

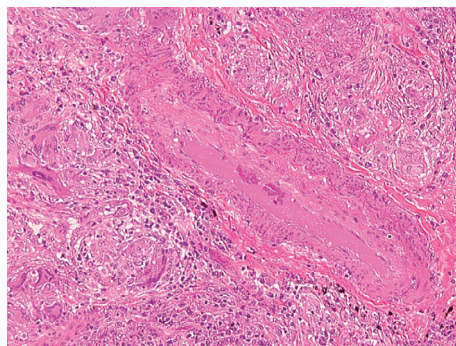


Figure 1. Pulmonary arterial involvement of sarcoidosis. Coalescent granulomas adjacent to the adventitia of an intralobular artery, which narrow the vascular lumen. Haematoxylin and eosin staining. Magnification $\times 100$.

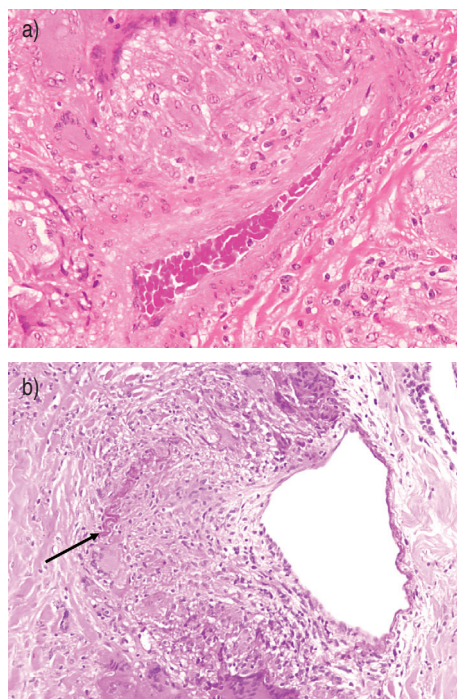


Figure 2. Pulmonary venous involvement of sarcoidosis. a) Granulomas in the wall of an interlobular vein, with a partial occlusion of the vascular lumen. b) Invasion of the venous wall by fibrotic granulomas, which results in hemi-circumferential destruction, with a disruption of the elastic laminae (arrow) and vascular luminal narrowing. Haematoxylin and eosin staining. Magnification $\times 100$.

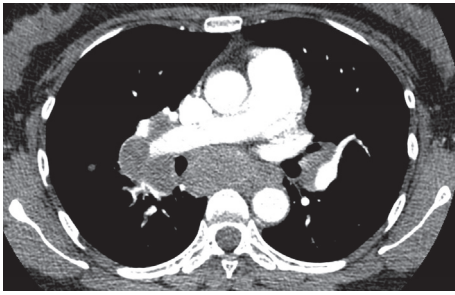


Figure 3. High-resolution computed tomography of the lungs of a patient with sarcoidosis-associated pulmonary hypertension and vascular extrinsic compression by lymphadenopathies. Multiple lymph nodes with an extrinsic compression of the right main pulmonary artery and a slightly increased calibre of the pulmonary trunk compared with the aorta are seen.

patients and 12 nonsmoking healthy controls in the study by TERASHITA *et al.* [31]. Levels were significantly higher in sarcoidosis and they were correlated with the number of alveolar macrophages harvested in BAL. Similarly, ET-1 immunoreactivity was localised mainly in alveolar macrophages. Lastly, BAL fluid (BALF) from the sarcoidosis patients stimulated fibroblast proliferation, compared with control BALF, and fibroblast proliferation was blocked in the presence of an ET-1 inhibitor [31]. Consistent with this, 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 [32].

Extrinsic compression of pulmonary vessels

Sarcoidosis-associated PH may be caused by extrinsic compression of the proximal pulmonary artery by enlarged lymph nodes or fibrosing mediastinitis (fig. 3) [14, 33, 34]. Compression of the large pulmonary veins is much rarer and can provoke localised oedema. Although occasionally described in early stages of sarcoidosis, pulmonary artery 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 sarcoidosis in the study of NUNES *et al.* [14].

Portal hypertension

PH may also be the consequence of hepatic sarcoidosis, which can rarely lead to cirrhosis and portal hypertension [35].

Post-capillary PH

Clinical myocardial involvement is seen in about 5% of sarcoidosis patients and can generate left ventricular (LV) systolic or diastolic impairment. Notably, unsuspected occult involvement is much more frequently revealed by pathological examination [36]. 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 [37, 38]. Similarly, in sarcoidosis patients awaiting lung transplantation, although within normal values for the vast majority of patients, pulmonary capillary wedge pressure (P_{pcw}) 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 [6].

Although newer techniques have improved the detection of LV dysfunction in sarcoidosis [36], the reliability of routine TTE is weak in such a context. The study by BAUGHMAN *et al.* [8] cited earlier

SOFIA *et al.* [28] 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 receiving corticosteroids, and the decrease concurred with clinical improvement. Urine ET-1 was significantly correlated with the intensity of lymphocytic alveolitis [28]. Conversely, plasma ET-1 was increased in sarcoidosis patients compared with healthy controls in the study by LETIZIA *et al.* [29]. In those who went into remission following successful corticosteroid therapy, ET-1 levels normalised in parallel with other parameters of disease activity [29]. REICHENBERGER *et al.* [30] examined ET-1 concentrations in bronchoalveolar lavage (BAL) specimens from patients with various pulmonary disorders and healthy controls. Elevated ET-1 levels were observed in sarcoidosis patients, which were comparable to those seen in scleroderma and IPF patients [30, 31]. BAL ET-1 was also compared between 22 nonsmoking sarcoidosis

in this chapter is extremely interesting in this regard. 130 sarcoidosis patients with persistent dyspnoea were thoroughly investigated by RHC [8]. LV dysfunction, defined as an elevated P_{pcw} , was revealed in 20 (15.4%) subjects, which represented 28.6% of all cases with PH [8]. Only seven (35%) of them had a reduced LV ejection fraction on TTE [8].

Comorbidities

A potential link between sarcoidosis and thromboembolic events has recently been emphasised [39, 40]. CRAWSHAW *et al.* [39] 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 in Oxfordshire, UK. 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 [39]. Using US death certificates from 1988 to 2007, SWIGRIS *et al.* [40] showed that pulmonary embolism was declared for 2.54% of decedents with sarcoidosis, compared with only 1.13% of the background population (OR 2.3, 95% CI 2.1–2.5; $p<0.0001$). The risk was significantly greater than for decedents with chronic obstructive pulmonary disease (COPD) [40]. However, to the best of our knowledge, post-embolic PH has been described only in unique patients with sarcoidosis showing exuberant granulomas inside the thrombi at pathology [41].

The reasons why sarcoidosis confers an increased risk for pulmonary embolism remain to be elucidated. The rate of either antiphospholipid immunoglobulin (Ig)G or IgM in sera reached 38% of sarcoidosis patients in the study of INA *et al.* [42], which was significantly more than in healthy controls. Several observations have described antiphospholipid syndrome occurring in sarcoidosis patients with [43] or without concomitant lupus [44, 45]. In addition, sarcoidosis can co-exist with various autoimmune disorders known to facilitate thromboembolic disease and/or PAH, including Takayasu arteritis [46] and systemic scleroderma [47].

Lastly, a higher than expected prevalence of obstructive sleep apnoea (OSA) has been observed in sarcoidosis [48, 49], attaining 17% in one study [48].

Diagnosis of sarcoidosis-associated PH

The clinical picture of an underlying respiratory disorder can mask PH and delay its recognition. However, several symptoms should prompt diagnostic intervention: dyspnoea more severe than one would expect from functional impairment; chest pain; palpitations; and near-syncope on exertion. Physical signs include: a loud P_2 component to the second heart sound; a fixed, split S_2 ; a holosystolic murmur of tricuspid regurgitation; and a diastolic murmur of pulmonic regurgitation. About one-quarter of patients with sarcoidosis-associated PH present with signs of right-sided heart failure [14, 15]. Raynaud's phenomenon is occasionally noted as in idiopathic PAH (IPAH) [14]. ECG may show signs of right ventricular (RV) strain and chest radiography may show right cardiomegaly and pulmonary artery enlargement.

Transthoracic echocardiography

Admittedly, TTE is an imperfect diagnostic method, but it remains the most appropriate modality for the noninvasive assessment of PH. In ILDs, the peak velocity of the tricuspid regurgitant jet is measurable in only 44–54% of patients and, even if available, estimation of the systolic P_{pa} is often inaccurate [50–52]. ARCASOY *et al.* [50] examined the performance of TTE in 106 patients with diverse forms of ILDs referred for lung transplantation, using RHC as the gold standard. Despite the significantly higher likelihood of achieving an estimation of systolic P_{pa} in ILDs, the accuracy of TTE was much worse than in COPD. There was a good correlation between systolic P_{pa} estimated by TTE and that measured by RHC but the values were within 10 mmHg in only 37% of patients with ILDs. When considering estimated systolic P_{pa} in excess of 45 mmHg as a

determinant of PH, the sensitivity, specificity, and positive and negative predictive values of TTE were 85%, 17%, 60% and 44%, respectively. When RV abnormalities were used as a surrogate diagnostic marker of PH, the values for TTE were 76%, 53%, 57% and 74%, respectively [50]. Unfortunately, there is little specific information for sarcoidosis available [8, 13]. In the study by BAUGHMAN *et al.* [8], 80 patients underwent both echocardiographic and haemodynamic assessments. Of these, only 70% had sufficient tricuspid regurgitant jet identified such that systolic P_{pa} could be estimated. For these cases, there was a significant correlation between estimated and measured systolic P_{pa} ($r=0.62$, $p<0.0001$). Sensitivity and specificity of TTE were not reported in this study [8].

Hence, the absence of an increased systolic P_{pa} appears to be suboptimal to exclude significant PH and does not obviate the need for RHC in selected patients. RV abnormalities are valuable additional parameters to reinforce suspicion of PH, irrespective of tricuspid regurgitant velocity.

Right heart catheterisation

Although definite diagnosis relies on invasive measurements, not all patients with ILDs and suspected PH should undergo confirmatory RHC. The European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines assert the following reasonable indications for RHC in group 3 PH: 1) proper diagnosis of PH in candidates for transplantation; 2) suspected out-of-proportion PH potentially amenable to enrolment in a clinical trial with specific PAH drug therapy; 3) frequent episodes of right heart failure; and 4) inconclusive echocardiographic study in cases with a high index of clinical suspicion [4]. In sarcoidosis, a wider adoption of RHC has, however, gained credit following the published experience of BAUGHMAN and co-workers [8, 12]. As discussed previously, left-heart dysfunction is not uncommon in sarcoidosis and probably underrated by TTE [8]. Furthermore, RHC also provides important information on prognosis [8, 53, 54]: on the one hand, it allows assessment of the severity of haemodynamic impairment; on the other, the pre- or post-capillary nature of PH has not only therapeutic but also prognostic implications [8].

The haemodynamic severity of sarcoidosis-associated PH is extremely variable. In the study by BAUGHMAN *et al.* [8] on 50 patients with pre-capillary PH, median mean P_{pa} was 33 mmHg (range 25–75 mmHg) and median pulmonary vascular resistance (PVR) was 4.3 Wood units (range 0.9–21.2 Wood units). These patients displayed a similar mean P_{pa} but a significantly higher PVR than those with PH due to LV dysfunction. Mean P_{pa} was over 35 and 40 mmHg in 46% and 28% of patients with pre-capillary PH, respectively [8]. Out-of-proportion PH seems more frequent in patients without than with pulmonary fibrosis [6, 14]. As therapy with high doses of calcium channel blockers (CCBs) 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 varied between 0% and 87.5% in three series [14, 19, 26, 27], depending on the agent used and the definition of response.

Pulmonary function tests and the 6-minute walk test

Most studies have shown statistically lower forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (DL_{CO}) values in sarcoidosis patients with PH [7, 8, 13–15]. These patients are also more hypoxaemic and/or require more frequent supplemental oxygen than those without PH [6, 7, 8, 13–15]. Nonetheless, the contribution of pulmonary function tests (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.* [6] (OR 8.39, 95% CI 3.44–20.47), 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 [6]. HANDA *et al.* [7] 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. Because the reduction of DL_{CO} can be related to both interstitial and vascular involvement, several authors have postulated that a high FVC/ DL_{CO} ratio (with a cut-off of 1.4–1.5), reflecting a disproportionately reduced DL_{CO} for the degree of restriction, may be a better tool for gauging PH in ILDs, alone or together with arterial oxygen saturation (S_{a,O_2}) [55–59]. The ability of the FVC/ DL_{CO} ratio to screen for PH has never been tested in sarcoidosis, although findings are significantly higher in patients with increased echocardiographic systolic P_{pa} (mean \pm SD 1.6 ± 0.7 versus 1.2 ± 0.4 , $p < 0.01$) [15]. No study has focused on the predictive value of the measure of membrane and blood components of DL_{CO} for the detection of PH in sarcoidosis.

BAUGHMAN *et al.* [60] prospectively evaluated the 6-minute walk test (6MWT) in 142 sarcoidosis patients. The 14 patients with documented PH accomplished a significantly shorter distance, with a median of 280 m versus 411 m for all other patients [60]. Similar results were found in the retrospective study of BOURBONNAIS *et al.* [13] on 162 patients, which aimed to determine the clinical predictors of PH in sarcoidosis. The 22 patients with PH walked shorter distances (343 ± 116 versus 426 ± 105 m, $p < 0.004$) and had greater desaturation ($8.85 \pm 4.22\%$ versus $2.99 \pm 2.14\%$, $p < 0.001$) and Borg score at 6 minutes [13]. After adjusting for body mass index (BMI) and age, multivariate analyses showed that the significant predictors of PH on TTE were $S_{a,O_2} < 90\%$ on 6MWT (OR 12.1, 95% CI 3.66–19.73) and $DL_{CO} < 60\%$ predicted (OR 7.3, 95% CI 1.98–24.82). DL_{CO} did not retain significance when PH was defined using RHC. These cut-off values for S_{a,O_2} and DL_{CO} were obtained from the receiver operating characteristic (ROC) curves. The other variables tested, including 6MWT distance and all other PFT parameters, failed to predict the presence of PH. Interestingly, all seven patients being misdiagnosed as having no PH on TTE desaturated to $< 90\%$ during the 6MWT, suggesting that a composite model combining the results of S_{a,O_2} on 6MWT with those of TTE would improve the pre-test probability before performing RHC [13]. 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 (HRCT) can show an increased pulmonary artery calibre (widest diameter of the main pulmonary artery > 29 mm or greater than that of the ascending aorta). Even so, the pulmonary artery diameter and pulmonary artery/aorta ratio are not reliable for predicting the presence of PH in ILDs [61, 62], possibly because the restrictive lung physiology may result in a traction effect on the mediastinal vascular structures, distending the pulmonary artery independently of the underlying P_{pa} . In sarcoidosis, contrast-enhanced HRCT helps delineate the mechanisms of PH. First, it allows the diagnosis of extrinsic vascular compression (fig. 3). Secondly, several findings may hint at PVOD, such as extensive ground-glass opacities and/or thickened interlobular septa (fig. 4). Although these features may be related solely to sarcoidosis, NUNES *et al.* [14] demonstrated that patients with sarcoidosis-associated PH showed a significantly higher frequency of ground-glass attenuation and septal lines compared with sarcoidosis controls without PH. The differentiation of extrinsic vascular

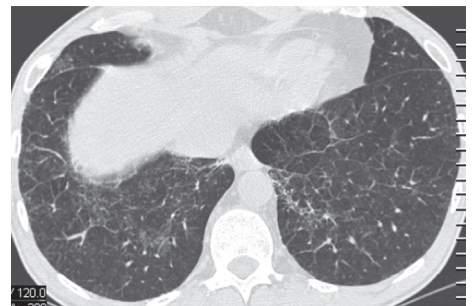


Figure 4. High-resolution computed tomography of the lungs of a patient with sarcoidosis-associated pulmonary hypertension and suspicion of pulmonary veno-occlusive disease. A network of septal reticulations in association with ground-glass opacities are seen, increasing the possibility of pulmonary veno-occlusive disease.

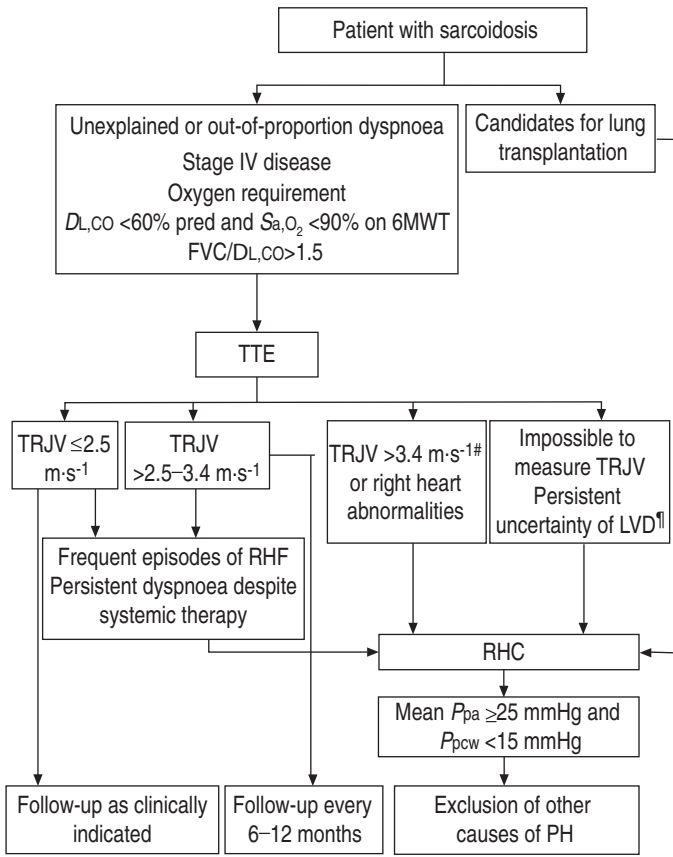


Figure 5. Proposed algorithm for the screening of sarcoidosis-associated pulmonary hypertension (PH). $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; S_{a,O_2} : arterial oxygen saturation; 6MWT: 6-minute walk test; FVC: forced vital capacity; TTE: transthoracic echocardiography; TRJV: tricuspid regurgitant jet velocity; LVD: left ventricular dysfunction; RHF: right heart failure; RHC: right heart catheterisation; P_{pa} : pulmonary artery pressure; P_{pcw} : pulmonary capillary wedge pressure. #: out-of-proportion PH can be suspected on TTE if $TRJV >3.4 \text{ m}\cdot\text{s}^{-1}$ (estimated systolic $P_{pa} >55\text{--}60 \text{ mmHg}$); ¶: particularly left ventricular diastolic dysfunction.

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 $103 \text{ pg}\cdot\text{mL}^{-1}$ based on ROC curves [67].

Screening of sarcoidosis-associated PH

As PH bears severe prognosis in sarcoidosis, early diagnosis and consideration of treatment options may be keys to improve patients' outcomes. Nonetheless, there is no consistent single clinical criterion that can be used to adequately segregate sarcoidosis patients with a high or low risk for PH. Owing to 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 LV dysfunction and/or who continue to experience dyspnoea despite systemic therapy. However, the balance of benefit, risk and costs of such a procedure has been questioned [68]. 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

compression from pulmonary embolism is sometimes tricky and occasionally requires pulmonary angiography. Hepatic ultrasound is necessary to exclude portopulmonary hypertension (POPH).

Natriuretic peptides

Plasma brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP may be helpful biomarkers for the detection of PH in patients with ILDs. In the study by LEUCHTE *et al.* [63] in patients with diverse ILDs, elevated plasma BNP levels were predictive of moderate-to-severe PH, defined as mean $P_{pa} >35 \text{ mmHg}$ on RHC, with 100% sensitivity and 89% specificity. BNP is also independently associated with a higher risk of mortality in ILDs [64–66]. HANDA *et al.* [67] performed a prospective study of 150 consecutive sarcoidosis patients to investigate the utility of plasma NT-proBNP in the assessment of PH and cardiac involvement. Among the 130 subjects evaluable for PH status at TTE, 21 were diagnosed with PH (defined as a systolic $P_{pa} >35 \text{ mmHg}$). 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

suspected heart sarcoidosis, several cardiac tests complement RHC. A screening algorithm for sarcoidosis-associated PH is proposed in figure 5.

Clinical impact and prognosis of sarcoidosis-associated PH

PH is a debilitating condition in sarcoidosis patients, which accounts for refractory dyspnoea [12] and reduced exercise capacity [13, 60]. Additionally, the burden of PH on functional status and employment status is substantial [6]. Transplantation candidates with PH are more likely to need some or total assistance with their activities of daily living (nearly 70% of those with a mean $P_{pa} \geq 40$ mmHg) and PH increases the risk of being unemployed due to disease [6]. Furthermore, PH is well-known to portend a pejorative outcome [8, 14, 16, 18, 69, 70]. In sarcoidosis subjects waiting for lung transplantation, mean P_{pa} is an independent predictor of death together with oxygen requirement [69, 70]. In the cohort of NARDI *et al.* [71] consisting of 142 stage IV patients originating from a nontransplant centre, 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 primary cause of mortality (31.2%).

In the retrospective series of NUNES *et al.* [14] consisting of 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. BAUGHMAN *et al.* [8] demonstrated that the relative risk of death in the presence of PH without LV dysfunction *versus* no PH was 10.39 (95% CI 2.99–13.78, $p<0.0001$) and 3.14 (95% CI 1.01–5.62, $p<0.05$) when comparing PH without or with LV dysfunction. 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 PVR (<3 or ≥ 3 Wood units). On multivariate analysis, only two independent parameters were proven to be predictors of mortality in the studied population: stage IV radiography and presence of PH (hazard ratio 7.43, 95% CI 2.26–24.45) [8].

Treatment of sarcoidosis-associated PH

In view of limited reports on the subject, no recommendation can be drawn on the optimal therapeutic strategy for sarcoidosis-associated PH, which should take into account the prominent underlying mechanism of PH. Obviously, supportive therapy is the cornerstone of management, including supplemental oxygen in patients who are hypoxaemic at rest or during exercise, and diuretics as needed.

With respect to therapy directed against sarcoidosis, published results are somewhat discrepant. PH has been shown both to worsen despite corticosteroids [72–76] and to improve dramatically [77, 78]. GLUSKOWSKI *et al.* [76] evaluated the effect of 12 months of corticosteroid treatment on the haemodynamics of 24 patients with pulmonary sarcoidosis, of whom three had PH at rest and 18 had PH on exercise. Whereas most patients had improvements on chest radiography and PFTs, only half showed improved haemodynamics [76]. In the study by NUNES *et al.* [14], 10 patients with sarcoidosis-associated PH received high doses of oral prednisone. This was inefficient in the five patients with stage IV but a sustained improvement was obtained in three out of the five cases without pulmonary fibrosis [14]. Interestingly, in one reported case, comparisons of subsequent specimens taken before and after established PH (open-lung biopsy and autopsy) showed a clear progression of the pulmonary vascular involvement whereas parenchymal lesions of sarcoidosis stayed relatively stable with corticosteroids [75].

There are four classes of PAH agents: 1) CCBs, which are reserved for a small subgroup of patients with positive acute vasoreactivity tests; 2) prostacyclin analogues; 3) endothelin receptor antagonists (ERAs); and 4) phosphodiesterase type-5 inhibitors (PDE-5 I) [4]. According to the ERS/ESC guidelines, the use of PAH-targeted therapy is discouraged in group 3 PH when mean P_{pa} is <40 mmHg [4]. It may be proposed to patients with out-of-proportion PH in expert centres, ideally as part of randomised controlled trials [4]. There has long been concern over systemic pulmonary vasodilators leading to an aggravation of hypoxaemia, because of the

Table 2. Main studies on long-term pulmonary arterial hypertensive-targeted therapy for sarcoidosis-associated pulmonary hypertension

First author [ref.]	Patient characteristics	Agent	Effect	Outcomes
PRESTON [19]	n=7 Stage: III, n=1; IV, n=6 Baseline mean P_{ba} mean \pm SE 55 \pm 4 mmHg Baseline PVR mean \pm SE 896 \pm 200 dyn·s·cm ⁻⁵	iNO, n=4 iNO+epoprostenol, n=1 CCBs, n=2	Patients treated with iNO: improvement of 6MWD in 5/5 and NYHA FC in 3/5; worsening of haemodynamics in 3/3 Patients treated with CCBs: worsening in 2/2	6 patients died 2 patients alive under iNO for 1.5 and 2 years, respectively, awaiting transplantation
BAUGHMAN [82]	15 out of 22 (7 patients could not complete 16 weeks therapy for several reasons) Stage: 0, n=1; I, n=1; II, n=1; III, n=1; IV, n=11 Baseline mean P_{ba} 36 (20–62) mmHg Baseline PVR 488 (157–1304) dyn·s·cm ⁻⁵	Inhaled iloprost	Patients were followed prospectively At 16 weeks, 8/15 were considered responders, defined as either an increase in 6MWD \geq 30 m or a decrease in PVR \geq 20% Globally, SGRQ activity score decreased significantly	NA
FISHER [27]	n=5 Stage: I, n=1; III, n=1; IV, n=3 Baseline mean P_{ba} 58 \pm 7 mmHg Baseline PVR 1142 \pm 568 dyn·s·cm ⁻⁵	<i>i.v.</i> epoprostenol	Improvement in NYHA FC for all patients	4 patients alive and 1 transplanted after an average of 29 months therapy
MINAI [83]	n=6	<i>i.v.</i> epoprostenol, n=3 Bosentan, n=3	4 initial responders (increase in 6MWD >50 m at 3–6 months); 2 with epoprostenol and 2 with bosentan Only 1 responder at 12 months	NA
BAUGHMAN [12]	n=7 Baseline mean P_{ba} 53.4 \pm 13.4 mmHg	Bosentan, n=4 Bosentan+epoprostenol, n=1 Epoprostenol, n=1 CCBs, n=1 Sildenafil	Significant improvement of haemodynamics in 4/5 (bosentan, n=2; epoprostenol, n=1; CCBs, n=1) and stability in 1/5 (CCBs)	Follow-up between 4 and 8 months 2 patients died
MILMAN [84]	n=12 Patients with end-stage disease referred for lung transplantation Baseline mean P_{ba} 48 \pm 15 mmHg Baseline PVR 856 \pm 384 dyn·s·cm ⁻⁵	Sildenafil	Treatment was given for a median duration of 4 (1–12) months Significant improvement of haemodynamics in 9 tested patients (mean P_{ba} -8 mmHg, PVR -392 dyn·s·cm ⁻⁵) with a decrease in PVR \geq 20% in 6/9 No significant change in 6MWD	NA

Table 2. Continued

First author [ref.]	Patient characteristics	Agent	Effect	Outcomes
BARNETT [16]	n=22 Stage: 0, n=3; II, n=3; III, n=1; IV, n=15 Baseline mean P_{pa} 46.1 ± 2.7 mmHg Baseline PVR 810 ± 89.1 dyn·s·cm ⁻⁵	Initial monotherapy: Bosentan, n=12; Sildenafil, n=9; Epoprostenol, n=1 Various combination therapies (inadequate response to initial monotherapy), n=8 Ambrisentan	Improvement of NYHA FC in 9 patients, significant increase in 6MWD in 18 patients (+59 m), significant improvement of haemodynamics in 12 patients (mean P_{pa} -9.1 mmHg, PVR: -350 dyn·s·cm ⁻⁵) Patients with higher FVC had greater increase in exercise capacity	Median of 11 months of follow-up 1- and 3-year transplant-free survival rates 90% and 74%, respectively
JUDSON [85]	n=21 (11 patients could not complete 24 weeks therapy for several reasons) Stage: 0, n=2; I, n=0; II, n=8; III, n=2; IV, n=8 Baseline mean P_{pa} 32.7 ± 7.3 mmHg Baseline PVR 5.9 ± 2.3 Wood units		Patients were followed prospectively Overall, at 24 weeks, no significant change in 6MWD, Borg scale, serum BNP or QoL For patients who completed therapy, nonsignificant improvement of WHO-FC and SGRQ	NA

Data are presented as median (range) or mean ± sd, unless otherwise stated. All studies were retrospective, except for two prospective, open-label, uncontrolled studies [82, 85]. P_{pa} : pulmonary artery pressure; PVR: pulmonary vascular resistance; iNO: inhaled nitric oxide; CCB: calcium channel blocker; 6MWD: 6-minute walking distance; NYHA: New York Heart Association; FC: functional class; SGRQ: St George's Respiratory Questionnaire; FVC: forced vital capacity; BNP: brain natriuretic peptide; QoL: quality of life; WHO: World Health Organization; NA: not available.

inhibition of hypoxic pulmonary vasoconstriction with subsequent increased ventilation/perfusion mismatch and shunting. Therefore, delivery of these medications, including nitric oxide or prostanoids, to well-ventilated lung units *via* inhalation has been preferred [79]. Yet, while decreased arterial oxygenation is observed with CCBs and intravenous epoprostenol [79, 20], it is not observed with oral sildenafil (a PDE-5 I) [80] or bosentan (a dual ETA and ETB ERA) [81].

In sarcoidosis-associated PH, the intrinsic vasculopathy that exists in a subset of patients makes the use of PAH-specific agents appealing. Unfortunately, available data are scarce and results are variable. The main studies on long-term responses to PAH therapy are summarised in table 2 [12, 16, 19, 27, 82–86]. These include only two prospective uncontrolled trials [82, 85], the others being retrospective small series or case observations.

These conflicting results are confusing for clinicians and spark the need for prospective randomised, placebo-controlled trials. A more rational approach is critical to define which patients to treat (perhaps on the basis of radiographic stage and/or lung function and/or mean P_{pa}), which drug to prescribe and whether it should be used after immunosuppressive therapy or in association with it. In any case, 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 *i.v.* epoprostenol [27]. Clinical trials are underway to determine the efficacy and safety of PAH therapy in sarcoidosis-associated PH.

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 pulmonary artery with sustained haemodynamic and functional improvement has been reported in two sarcoid patients with extrinsic compression from mediastinal fibrosis [33].

Conclusions

PH is a challenging complication of sarcoidosis in terms of both diagnosis and management. There are recent shreds of evidence suggesting that sarcoidosis-associated PH may be more complex than simply being the result of parenchymal lung disease and hypoxaemia. 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, randomised controlled trials are warranted. At the very least, great effort should be put into setting up international registries to obtain data from patients with sarcoidosis-associated PH.

Statement of Interest

M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. D. Valeyre is a member of the advisory board of IPF InterMune. He has participated as an investigator or a member of steering committee in trials on IPF (CAPACITY, BUILD3 and BIBF) and the CENTOCOR trial on sarcoidosis. His accommodation at and travel to medical meetings (ATS, ERS and CPLF) was funded by AstraZeneca, GSK, Boehringer, Nycomed and PneumoPharma.

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