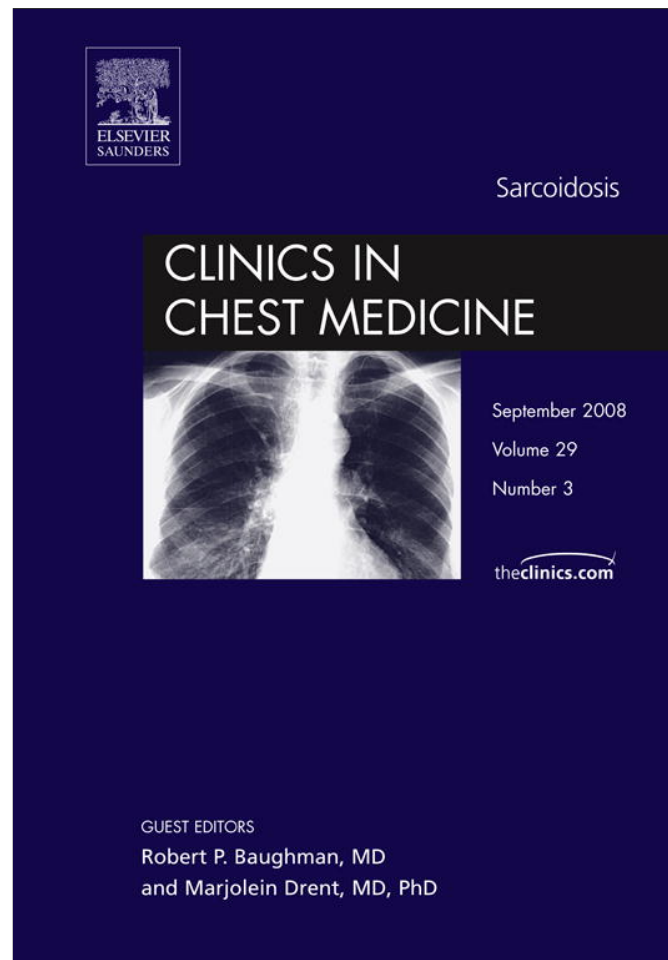


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Pulmonary Hypertension Caused by Sarcoidosis

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...the lungs, heart, and circulation should be thought of as a single apparatus for the transfer of oxygen and carbon dioxide between the atmosphere and the working tissues [1].

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) higher than 25 mm Hg at rest or 30 mm Hg with exercise [2,3]. The disease can be idiopathic (familial or sporadic) or associated with several disorders that ultimately induce remodeling of the pulmonary circulation and result in a permanent elevation of the pulmonary vascular resistance. Idiopathic pulmonary arterial hypertension is a rare disease affecting 6 to 15 individuals per million [4,5]; nonidiopathic forms are considered to be much more common, particularly in patients with chronic respiratory disorders.

Sarcoidosis is a multisystem granulomatous disorder that affects the lungs in 90% to 95% of patients [6]. The disease has an estimated incidence of 10 to 35 cases per 100,000 people in the United States, with an overall mortality of 1% to 5% [7,8]. Initially considered a rare manifestation of long-standing sarcoidosis, sarcoidosis-associated pulmonary hypertension (SAPH) is now being recognized as an important complication that can result in significant morbidity and

mortality. Although SAPH occurs more frequently in patients with evidence of advanced parenchymal fibrosis, it can also be present despite no apparently significant interstitial lung disease. Severe untreated pulmonary arterial hypertension carries an extremely poor prognosis and is associated with higher mortality in patients with interstitial lung diseases and sarcoidosis [9,10]. Early diagnosis and consideration of treatment options may be keys to improve patient outcomes.

History

The modern history of sarcoidosis probably began in 1898, when Hutchinson [11], a London dermatologist, described a case of a patient with “Mortimer’s malady,” allegedly a patient with evidence of cutaneous disease. In the initial description, the disease was thought to be a form of cutaneous lupus. Sarcoidosis was recognized as a distinct pathologic entity a year later, when Boeck [12] described the histology of the “sarkoid” granulomas. By 1929, Bernstein [13] had described cardiopulmonary system involvement by sarcoidosis, the same year that Forssman [14] revolutionized the study of cardiac and pulmonary hemodynamics by demonstrating that cardiac catheterization was possible in human beings.

Between 1930 and 1950, several clinical, radiologic, and pathologic studies established that the involvement of the lung was common in patients with sarcoidosis [15–17]. Furthermore, right ventricular failure was recognized as an explanation for dyspnea, cyanosis, and death in patients with advanced lung disease. In 1948, for example,

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Mallory [18] described six patients with granulomatous pneumonitis consistent with sarcoidosis and parenchymal fibrosis. In this article, the investigator presented evidence of invasion and thrombosis of the pulmonary vasculature. Two years later, the clinical relevance of these findings was suggested by Austrian [19], who noted elevated pulmonary artery pressures in two patients with sarcoidosis. In the following decades, several small cohorts of patients with SAPH began to elucidate the frequency, pathophysiology, and prognosis of pulmonary hypertension in sarcoidosis patients. In the past decade, with the advent of specific medications for treatment of pulmonary arterial hypertension (PAH), interest in SAPH has burgeoned dramatically.

Epidemiology

The actual prevalence of SAPH has not been established. In patients with significant parenchymal lung disease, the disease was historically thought to be rare, with involvement of the pulmonary vasculature in less than 5% of the cases. Unfortunately, most of the early cohorts were identified retrospectively based on autopsies or case series of patients with clinically diagnosed right heart failure. For example, Mayock and colleagues [20] performed a review of 145 patients with sarcoidosis from nine published series, and found only six (4.1%) patients with evidence of pulmonary hypertension and cor pulmonale. Similarly, a series of 320 autopsies in Japanese patients with sarcoidosis revealed 18 cases of cor pulmonale (5.6%) [21]. No hemodynamic measurements were made in any of these reports.

It is clear that the measurement technique and the entry criteria for performing screening influence the ascertained prevalence of SAPH. It is also probable that ethnicity affects development of the disease. Thus, estimates of prevalence have been widely variable (Table 1). Separate reviews of right heart catheterization (RHC) results among 104 subjects in Italy and Poland suggested that the prevalence of resting PH is 6% to 23% [22–24]. Higher chest radiograph (CXR) stage was associated with increased risk in all three series, with approximately one-half of those with stage III CXR demonstrating at least mild elevations of mPAP. When the screening is limited to patients with more advanced parenchymal disease, the prevalence is substantially higher. Emirgil and colleagues [25] reported 15 patients with

sarcoid-related pulmonary fibrosis who had RHC, of whom 10 (67%) had evidence of PH at rest. In a retrospective evaluation of 106 subjects with sarcoidosis, Sulica and colleagues [26] found that 51% of the subjects with a pre-existing clinical indication for performing echocardiography had evidence of PH by transthoracic echocardiography (TTE). In this study, the majority of subjects also had radiographic evidence of advanced disease. Finally, in a cohort of 363 sarcoidosis patients listed for lung transplantation between 1995 and 2002, 74% of the group who had RHC had some form of PH; approximately one third of the patients had severe PH (mPAP \geq 40 mm Hg) [27].

In a prospective observational study using TTE, 246 Japanese patients with predominantly chronic sarcoidosis but good overall lung function were evaluated at a referral center [28]. Of the 212 patients with adequate echocardiograms, only 12 (5.7%) had PH (defined as systolic PAP \geq 40 mm Hg). Restrictive pulmonary physiology was the only independent risk factor for SAPH. In contrast, when only patients with unexplained dyspnea are studied, the prevalence appears to be higher. For example a recent single-center retrospective review of 53 subjects with sarcoidosis found that 25 out of 53 (47%) of the subjects with persistent dyspnea had a mean PAP greater than or equal to 25 mm Hg [29]. Importantly, only 69% of the subjects in this study had evidence of CXR stage III or IV sarcoidosis. A recent review of Danish patients prospectively characterized with right heart catheterization at the time of referral for lung transplantation reported that 79% (19 out of 24 subjects) had a mPAP greater than 25 mm Hg [30]. These subjects had severe pulmonary sarcoidosis, as evidenced by chronicity (median duration 11 years), CXR stage (75% with stage IV) and forced vital capacity (FVC) (median 41% predicted).

A subgroup of patients with sarcoidosis appears to have excessive elevations of pulmonary arterial pressures during exercise. In an Italian cohort of 62 sarcoidosis subjects published more than two decades ago, 10 subjects with normal resting hemodynamics exhibited exercise-induced PH [22]. Two subsequent studies from the same group in Poland demonstrated similar findings. In the first study, 3 of 10 subjects with stage II CXR developed PA pressure elevation of 20 mm Hg above baseline, and all 10 subjects with stage III CXR had increases greater than 10 mm Hg [23]. Some of the subjects demonstrated very

Table 1
Ascertained prevalence of sarcoidosis-associated pulmonary hypertension in several populations

Author	Location	Population	Number	Method	Prevalence (%)
Handa [28]	Single center, Japan	Prospective study of unselected clinic patients	212 ^a	TTE	5.7
Rizzato [22]	Single center, Italy	Unspecified patients who had RHC	50	RHC	6 ^b
Gluskowski [24]	Single center, Poland	Prospective study of CXR stage II and III	24	RHC	12.5 ^b
Gluskowski [23]	Single center, Poland	Unspecified patients who had RHC	30	RHC	23
Baughman [29]	Single center, United States	Subjects with dyspnea disproportionate to PFTs	53	RHC	47
Sulica [26]	Single center, United States	Retrospective review of patients who had TTE for clinical indications	106	TTE	51
Emirgil [25]	Single center, United States	Series of severe sarcoidosis patients	15	RHC	67
Shorr [27]	UNOS database, United States	All lung transplant candidates who also had RHC	363	RHC	74 ^c
Milman [30]	Single center, Denmark	All lung transplant candidates who also had RHC	24	RHC	79

Abbreviations: PFT, pulmonary function test; RHC, right heart catheterization; TTE, transthoracic echocardiography; UNOS, United Network for Organ Sharing.

^a 34 out of 246 subjects had no evaluable tricuspid regurgitation jet.

^b Additional 20% to 33% of subjects had exercise-induced PH (mPAP \geq 30 mm Hg).

^c 36% had severe PH (mPAP > 40 mm Hg).

dramatic (50 mm Hg–100 mm Hg) elevations of mPAP with exercise, despite normal resting PA pressures. A prospective follow-up study of unselected patients with stage II or III CXR, persistence of disease for at least 6 months, and mild average restriction (mean FVC $82 \pm 17\%$ predicted) revealed an even higher prevalence [24]. Based on a threshold of 10-mm Hg increase in mPAP with exercise, 18 of 24 subjects demonstrated exercise-induced SAPH. Finally, using multiple-uptake gated acquisition scans in subjects with unremarkable echocardiograms, Baughman and colleagues [31] noted 12 of 14 had a significant drop in the right ventricular ejection fraction associated with exercise and attributed to the development of PH.

Most of the available studies have shown an average age at the time of diagnosis of 40 to 60 years. In the United States, SAPH appears to be more common in females and African Americans, but this finding reflects only the overall

demographic trends for sarcoidosis, and neither gender nor race has been independently associated with the disease. In the Japanese experience, male gender was associated with SAPH in univariate analysis, although the total number was small [28]. Finally, although some reports have suggested that the incidence of SAPH may be even higher when including hemodynamic evaluations with exercise, the prevalence of exercise-induced SAPH in larger cohorts of unselected sarcoidosis patients is currently unknown.

In conclusion, currently, ascertainment bias has confounded efforts to accurately assess the true prevalence of PH in patients with sarcoidosis. Almost all the published data are derived from referral centers, and most of the data are from selected patient populations within these institutions. Translating the findings in the Japanese and European centers to the United States experience is also problematic, because ethnicity substantially influences sarcoidosis phenotype. For example, in

Japan cardiac involvement is extremely common and could contribute to SAPH. In general, the lack of prospective surveys, reliance on echocardiography, and selection bias have led to poorly generalizable estimation of the overall prevalence.

Pathophysiology

The World Health Organization (WHO) currently classifies pulmonary hypertension into five groups, with sarcoidosis included as Class V (miscellaneous) [32]. Compared with idiopathic pulmonary fibrosis, where pulmonary hypertension is probably caused by fibrotic destruction of the distal capillary bed, several mechanisms may be relevant in SAPH. Thus, it is not incorrect to state that the mechanisms for SAPH could be grouped into all five WHO categories [33].

The granulomatous inflammation in sarcoidosis involves the lung in a lymphatic distribution. This distribution places the granulomas adjacent to the pulmonary artery in the bronchovascular area and to the veins that run within the interlobular septae (Fig. 1). Because of this proximity, the pulmonary arteries are commonly involved by granulomas (Fig. 2A) or giant cells (see Fig. 2B) in pulmonary sarcoidosis. This vascular involvement may involve the adventitia, media, or intima of the pulmonary arteries. Pathologic studies have shown that 69% to 100% of subjects have invasion of the vessel walls by granulomas that result in occlusive changes, perivascular fibrosis, or granulomatous pulmonary angiitis [34,35]. Similarly, scarring and occlusion by granulomas and giant cells may occur in the pulmonary veins (Fig. 3), mimicking pulmonary veno-occlusive disease from a hemodynamic

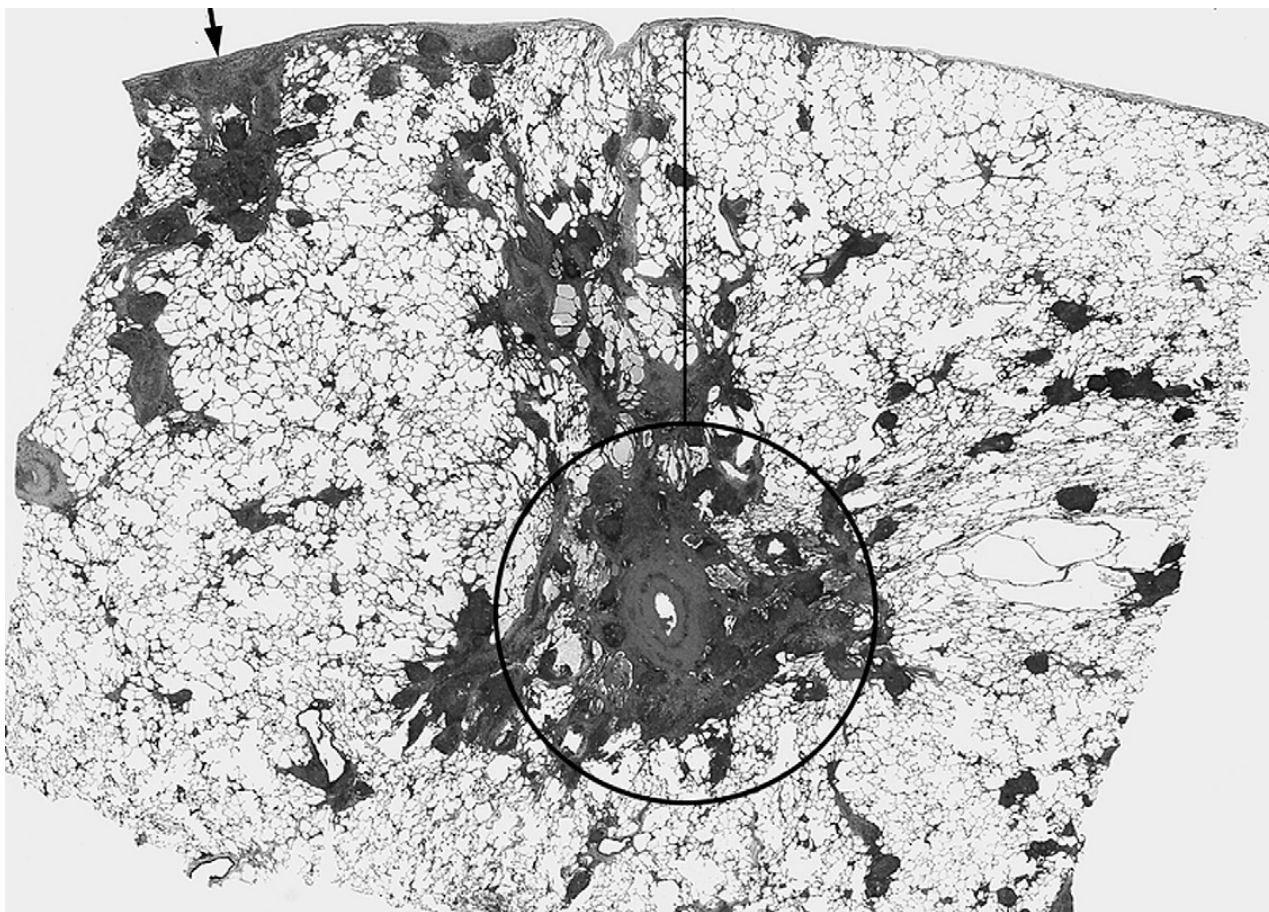


Fig. 1. Distribution of granulomas in pulmonary sarcoidosis. Sarcoidosis granulomas are found in a lymphatic distribution, including surrounding the bronchovascular bundle (circled area), the interlobular septae which also contain the pulmonary veins (adjacent to the line), and the subpleural area (arrow). Because of this anatomic orientation, granulomatous inflammation frequently encroaches on the vascular structures, even in the absence of overt fibrosis or vascular wall inflammation (Hematoxylin and eosin stain). (From Farver CF. Sarcoidosis. In: Tomaszewski JF, Cagle PT, Farver CF, et al, editors. Dail and Hammar's pulmonary pathology. New York: Springer-Verlag; 2008; with permission.)

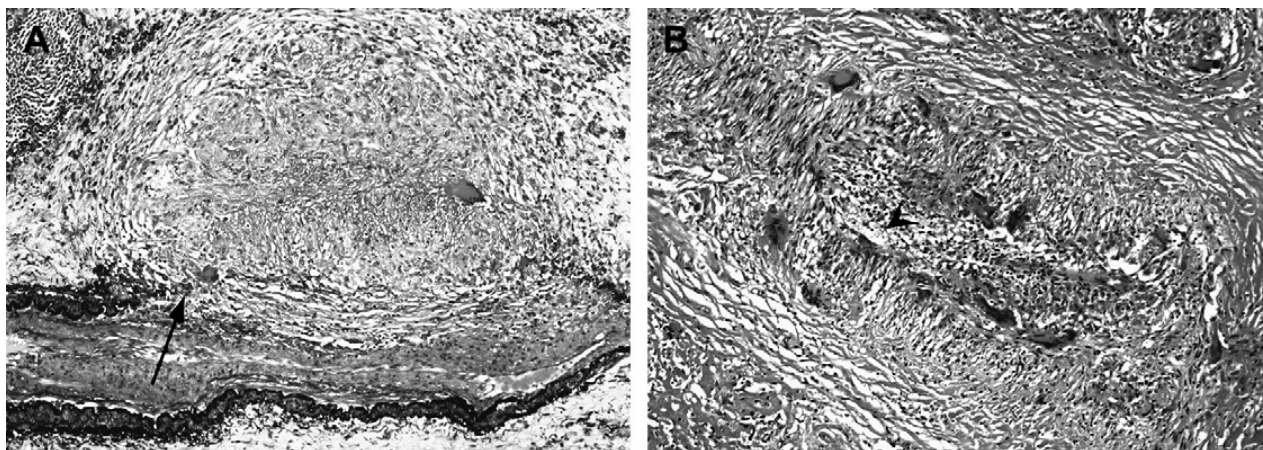


Fig. 2. Granulomatous arteritis in sarcoidosis. (A) Movat pentachrome stain showing granulomas obliterating the internal and external elastic laminae and smooth muscle (*arrow*) of medium size artery. There is secondary intimal fibroplasia seen in the center of the artery. (Movat pentachrome stain) (B) In some cases, only giant cells and mononuclear cell infiltrates may be seen in sarcoidosis-associated arteritis. Arrowhead indicates the vascular lumen. Numerous giant cells may be seen in the vessel wall (Hematoxylin and eosin).

standpoint [34–37]. Obliteration of these vessels by either active granulomatous inflammation and by fibrosis affords one mechanism for development of pulmonary hypertension in patients with advanced radiographic stages. Furthermore, this preferential location of the granulomas adjacent to these vessels may explain the presence of SAPH, even in patients with little apparent radiologic involvement of the lung parenchyma.

Although the hypothesis that SAPH results from fibrotic or granulomatous obliteration of the pulmonary microvasculature in advanced disease fits most patients, this may not fully explain why

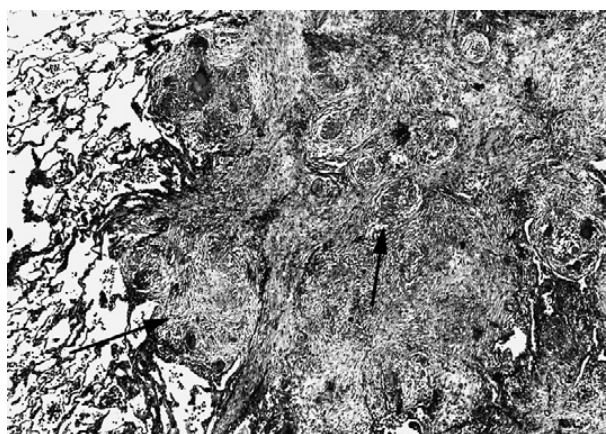


Fig. 3. Obliteration of pulmonary venous drainage by exuberant granuloma formation. Movat pentachrome stain of an interlobular septum showing extensive fibrosis and obliteration of the venous structures by granulomas. Perivenular distribution of granulomas is typical in sarcoidosis. Arrows indicate compressive granulomas (Movat pentachrome stain).

some individuals with no radiographic evidence of interstitial lung disease develop PH [38,39]. In a recent retrospective review of 22 patients with SAPH, 32% of the patients developed pulmonary hypertension in the absence of overt parenchymal fibrosis [40]. Fifty percent of the patients had an elevation in the mPAP that was considered out of proportion to the changes in lung mechanics [40]. An isolated case study described the presence of plexiform lesions in patients with SAPH, but the significance of this observation is unclear because these lesions have not been observed in larger series of SAPH [40,41]. Several reports suggest other possible mechanisms, including extrinsic compression of pulmonary arteries by enlarged hilar lymph nodes (Fig. 4) [40,42,43], diastolic or systolic dysfunction from myocardial sarcoidosis [44,45], and hypoxic vasoconstriction. Obstructive sleep apnea, which is common in sarcoidosis patients [46], may also contribute to the development of elevated pulmonary resistance. Finally, although the possibility of isolated vaso-reactivity has been deemed to be a sufficient explanation for some cases of SAPH [47], this concept continues to be mainly hypothetical in the absence of corresponding pathologic data demonstrating that there is not granulomatous inflammation in these subjects.

Endothelin has been implicated in the development of idiopathic pulmonary hypertension. Endothelin-1 (ET-1) is found in abundance in the lung, where it is produced by smooth muscle, endothelial, and airway epithelial cells [48]. Binding of ET-1 with its receptor, ET_A, induces

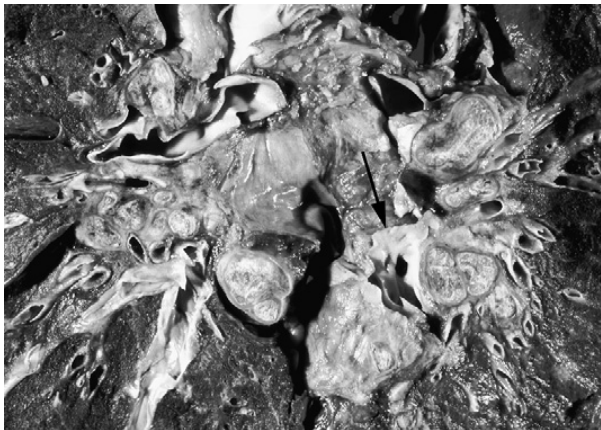


Fig. 4. Compression of central pulmonary vascular structures by bulky lymph nodes. Coronal section of thorax of post-mortem specimen from a patient who died from end-stage SAPH. There is extensive hilar compression of the main pulmonary arteries. Arrow denotes the left lower lobe pulmonary artery, which is subtotally occluded by extrinsic compression of calcified lymph nodes that are present throughout the mediastinum. (From Farver CF. Sarcoidosis. In: Tomashefski JF, Cagle PT, Farver CF, et al, editors. Dail and Hammar's pulmonary pathology. New York: Springer-Verlag; 2008; with permission.)

significant pulmonary vasoconstriction; in addition, ET-1 promotes proliferation of smooth muscle cells and fibroblasts, and in animal models has been linked to development of pulmonary fibrosis [49,50]. Urinary and plasma levels of ET-1 are elevated in patients with sarcoidosis, and in some instances treatment with corticosteroids is associated with a normalization of the plasma ET-1 levels [51]. Similarly, ET-1 levels appear to be elevated in bronchoalveolar lavage (BAL) fluid from patients with sarcoidosis, systemic sclerosis, and idiopathic pulmonary fibrosis [52]. A study that limited BAL analysis to 22 subjects with sarcoidosis found approximately 25% had elevated levels of ET-1 [53]. Immunostaining in these patients suggested that alveolar macrophages may be an important source for ET-1. However, it is currently unknown whether ET-1 is only a biomarker for the severity of inflammation or an important mediator of vascular remodeling in sarcoidosis.

Clinical presentation

Pulmonary hypertension should be suspected in any sarcoidosis patient with dyspnea, hypoxemia, or clinical evidence suggesting right heart failure, particularly if symptoms appear to be out of proportion to the degree of parenchymal lung

disease. Unfortunately, these symptoms are often present in patients without PH. Other considerations when patients present with unexplained dyspnea or exercise limitation include myopathy (skeletal or respiratory muscle), large airway obstruction, occult cardiac disease, depression, and anemia [54–56].

The most common symptom in patients with SAPH is progressive dyspnea on exertion. Other common complaints include cough, chest pain, palpitations, and symptoms suggesting right heart failure, such as lower extremity edema and syncope. Only the signs of right heart failure are independent predictors of elevated right-sided pressures, but their sensitivity is low. In a retrospective analysis of 106 patients who had echocardiography for clinical reasons, only 21% of the patients with SAPH had pretest evidence of right heart failure (elevated jugular venous pressure, lower extremity edema or right ventricular heave) compared with none of the patients without pulmonary hypertension [26].

Other rare reported presentations of SAPH include sudden death because of compression of large pulmonary arteries [57], main pulmonary vein occlusion caused by intravascular sarcoidosis [58], and combined SAPH and portal hypertension [59]. Although there are case reports of SAPH simulating pulmonary veno-occlusive disease (PVOD) [36,37,40,60], the authors believe that this simply represents the usual distribution of granulomatous inflammation, as the pulmonary venous drainage is closely approximated with the lymphatics. The histopathology of the reported sarcoid-induced PVOD more closely resembles burned-out sarcoidosis than actual PVOD (see Fig. 3). The term PVOD associated with sarcoidosis therefore represents a misnomer and should be avoided.

Imaging studies

Pulmonary hypertension may be present despite the absence of overt fibrotic changes on chest imaging, but the great majority of patients with SAPH appear to have stage III or IV chest radiographs. In an initial study of subjects with chronic cor pulmonale and sarcoidosis, 30% were found to have only perihilar infiltrates [61]. Subsequent studies have confirmed that fibrosis is present in approximately two thirds of subjects, and the CXR may be normal in 9% to 10% [26,40]. High resolution computed tomography of the chest may suggest additional mechanisms. For

example, 3 of 14 (21%) of a series of SAPH subjects with pulmonary fibrosis also had extrinsic compression of large pulmonary arteries [40]. Overall, however, specific high-resolution chest CT findings are not generally helpful for predicting the presence versus absence of SAPH [28].

A common clinical strategy is to measure the main pulmonary artery diameter, the ratio of the pulmonary artery to ascending aorta, or the ratio of segmental artery to bronchus to detect the presence of PH in patients with parenchymal lung disease. Unfortunately, this strategy appears to be unreliable in pulmonary fibrosis [62] and sarcoidosis [29].

Pulmonary function tests and oxygenation

Depending on the degree of parenchymal involvement, patients with SAPH typically exhibit hypoxemia, decreased carbon monoxide diffusing capacity (DLCO), and restrictive physiology. Most patients with SAPH require at least some supplemental oxygen; among lung transplant candidates, a requirement for 3 L or more of supplemental oxygen more than doubled the risk of PH [27]. In the same cohort, 93.4% of the subjects with mPAP greater than 40 mm Hg required at least some supplemental oxygen. In the experience at Mt. Sinai hospital in New York, all patients identified with SAPH by TTE exhibited exercise-induced desaturation [26]. Based on these reports, it can be concluded that the absence of desaturation below 90% with exercise suggests a low likelihood of significant SAPH.

In radiographic stages 0 to 3, SAPH patients classically exhibit a mild restrictive defect with a disproportionate decrease in DLCO. In the Mt. Sinai series, of the 46 subjects without pulmonary fibrosis, the ratio of percent predicted FVC to percent predicted DLCO was 1.9 plus or minus 1.1 in SAPH versus 1.3 plus or minus 0.6 in subjects without PH [26]. The scleroderma experience suggests that serial decline in DLCO despite FVC greater than 70% predicted portends the development of pulmonary hypertension [63]; the utility of serial PFT data has not been reported in SAPH. In patients with pulmonary fibrosis, there is characteristically a marked reduction in FVC, forced expiratory volume in the first second of expiration, DLCO, and PaO₂. However, these abnormalities may be more pronounced in SAPH, compared with patients without pulmonary hypertension [26,40]. It is important to recognize that pulmonary function tests, while more

severely impaired in patients with SAPH [28], may not correlate well with measured pulmonary artery pressures [29,40].

Finally, the 6-minute walk test is useful only when it is normal, as there are multiple reasons for abnormal tests in sarcoidosis patients. It is probably most helpful for serial measurements of cardiopulmonary function. A prospective study of 142 consecutive patients seen at a tertiary center evaluated the utility of the 6-minute walk [64]. The 14 patients with proven SAPH had a shorter 6-minute walk distance (median, 280 m; range, 61 to 404) than those without proven SAPH (median, 411 m; range, 46 to 747; $P < .0001$). Although the lowest oxygen saturation was correlated with 6-minute walk distance, the presence of PH was not an independent risk factor in this series.

Hemodynamics

The gold standard for the diagnosis of SAPH is direct measurement of the pulmonary artery pressures with RHC. Pulmonary hypertension is present when the mPAP exceeds 25 mm Hg at rest or 30 mm Hg with exercise. Measurement of the transpulmonary gradient (the difference between the mPAP and the pulmonary capillary wedge pressure or PCWP) is useful to exclude left ventricular disease associated with cardiac sarcoidosis or other causes. However, because left ventricular end-diastolic volume may be impaired by septal flattening in severe pulmonary hypertension, it is mandatory to correlate PCWP measurements with echocardiographic assessment of interventricular dependence.

The importance of RHC was emphasized by a recent series of 53 subjects who had both echocardiography and RHC [29]. In these subjects, TTE was unable to establish the diagnosis of elevated right ventricular systolic pressure (RVSP) in 16 out of 53 (30%) of the subjects with increased pulmonary artery pressures. In addition, 24% of the subjects with elevated pulmonary pressures had a PCWP greater than 20 mm Hg. These findings suggest that intrinsic cardiac disease (eg, diastolic left ventricular dysfunction) should be excluded before diagnosing SAPH. Despite the presence of increased PAP with exercise in a subset of sarcoidosis patients, the role of routine exercise testing during RHC is unknown.

Echocardiography

Doppler echocardiography is frequently used to evaluate patients with pulmonary hypertension.

Although studies have reported that Doppler analysis of the tricuspid regurgitant velocity by echocardiography may be used to estimate pulmonary pressures [65], many patients with PH have no evidence of tricuspid regurgitation. When useful data are obtained, the sensitivity and specificity of TTE for diagnosing any degree of pulmonary hypertension has varied from 0.69 to 1.0 and 0.68 to 0.98, respectively, in idiopathic PH; correlation coefficients between echocardiography and RHC are generally robust for PAP between 50 mm Hg and 100 mm Hg [66–69]. These data have generated enthusiasm among clinicians for use of TTE as a screening tool when PH is suspected.

However, patients with parenchymal lung disease pose a challenge, because the presence of lung disease may obscure echocardiographic windows and render accurate estimation of PAP difficult [70]. In these patients, the correlation between RVSP and PAP is highly variable, and TTE may underestimate peak right ventricular pressures, particularly in patients with severe PH [71,72]. In a large study that included 374 transplant candidates, estimation of the RVSP was possible in only 44% [73]. Moreover, although the overall correlation between echocardiogram-estimated systolic PAP and RHC was moderately good ($r = 0.69$), approximately half of the pressure estimations were inaccurate by more than 10 mm Hg. Echocardiographic estimation of PAP thus appears to have inadequate positive and negative predictive value in patients with advanced lung disease. A more recent single-center review of patients with sarcoidosis who had RHC when persistent dyspnea was deemed disproportionate to PFT abnormalities showed a similar correlation between TTE and RHC ($r = 0.79$) [29]. Nevertheless, the investigators reported that seven out of nine patients for whom RVSP could not be assessed by TTE had SAPH confirmed by pulmonary artery catheterization.

In patients with SAPH, echocardiography can establish the presence of other cardiac causes of dyspnea, such as left ventricular systolic or diastolic dysfunction, valvular abnormalities, pericardial effusion, or the presence of right to left shunts. In the absence of tricuspid regurgitation, the diagnosis of SAPH should be suspected when there are echocardiographic findings of right ventricular pressure overload, including right ventricular hypertrophy, systolic dysfunction, flattening of the interventricular septum, or an abnormal ratio of the interventricular septum to

posterior left ventricular wall thickness [74]. The absence of these findings, nevertheless, does not exclude the possibility of SAPH [22], and therefore RHC is currently still considered necessary for definitive diagnosis.

Management

The optimal management strategy for pulmonary hypertension associated with sarcoidosis is unknown. Treatment has typically involved use of systemic anti-inflammatory medications, anticoagulants, pulmonary vasodilators, endothelin receptor antagonists, and supplemental oxygen. The available literature regarding these therapeutic strategies is limited to small cohort studies, retrospective analyses, and case reports.

Immunomodulating medications

Theoretically, anti-inflammatory medications could have a major impact on some patients with SAPH [75,76]. The results of the available trials, however, have not demonstrated consistent benefits from use of immunosuppressants in SAPH. In a small study of 24 subjects, the effects of corticosteroid treatment on pulmonary hemodynamics were evaluated by RHC [24]. The subjects were treated with an initial dose of 60 mg per day of prednisolone, tapered to 25 mg at 6 months, and continued for 1 year. Only two of four subjects with PH at rest had significant improvement of pulmonary pressures after 1 year of therapy. Interestingly, although almost all patients had improvement in pulmonary function, elevated exercise-induced pulmonary pressures decreased in only half of the group. Other investigators have noted similar results, with hemodynamic improvements noted in 0% to 30% after corticosteroid treatment [29,40].

Although these results suggest that corticosteroids may be helpful in a subset of patients with SAPH, it appears that the benefits are difficult to predict. Based on the available data, corticosteroids or other immunomodulators may be most useful for patients with evidence of active inflammation or compression of central vascular structures by bulky lymph nodes. The role of steroids in patients with established parenchymal fibrosis is less clear. To the authors' knowledge, there are no available studies that have systematically addressed the use of other immune modulating agents in SAPH.

Pulmonary vasodilators

Currently available vasodilators include prostacyclin analogs, calcium channel blockers, and phosphodiesterase inhibitors. Use of these agents in patients with pulmonary fibrosis has been controversial, given concerns for severe hypoxemia or pulmonary edema caused by intrapulmonary shunting [77–79]. Because SAPH is often caused by fibrosis with end-stage pulmonary microcirculatory “fixed” abnormalities, it has also been unclear whether these agents have any beneficial impact on the pulmonary vascular resistance.

To address this issue, Preston and colleagues [44] treated eight subjects with SAPH using intravenous epoprostenol (EPO), inhaled nitric oxide (iNO), or calcium channel blockers (Table 2). All subjects had advanced sarcoidosis (CXR stages III and IV) and severe pulmonary hypertension (average mPAP, 55 mm Hg). The acute response in mPAP was greater for those receiving iNO (decrease of $18 \pm 4\%$) compared with patients that received EPO at doses of 2 ng/kg to 8 ng/kg per minute ($6 \pm 2\%$ decrease). No subjects had an acute response with nifedipine. Five subjects continued treatment with iNO at 100 ppm to 200 ppm and one received iNO plus EPO; follow-up showed that patients were able to maintain stable functional class, although both mPAP and pulmonary vascular resistance (PVR) tended to increase. Other reports that included patients with sarcoidosis and parenchymal fibrosis who received low dose epoprostenol therapy reported favorable hemodynamic responses without worsening hypoxemia [80]. A more recent study that included two subjects with severe SAPH reported an excellent initial hemodynamic response (40% decrease in mPAP) in one subject [29].

Fatal pulmonary edema has been reported after initiation of intravenous prostacyclin agents in patients with pulmonary hypertension associated with PVOD or other fibrotic lung diseases, such as scleroderma [81,82]. Fisher and colleagues [83] reported one patient out of seven who developed non-cardiogenic pulmonary edema after treatment with epoprostenol. Given that patients with SAPH may have significant impairment of the pulmonary venous system, therapy with pulmonary vasodilators should be started with caution. However, the available literature does not indicate that patients with SAPH have an excessively elevated risk of developing this complication.

Little is known about the use of other inhaled agents in SAPH. In the article by Nunes and colleagues [40], one patient with SAPH and pulmonary fibrosis was treated with inhaled iloprost without any clinical benefit.

In the authors' center, eight patients received treatment with prostanoid agents alone or in combination with endothelin antagonists, in addition to standard therapy with immunosuppressants [84]. Despite a high proportion of patients with evidence of severe parenchymal scarring (63%), none experienced episodes of vasodilator-induced shunting. Significant short-term benefits of vasoactive therapy were observed among most of the patients, especially those with preserved vital capacity ($FVC \geq 70\%$ of predicted). However, progression to lung transplant or death over 12 to 18 months was extremely common.

The largest published long-term experience with prostanoids, however, suggests that circumspection is warranted before use of these agents [83]. In this study, which included mainly patients with severe restrictive physiology, six of seven subjects demonstrated an acute vasodilator response to low doses of EPO (75% had $\geq 25\%$ drop in PVR). Six subjects were subsequently treated with EPO and one subject received treatment with subcutaneous treprostinil. However, one subject developed pulmonary edema and another subject died hours after administration of EPO. After a mean follow-up of 29 months, only four subjects enjoyed transplant-free survival, with continued EPO dose titration (mean dose 55 ng/kg per minute).

In summary, most of the available literature regarding the use of pulmonary vasodilators includes patients with advanced stage sarcoidosis. The experience is greatest with the use of epoprostenol. In many cases, it has been used as a palliative measure or a “bridge” to transplantation. The limited evidence suggests that some patients with SAPH may respond well to prostanoid therapy, but that a few individuals do develop pulmonary edema. For the remainder, the therapy appears to be well tolerated, despite use of high doses, and long-term outcomes may be improved. It is still unknown if the potential benefits from prostanoids differ between patients with or without advanced parenchymal disease.

Endothelin antagonists

There is some evidence that endothelin may play a role in the pathogenesis of SAPH.

Table 2
Reports of vasodilator therapy in sarcoidosis

	Number treated	FVC% ^a	mPAP ^a (mm Hg)	Treatment (number)	Follow up (mo)	Outcome	Observations
Preston [44]	8	48	55	iNO (5) CCB (2)	6–24	5 out of 8 subjects died in 0–18 months	Acute vasodilator response in 7 out of 8 subjects
Culver [84]	11	57	76 ^b	EPO (4) EPO + Bos (4) Bos (3)	2–30	8 out of 11 subjects died or required lung transplant Short-term hemodynamic or functional benefit observed in all subjects	Hemodynamic response most evident in patients with FVC ≥70%
Foley [85]	1	64	55	Bosentan	24	mPAP decreased to 23 mm Hg at 6 months	Improved functional class (NYHA IV to II)
Sharma [86]	1	40	78 ^c	Bosentan	12	Improved 6-minute walk distance	Improved functional class (NYHA IV to II)
Nunes [40]	1	N/A	N/A	Iloprost (1)	4	Died awaiting lung transplant	—
Baughman [29]	7	64	83	EPO (1) EPO + Bos (1) Bos (4) CCB (1)	6	Significant decrease in mPAP after 6 months in 5 out of 7 patients	Immunosuppressive therapy was increased
Fisher [83]	7	59	57	EPO (7)	0–49	The majority of subjects responded to EPO therapy; 4 out of 7 subjects alive and without transplant	One episode of pulmonary edema; One sudden death 4 hours after EPO initiation
Milman [30]	12	41	36	Sildenafil	1–12	mPAP decreased >20% in 50% of subjects; cardiac output improved in 86%	No benefit on 6-minute walk test

Abbreviations: Bos, bosentan; CCB, calcium channel blocker; NYHA, New York Heart Association.

^a Mean or median value for the entire reported population, including those treated with vasodilators.

^b Right ventricular systolic pressure estimate by echocardiogram.

^c Systolic pulmonary artery pressure.

Bosentan, a specific endothelin-1 antagonist, has been approved by the Food and Drug Administration for the treatment idiopathic PAH and scleroderma-related PAH. The experience with bosentan in SAPH is limited to scattered case reports, often in combination with other agents [29,85,86].

At the authors' institution, seven patients with SAPH who were treated with bosentan were identified [84]. Three subjects received bosentan and four received bosentan in addition to prostanoid therapy. Four of the subjects demonstrated objective improvement after short-term (6–18 months) follow-up, but the other three died from their disease. A similar report that included four subjects treated with bosentan alone showed a significant drop in the pulmonary pressures after 6 months follow-up [29]. These reports are too few to provide guidance for clinicians, but they generally demonstrate the possibility of efficacy for some SAPH patients. The role of endothelin antagonists in combination with other pulmonary vasodilators, such as epoprostenol or sildenafil, remains unclear. As for other causes of PH, it seems reasonable to limit the first-line use of endothelin antagonists to patients with mild to moderate (New York Heart Association functional class II and III) dyspnea.

Phosphodiesterase inhibitors

Sildenafil, a potent phosphodiesterase type 5 inhibitor, has theoretic benefits in pulmonary hypertension caused by parenchymal lung disease, as it may preserve ventilation-perfusion matching better than prostanoids [79]. Small case series have suggested benefits in idiopathic pulmonary fibrosis [79], scleroderma [87], and cystic fibrosis [88]. Moreover, in patients with end-stage chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis-associated pulmonary hypertension, the beneficial hemodynamic effects of sildenafil may also impact exercise tolerance and 6-minute walk distance [89,90]. A recent series described the use of sildenafil in Danish patients listed for lung transplant because of end-stage sarcoidosis [30]. The subjects had severe restrictive lung disease (mean FVC 41% predicted). Twelve subjects with mPAP greater than 25 mm Hg were treated with oral sildenafil (median dose 150 mg daily) for 1 to 12 months. Although the 6-minute walk time did not improve, there were substantial reductions in mPAP (48 ± 15 mm Hg versus 39 ± 13 mm Hg), PVR (10.7 ± 4.8 versus

5.6 ± 4.0 Wood units), and improved cardiac index (2.3 ± 0.5 L/m² versus 2.9 ± 1.0 L/m² per minute). Although these findings are encouraging, the role of sildenafil compared with prostanoids or endothelin antagonists for SAPH is currently unknown.

Prognosis

Sarcoidosis is generally considered a disease with a favorable long-term prognosis. Although the disease remits spontaneously in nearly two-thirds of patients, about 1% to 5% of patients die from progressive respiratory failure, central nervous system disease, or myocardial involvement [8,91,92]. Right ventricular failure has been described in up to 30% of sarcoidosis-related deaths [20,93]. Patients with substantial pulmonary fibrosis have a particularly elevated risk. A single-center retrospective cohort study of 41 subjects with stage III and IV disease listed for orthotopic lung transplantation suggested that right atrial pressure greater than 15 mm Hg was the strongest independent predictor of mortality in this population [94]. Kaplan-Meier analysis estimated survival of 51% at 1 year and 25% at 2 years when mPAP was greater than or equal to 35 mm Hg. Right arterial pressure greater than or equal to 15 mm Hg increased the risk of death by 5.2-fold. A follow-up analysis of the United Network Organ System database confirmed that higher pulmonary artery pressures portend lower survival among patients awaiting lung transplant [10,95]. These reports have led the International Society for Heart and Lung Transplantation to recommend early assessment for lung transplantation in patients with SAPH [96]. However, these recommendations are limited by the ascertainment bias of the reports from which they are derived.

Compared to patients with radiographic evidence of advanced stage, little is known about the natural history and prognosis of SAPH in the absence of significant pulmonary fibrosis. A recent report proposed that the subset of patients with SAPH and no evidence of pulmonary fibrosis may have a shorter time between diagnosis of sarcoidosis and diagnosis of PH, as well as higher pulmonary vascular resistance compared with patients with parenchymal fibrosis [40]. However, ascertainment bias again is likely influencing this observation. It is currently not known if these patients represent a subgroup in early stages of the disease or if they have a different natural history

compared with patients with severe interstitial lung disease. The profound heterogeneity in this group of patients suggests that clinical caution and close follow-up for evidence of progression are warranted. Whether patients with SAPH without pulmonary fibrosis who are treated with pulmonary vasodilators or endothelin antagonists have better outcomes compared with patients with parenchymal fibrosis is also currently not known.

In conclusion, the presence of pulmonary hypertension appears to confer poor prognosis in patients with sarcoidosis. Particularly at risk are patients with evidence of severe parenchymal disease. Clinicians must be vigilant for the development of SAPH, as this complication appears to be associated with worse outcomes. Prompt recognition and referral to an experienced center for consideration of initiation of specific therapy or transplant evaluation are important considerations.

Summary

The authors conclude that SAPH may be present irrespective of the degree of parenchymal involvement. It may account for a substantial proportion of dyspnea among all sarcoidosis patients, and appears to be common in those with severe parenchymal disease. A major gap in current clinical practice is identification of a cost-effective, reliable, noninvasive method to screen for the presence of SAPH. Further studies are needed to characterize the natural history more closely, to establish whether there is a role for routine trials of augmented immunosuppression and to define the effects of the therapeutic options. Early identification of patients at risk for developing this complication might facilitate preventive efforts.

Variable response rates to different agents or combinations of drugs reflect the fact that this particular complication of sarcoidosis may be the consequence of quite complex underlying mechanisms, including granulomatous fibrosis, sarcoid-induced occlusive venopathy, and granulomatous inflammation of pulmonary arteries. Although the presence of pulmonary fibrosis may indicate the possibility of irreversible derangement and portend a worse outcome, its presence should not preclude a cautious therapeutic trial. If the patient is a candidate, concomitant evaluation for lung transplantation should be considered as well.

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