Pulmonary hypertension and granulomatous vasculitis in sarcoidosis

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Purpose of review

To examine the recent advancements of the epidemiology, pathophysiology, clinical characteristics, radiographic studies, diagnostic modalities, treatment, and prognosis of pulmonary hypertension in sarcoidosis.

Recent findings

A large retrospective study found 73.8% of patients with sarcoidosis listed for transplant had pulmonary hypertension. Several other studies found pulmonary hypertension to be associated mostly with advanced sarcoidosis, although frequencies in nonfibrotic disease were not uncommon. Destruction of vasculature due to fibrotic lung disease is most likely the common cause; however, other mechanisms have been proposed. In a small study, pulmonary venous occlusive disease was observed in the explanted lungs. Several studies have found an association with pulmonary function and the incidence of pulmonary hypertension. Right heart failure was seen in 21–23% of patients. In one study, high-resolution computer tomography findings, such as presence of lymphadenopathy, opacities, and thickened bronchovascular bundles, were not significantly different. Septal lines and ground-glass opacities were found at higher frequency in sarcoidosis-associated pulmonary hypertension. Corticosteroids were effective in treating some patients with sarcoidosis-associated pulmonary hypertension. Inhaled nitric oxide, epoprostenol, and bosentan have been shown to be efficacious in a small number of patients.

Summary

Pulmonary hypertension is not infrequently observed in sarcoidosis. Further studies are needed to elucidate the epidemiology, mechanisms, treatment, and significance of sarcoidosis-associated pulmonary hypertension.

Keywords

corticosteroids, doppler echocardiogram, pulmonary hypertension, sarcoidosis

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Abbreviations

DLCO	diffusion capacity of the lung for carbon dioxide
HRCT	high-resolution computed tomography
iNO	inhaled nitric oxide
PAP	pulmonary artery pressure
PVR	pulmonary vascular resistance
RHC	right heart catheterization
TLC	total lung capacity

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Introduction

Pulmonary hypertension in sarcoidosis is potentially a life-threatening complication that significantly impacts the management strategies and survival in these patients. To date, no studies have accurately assessed the epidemiology of pulmonary hypertension with various stages seen with sarcoidosis. The most common mechanism is thought to be due to fibrosis of the lung parenchyma leading to destruction of vascular beds; however, other potential mechanisms have been entertained. This review examines the recent advancements and provides a comprehensive overview on the epidemiology, pathophysiology, clinical characteristics, radiographic studies, diagnostic modalities, treatment, and prognosis of pulmonary hypertension in sarcoidosis.

Epidemiology

Sarcoidosis is a systemic granulomatous disease of unknown cause. It can affect any organ, although the lungs are the most commonly involved. The frequencies of pulmonary hypertension have been reported to range from 1 to 28% [1–5]. The wide distribution is likely due to varying definition of pulmonary hypertension and entry criteria of study subjects. Pulmonary hypertension is more commonly seen with fibrotic lung disease, especially with severe pulmonary hypertension [1,2,6,7,8••]. Recently, Shorr *et al.* reported the prevalence of pulmonary hypertension in a large cohort of patients with sarcoidosis [9]. They reviewed records of 363 patients with sarcoidosis on the United Network for Organ Sharing list for lung transplantation who had complete right heart catheterization (RHC) records available. The authors found 268 (73.8%) patients with sarcoidosis listed for transplant had pulmonary hypertension defined as mean pulmonary artery pressure (mPAP) of greater than 25 mmHg by RHC. Pulmonary hypertension, however, does occur in patients who seemingly have absent radiographic findings of fibrosis, and several studies have

attempted to provide a better understanding of the incidences of pulmonary hypertension in various stages of sarcoidosis [8••,10]. Sulica *et al.* provided a retrospective survey on 106 patients with sarcoidosis and divided them into two groups by the presence of pulmonary hypertension using Doppler echocardiography: group 1 with pulmonary hypertension ($n = 54$) and group 2 with no pulmonary hypertension ($n = 52$) [10]. The study found 60% of patients with pulmonary hypertension had fibrotic changes on chest radiography, while 40% had no evidence of fibrosis. No radiographic stages predominated in group 2. In another retrospective study, Nunes *et al.* reported similar findings where 31.8% of their patients with sarcoidosis had pulmonary hypertension diagnosed by RHC (mPAP at least 25 mmHg) in the absence of lung fibrosis on chest radiograph [11••]. More recently, Handa *et al.* provided a prospective, observational study of 246 consecutive patients with sarcoidosis in Japan, which investigated the frequency of pulmonary hypertension by Doppler echocardiography [8••]. Pulmonary hypertension was diagnosed if systolic PAP (sPAP) was at least 40 mmHg. Of the 246 patients, 212 (86%) underwent measurement of systolic PAP and 12 (5.7%) had pulmonary hypertension. Furthermore, advanced chest radiographic stages were found to be associated with pulmonary hypertension; however, some patients without radiographic evidence of fibrosis were also demonstrated to have pulmonary hypertension. Future studies will be needed to clarify the role of Doppler echocardiography, specifically with pulmonary hypertension in sarcoidosis.

Pathophysiology

The development of pulmonary hypertension in sarcoidosis is mostly believed to be related to fibrosis and destruction of pulmonary vessels from parenchymal involvement in sarcoidosis. In the absence of fibrotic lung disease, however, granulomatous vasculopathy, extrinsic compression of pulmonary vasculature, increased vasoresponsiveness of the pulmonary vasculature, and diastolic dysfunction from myocardial sarcoidosis have been described and proposed as the cause of pulmonary hypertension (Table 1) [12–15]. In fact, vasculopathy resulting from granulomatous vasculitis or perivascular fibrosis from sarcoidosis have been found in 69–100% of pathological cases [16,17]. All vessels were affected, although most of these changes were more commonly seen in the veins than the arteries. More recently, Nunes *et al.* reported similar findings in five patients with pulmonary hypertension from sarcoidosis who were referred for lung transplantation [11••]. The majority of the patients (80%) had granulomas present in the veins; two of the five patients (40%) had granulomatous arteritis, and one patient had no evidence of granulomatous changes in either veins or arteries. Moreover, occlusive venopathy with intimal fibrosis, recanalization, and evidence of chronic hemosiderosis were seen in all patients, suggesting the presence of venous occlusive disease. While all patients had intimal fibrosis and/or medial hypertrophy in the arteries, plexiform or thrombotic lesions were not observed. The authors suggested that specific vasculopathy, such as pulmonary venous occlusive disease (PVOD), may be the mechanism of nonfibrotic sarcoidosis. Exact mechanisms of pulmonary hypertension in sarcoidosis appear variable and need to be further elucidated in future studies.

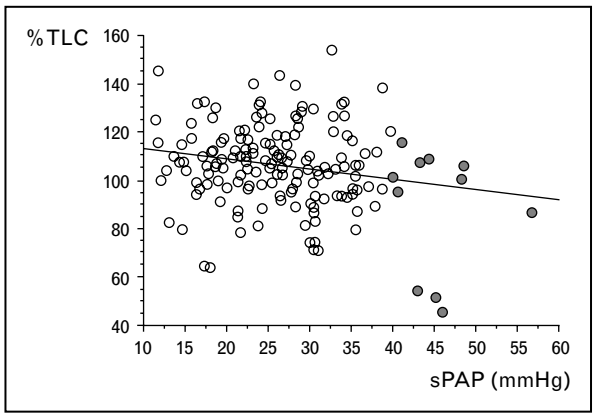
Table 1 Proposed mechanisms for sarcoidosis-associated pulmonary hypertension

Perivascular fibrosis from destruction of lung parenchyma
Increased vasoreactivity
Granulomatous arteriovenopathy
Myocardial dysfunction
Extrinsic compression from enlarged mediastinal adenopathy or fibrosis
Deficiency of nitric oxide synthesis and/or release in the pulmonary vessels
Pulmonary venous occlusive disease

Clinical characteristics

Recent studies aimed to delineate the clinical characteristics of patients with sarcoidosis-associated pulmonary hypertension have confounding results. A series by Handa *et al.* comparing patients with and without pulmonary hypertension revealed male gender, advanced chest radiography, decreased oxygen saturation, and decreased percentage of predicted vital capacity (%VC), predicted forced vital capacity (%FVC), predicted FEV_1 (%FEV_1), predicted functional residual capacity (%FRC), and predicted total lung capacity (%TLC) to be associated with pulmonary hypertension [8••]. In a multivariate logistic regression analysis, %TLC was independently associated with pulmonary hypertension. Furthermore, all subjects with %TLC of less than 60% had pulmonary hypertension (Fig. 1). Sulica *et al.* showed similar findings associated with pulmonary hypertension: advanced chest radiography, %FVC, %FEV_1, forced expiratory flow, and midexpiratory phase [10]. In contrast to the previous study, gender and arterial oxygen saturation did not differ among patients with and without pulmonary hypertension, and percentage of predicted single-breath diffusion capacity of the lung for carbon dioxide (%DLCO) was associated with pulmonary hypertension. Interestingly, spirometric values and 6-min walk distance failed to show an association between hemodynamic measures in sarcoidosis patients with pulmonary hypertension [9]. In this study, however, it is important to note that these patients did not have measurements of %DLCO and they represented a very small subset of patients with sarcoidosis awaiting lung transplantation. With the exception of %DLCO, Nunes *et al.* also failed to show a correlation between hemodynamic measures and lung function tests in advanced sarcoidosis [11••]. The difference in some of

Figure 1 Correlation between systolic pulmonary artery pressure estimated by Doppler echocardiography and % total lung capacity ($n = 165$)



A weak negative correlation was found between systolic pulmonary artery pressure (sPAP) and % total lung capacity (TLC) ($P < 0.05$, $R = -0.16$). Gray circles represent patients with sPAP ≥ 40 mmHg. Analysis was performed with the Spearman rank correlation coefficient. Reproduced from [8••].

these results may be due to the different background of study design and participants or other factors yet to be elucidated. Lastly, clinical evidence of right heart failure was seen in 21–23% of patients with pulmonary hypertension [10,11••].

Radiographic studies

Previous studies have reported relatively low incidences of pulmonary hypertension by RHC in sarcoidosis without radiographic evidence of fibrosis [2,4]. In recent studies that used different methods to diagnose pulmonary hypertension, the majority of the cases indeed showed advanced radiographic evidence of fibrosis [8••,10,11••,14]. Fibrotic changes were absent in many of the cases with pulmonary hypertension in these studies [8••,10,11••]. Compression of pulmonary arteries from enlarged mediastinal lymph nodes has been reported to cause pulmonary hypertension in sarcoidosis [13]; however, the two studies where data were available failed to report these findings in nonfibrotic patients [8••,11••]. Findings from high-resolution computed tomography (HRCT) were investigated in these studies to elucidate an association with pulmonary hypertension and sarcoidosis. In the study from Handa *et al.*, the presence of lymph node enlargement, opacities in lung fields, and thickening of bronchovascular bundles from HRCT when compared with patients with and without pulmonary hypertension did not show statistical significance [8••]. In contrast, Nunes *et al.* were able to demonstrate specific HRCT findings to be significantly increased in their sarcoidosis patients with and without pulmonary hypertension, separated by presence of fibrosis on chest radiography [11••]. The authors showed that patients with nonfibrotic chest radiography were associated with a higher frequency of ground-glass attenuation (85.7% compared with 14.3%; $P < 0.01$), and patients with fibrotic chest radiography had a significantly higher frequency of septal lines (78.6% compared with 46.4%; $P = 0.047$). While these changes may be seen solely from sarcoidosis, the authors proposed the possibility of PVOD from granulomatous venopathy as a cause of pulmonary hypertension.

Diagnostic modalities

Many of the recent studies have used Doppler echocardiography to detect pulmonary hypertension, due to its ease of use and noninvasiveness [8••,10]. The estimated sPAP measured by the Doppler echocardiography has been shown to provide a good estimation of the actual pulmonary artery pressure when compared simultaneously with RHC [18]. In a recent study, Doppler echocardiography showed good agreement with RHC ($P < 0.0001$) in the subset of patients who were started on specific treatment with steroids for sarcoidosis because of pulmonary hypertension [11••].

It is important to note that once the presence of pulmonary hypertension is confirmed, careful exclusion of other known causes of pulmonary hypertension, including appetite suppressants, human immunodeficiency virus infection, thromboembolic disease, portopulmonary hypertension, connective tissue disease, and congenital heart disease, must be excluded by performing careful history-taking, physical examination, serologic tests, and other imaging studies.

Treatment

In general, corticosteroids remain as the mainstay of treatment for sarcoidosis. The usefulness of corticosteroids for pulmonary hypertension in sarcoidosis in the current literature has been confusing, however. Several case studies have reported improvement of pulmonary hypertension [19–21], while some described no improvement [3,13,22]. Most recently, Nunes *et al.* treated 10 sarcoidosis patients (stage 0, $n = 1$; stage II, $n = 4$; stage IV, $n = 5$) complicated by pulmonary hypertension with oral prednisone ranging from 0.5 to 1 mg/kg/day [11••]. One patient received methotrexate 15 mg weekly (patient with stage 0) and another patient received three monthly boluses of cyclophosphamide (patient with stage IV) in combination with prednisone. The therapeutic response was evaluated at 3 or 6 months by Doppler echocardiography. The authors found three patients (stage 0, $n = 1$; stage II, $n = 2$) had improvement in pulmonary hypertension as defined by sPAP reduction of more than 20% from baseline. All stage IV sarcoidosis patients failed to show an improvement of pulmonary hypertension. The three responders were continued on low-dose corticosteroids and were reported to have

a normal Doppler echocardiogram at 12, 14, and 36 months, respectively.

Many vasodilator treatments have been proven to be effective in various types of pulmonary hypertension although, to date, available data are limited in sarcoidosis-associated pulmonary hypertension. Nunes and colleagues reported that none of their patients had acute vasodilator response with either inhaled nitric oxide (iNO) or intravenous epoprostenol [11••]. Nine out of 22 patients, however, did not have this test performed. In a prospective observational study to assess the vasoresponsiveness of sarcoidosis-associated pulmonary hypertension, Preston *et al.* performed RHC in eight patients with moderate to severe pulmonary hypertension [14]. Patients were assessed to be vasoresponsive if more than a 20% reduction was seen in pulmonary vascular resistance (PVR) with inhaled iNO, intravenous epoprostenol, and/or calcium-channel blockers. Seven of eight patients receiving iNO, four of six patients receiving epoprostenol, and two of five patients receiving calcium-channel blockers demonstrated vasoresponsiveness. In addition, iNO showed greater reduction in mPAP and PVR when compared with intravenous epoprostenol. Five of eight patients received long-term treatment with iNO (one patient also received intravenous epoprostenol) and all patients showed significant improvement in a 6-min walk test. The authors proposed that relative deficiency of nitric oxide synthesis and/or release in the pulmonary vasculature may cause pulmonary hypertension in sarcoidosis. Most recently, Fisher *et al.* reported a retrospective study on the effect of intravenous epoprostenol in seven patients with sarcoidosis-associated pulmonary hypertension [23••]. The authors reported six of the seven patients demonstrated vasoresponsiveness (greater than 25% reduction in PVR), which was in concert with Preston *et al.* In addition, the authors noted that the mean decrease in PVR was greater than in the study from Preston *et al.* and suggested that sarcoidosis-associated pulmonary hypertension may be responsive to epoprostenol. Five of their six patients continued on to be treated with long-term intravenous epoprostenol and all patients showed improvement by one to two functional New York Heart Association (NYHA)/World Health Association (WHO) classes. Three of their five patients were treated concomitantly with corticosteroids, however, and it is uncertain to what degree this may have affected pulmonary hypertension from sarcoidosis. Lastly, bosentan (an endothelin receptor antagonist) was reported to be useful in one case of sarcoidosis-associated pulmonary hypertension [24].

Prognosis

The presence of pulmonary hypertension in general adversely affects the prognosis of interstitial lung diseases [25], although data in sarcoidosis are limited. Shorr *et al.* provided a retrospective cohort study of 405 patients with sarcoidosis listed for lung transplantation [26]. The investigators found survivors had significantly lower mPAP than the nonsurvivors, which was predictive of mortality (31.7 ± 11.5 mmHg compared with 41.1 ± 14.4 mmHg; $P < 0.01$). The mPAP was not affected by differences in cardiac index and pulmonary capillary wedge pressure among survivors and nonsurvivors. Further studies are needed to clarify the significance of pulmonary hypertension in various stages of sarcoidosis in respect to its treatment and referral for lung transplantation.

Conclusion

Pulmonary hypertension is not infrequently observed in sarcoidosis. It most commonly is seen with the presence of fibrotic changes on chest radiography, although it does occur in various stages of sarcoidosis. Destruction of lung parenchyma, granulomatous vasculitis, lymphadenopathy, increased vasoresponsiveness, and myocardial involvement are some of the proposed mechanisms. Doppler echocardiography may be a useful screening tool. RHC should be used to confirm the diagnosis, and other known causes of pulmonary hypertension must be excluded. Response to corticosteroids is variable and other vasodilatory modalities have been found to be promising. Further studies are awaited to better understand the significance of pulmonary hypertension in sarcoidosis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 468).

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