

**PULMONARY HYPERTENSION ASSOCIATED WITH SARCOIDOSIS:  
mechanisms, hemodynamics and prognosis.**

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## **ABSTRACT**

*Background:* Pulmonary hypertension is a rare complication of sarcoidosis (sarcoidosis-PH) although not uncommon in advanced disease.

*Methods:* Retrospective series of 22 patients (16 men and 6 women, age:  $46 \pm 13$  years) with sarcoidosis-PH. The population was divided into 2 groups, depending on the absence (stage 0: n=2, stage II: n=4, stage III: n=1) or presence (n=15) of radiographic pulmonary fibrosis at the time of PH diagnosis.

*Results:* In both groups, PH was moderate to severe and there was no responder to acute vasodilator challenge. In non fibrotic cases no other cause of PH was found suggesting a specific sarcoid vasculopathy although no histological specimen was available. In fibrotic cases there was no correlation between hemodynamics and lung volumes or PaO<sub>2</sub>, suggesting other mechanisms for PH in addition to pulmonary destruction and hypoxemia. These included extrinsic arterial compression by lymphadenopathies in 3 cases and histologically proved pulmonary veno-occlusive disease in the 5 patients who underwent lung transplantation. Ten patients received high doses of oral prednisone for PH (stage 0: n = 1, stage II: n = 4 and stage IV: n = 5); 3 patients without pulmonary fibrosis experienced a sustained hemodynamic response. Survival of the overall population was poor (59 % at 5 years). Mortality was associated with NYHA functional class IV but not with hemodynamic parameters nor with lung function.

*Conclusion:* Two very different phenotypes of sarcoidosis-PH are observed depending on the presence or not of pulmonary fibrosis. PH is a severe complication of sarcoidosis.

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## **INTRODUCTION**

Pulmonary hypertension (PH) is a well-recognized complication of sarcoidosis which prevalence does not exceed 5 % of all sarcoid patients according to reference works (1-4) although in advanced disease PH is not uncommon (5). PH is usually attributed to the destruction of distal capillary bed by fibrotic process and/or to the resultant chronic hypoxemia (1-4). However, the severity of PH does not correlate well with the degree of pulmonary fibrosis and blood gases (6) and PH has also been reported as an early primary manifestation of sarcoidosis, suggesting that other mechanisms may contribute to the development of PH in the context of sarcoidosis. Such mechanisms include extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis (2, 7), specific granulomatous vascular involvement (2, 8-12) which sometimes simulates secondary pulmonary veno-occlusive disease (PVOD) (11, 12) and pulmonary vasoconstriction by vaso-active factors (13, 14). Uncommonly, portal hypertension secondary to liver sarcoidosis can also provoke PH (15).

PH is known to carry an extremely poor prognosis in patients with sarcoidosis (16, 17). Yet, the response of sarcoidosis-PH to corticosteroids is unclear.

We report a large retrospective series of 22 consecutive patients with sarcoidosis-PH. The objectives of the study were: (i) to evaluate baseline pulmonary hemodynamics in these patients, (ii) to discuss the underlying mechanisms of PH and (iii) to assess the efficacy of corticosteroids and the prognosis of affected patients.

## **METHODS**

### **Patients**

This retrospective study was conducted in two centers, Avicenne and Antoine Bécère Hospital. Patients with a history of sarcoidosis and PH observed between January 1988 and December 2002 were evaluated. Complete information was obtained from hospital and referring physician medical records and reviewed by two of us (HN and DV). The diagnosis of sarcoidosis was established by pathological examination and compatible clinical and radiographic features. PH was defined by a mean resting pulmonary artery pressure (mPAP)  $\geq$  25 mmHg and normal pulmonary wedge pressure (PWP  $\leq$  12 mmHg) during right-heart catheterization. Hemodynamic study was performed at Antoine Bécère Hospital (MH, OS, GS) as described elsewhere (18). Other causes of pre-capillary PH including thrombo-embolic

disease, appetite suppressant ingestion, portal hypertension, connective tissue disease, HIV infection, sickle cell disease and congenital heart disease were excluded on the results of history, physical examination, ventilation-perfusion lung scan and/or pulmonary angiography, Doppler-echocardiography, abdominal Doppler-echography, HIV serology and antinuclear antibody.

Twenty-five consecutive patients with sarcoidosis-PH were reviewed. Among them, 3 were excluded from the study: 1 patient with splenectomy had chronic thrombo-embolic disease, 1 had evidence of mixed connective tissue disease and had also taken fenfluramine, and 1 had portal hypertension. The 22 studied patients underwent a standard evaluation at the moment of first right-heart catheterization including chest X-ray, pulmonary function tests as recommended (19), contrast-enhanced high resolution computed tomography (HRCT) and serum angiotensin converting enzyme (SACE) measure.

### **Controls**

Patients with sarcoidosis-PH were compared with sarcoid controls without PH on Doppler-echocardiography. Each patient was matched with 2 controls for sex, age and radiographic stage. The pneumology department of Avicenne Hospital is highly specialized in sarcoidosis and has a unique and large cohort of sarcoid patients. Each sarcoid patient referred to the department is registered according to the date of admittance, age, sex and radiographic stage and is assigned with a recruitment number according to the date of admittance. Controls were selected by 2 steps. First, for each patient with sarcoidosis-PH, the 2 sarcoid patients whom number was immediately before and after and who had the same gender, age ( $\pm 5$  years) and radiographic stage were reviewed. Second, the sarcoid patient was selected as a control if a Doppler-echocardiography was available in his chart and did not evidence PH. If not, the following sarcoid patient according to his recruitment number was reviewed, and so forth.

### **HRCT analysis**

All the scans of patients and controls were collected and randomly reviewed by one chest radiologist who was blinded to the subjects' diagnoses (MB). HRCT were analyzed for the presence or absence of pulmonary elementary lesions as previously described (20, 21).

### **Statistical analysis**

Analysis was performed using the Statview version 5.0 statistical package (SAS Institute, Cary, North Carolina). Results are expressed as mean  $\pm$  standard deviation. Groups were compared by unpaired Student's t test and chi-square test when appropriate. Simple

regression analysis was used for correlations. The probability of survival of patients and controls was estimated by the Kaplan-Meier method and compared by the logrank test. Survival was calculated from PH diagnosis for patients and from normal Doppler-echocardiography for controls until the end of the follow-up period. Transplanted patients were considered as censored at the date of transplantation. Univariate analysis was based on the proportional hazards model. Results are expressed as hazard ratios with 95% confidence intervals.

## RESULTS

### Clinical findings

The studied population included 22 patients (16 men and 6 women, mean age  $46 \pm 13$  years). Seventeen patients were referred because of the detection of PH by Doppler-echocardiography while they had an increase of dyspnea; 5 were referred to be listed for lung transplantation and systematic right-heart catheterization evidenced PH. According to chest X-ray, the population was divided into 2 groups, depending on the absence (group A) or presence (group B) of pulmonary fibrosis. Group A included 7 patients (stage 0: n=2, stage I: n=0, stage II: n=4, stage III: n=1). Group B included 15 patients (stage IV).

The patients' demographic and clinical characteristics are summarized in Table 1. Sarcoidosis involved at least one extra-respiratory organ in 11 out of the 22 patients (skin: n = 6, liver: n = 4, peripheral adenopathy: n = 3, spleen: n= 1, articular: n = 1, eye: n = 1 and stomach: n = 1) and one patient had hypercalcemia. Sarcoidosis and PH were diagnosed simultaneously in one patient of group A with radiographic stage II. One patient of group A had symptoms of Raynaud's phenomenon.

Two patients had a radiographic stage 0 at the moment of PH diagnosis. The first stage 0 patient was a 55 year-old woman with a known sarcoidosis affecting the skin and the stomach and hypercalcemia. We have no information about her chest X-ray until she noted exertional dyspnea 10 months after corticosteroids were stopped. At that time, chest X-ray was unremarkable but Doppler-echocardiography revealed severe PH. PH was reversible under corticosteroids but relapsed 12 months after this treatment was tapered off, concomitantly with an increase of SACE at twice the upper limit of normal value. Chest X-ray remained normal. The patient was then referred for hemodynamic investigation. The second stage 0 patient was a 37 years-old woman who was discovered with a stage II disease

on routine chest X-ray while she was clinically asymptomatic. She was placed on corticosteroids for 20 months and chest X-ray normalized. Six months later she complained of increasing shortness of breath. Chest X-ray remained normal but Doppler-echocardiography detected severe PH. SACE was not available. The patient was then referred for hemodynamic investigation.

Patients were similar to controls regarding demographic characteristics (32 men and 12 women, mean age  $46 \pm 13$  years, Caucasian: 75.0% and Afro-Caribbean: 25.0%) and extra-respiratory manifestations of sarcoidosis.

### **Hemodynamic findings**

Results are presented in table 1. When comparing group A and B, PH tended to be more severe in group A (mPAP:  $51.7 \pm 16.0$  versus  $40.1 \pm 11.6$  mmHg,  $p=0.07$  and pulmonary vascular resistance index (PVRI):  $23.0 \pm 10.4$  versus  $14.6 \pm 8.9$  IU.m<sup>-2</sup>,  $p=0.06$ ). PH was moderate (mPAP < 35 mmHg) in 1 patient of group A (14.3%) and in 7 patients of group B (46.7%) ( $p=NS$ ).

### **Functional ventilatory findings**

Results are shown in table 2. Group A patients had nearly normal spirometry or only mild restrictive defect, but a severe decrease in transfer coefficient of carbon monoxide (DLCO) and DLCO on alveolar volume (KCO). Two patients (28.6%) had an important hypoxemia  $\leq 55$  mmHg, of whom one had right-to-left intra-cardiac shunting through a patent *foramen ovale*. No significant difference was found between patients of group A and controls for lung volumes and flows but DLCO, KCO and PaO<sub>2</sub> were significantly lower in patients with sarcoidosis-PH (table 2).

In group B, pulmonary function tests were markedly altered as presented (table 1). PaO<sub>2</sub> was  $\leq 55$  mmHg in 6 patients (40.0%). All parameters were significantly more reduced in patients of group B with sarcoidosis-PH than in controls except for TLC and FEV<sub>1</sub>/FVC which were similar (table 2).

### **HRCT findings**

HRCT was unavailable in one patient of group B. Patients of group A significantly differed from controls for the frequency of ground glass attenuation (85.7% versus 14.3%,  $p<0.01$ ). Patients of group B significantly differed from controls for the frequency of septal lines (78.6% versus 46.4%,  $p=0.047$ ) particularly when they drew polygonal reticulations (71.4% versus 25%,  $p=0.004$ ) (figure 1). Extrinsic compression of large pulmonary arteries by

adenopathies, as defined by a reduction of vascular lumen over 50% after injection of contrast material, was never seen in group A and was present in 3 patients of group B (21.4%) at mediastinal or hilar level. In these patients extrinsic arterial compression was ascertained by pulmonary angiography. HRCT never showed evidence of pulmonary venous compression.

#### **Serum angiotensin converting enzyme**

SACE was measured in 18 patients at the moment of PH diagnosis: it was increased in 3/5 cases of group A and in 3/13 cases of group B.

#### **Correlations between hemodynamic and functional ventilatory findings**

In each group we attempted to correlate mPAP and PVRI with pulmonary function parameters including forced expiratory volume in 1 second (FEV<sub>1</sub>) % of predicted, forced vital capacity (FVC) % of predicted, total lung capacity (TLC) % of predicted, FEV<sub>1</sub>/FVC %, DLCO % of predicted, KCO % of predicted and room air PaO<sub>2</sub>. In group A, mPAP only significantly correlated with DLCO (r = 0.847, p = 0.03) and tended to correlate with KCO without reaching the level of significance (r = 0.762, p = 0.08). PVRI only significantly correlated with PaO<sub>2</sub> (r = 0.775, p = 0.04). In group B, mPAP only significantly correlated with DLCO (r = 0.684, p = 0.01) and there was a trend for mPAP to correlate with KCO (r = 0.521, p = 0.07). No relation was found between PVRI and any pulmonary function parameters.

#### **Treatment**

Fourteen patients (63.6 %) were treated with long-term oxygen and 6 patients received warfarin. No patient was given long-term systemic vasodilator agents. One patient with radiographic stage IV received nebulized iloprost without any clinical benefit and died within 4 months while waiting on the lung transplant list.

#### ***Patients treated with corticosteroids.***

Specific treatment for sarcoidosis was reinforced because of PH in 10 patients (stage 0: n = 1, stage II: n = 4 and stage IV: n = 5). All the patients had high doses of oral prednisone ranging from 0.5 to 1 mg.kg<sup>-1</sup> per day, associated with methotrexate 15mg weekly in one case and with 3 monthly boluses of cyclophosphamide in another case. At the initiation of therapy the patients had right-heart catheterization and concurrent Doppler-echocardiography. Systolic PAP was estimated as previously described (22). The echocardiographic measures of sPAP were in good concordance with those obtained invasively (r = 0.967, p < 0.0001). The therapeutic response was evaluated after 3 or 6 months by Doppler-echocardiography

performed by the same cardiologist in all the cases and also right-heart catheterization in 3 cases.

The results are shown in table 3. Systolic PAP remained stable or increased in 7 cases (stage II: n = 2 and stage IV: n = 5) and decreased more than 20% from baseline in the 3 remaining cases (stage 0: n = 1 and stage II: n = 2). In these 3 patients corticosteroids were maintained at low doses and Doppler-echocardiography totally normalized respectively at 12, 14 and 36 months. Interestingly, before being referred to our center one of these 3 patients had already a history of sarcoidosis-PH that was reversible with corticosteroids but relapsed after this treatment was stopped (see above).

### **Mortality and survival**

Patients were observed for  $3.7 \pm 3.5$  years. At the end of the follow-up period, 10 patients were alive, 7 died and 5 were transplanted (stage IV: n=5). The causes of mortality were right ventricular failure in 3 cases (stage II: n=2, stage IV: n=1), sudden death in one (stage IV), end-stage respiratory insufficiency in one (stage IV), pulmonary cancer in one (stage IV) and unknown in the remaining case (stage IV). Controls were observed for  $7.5 \pm 4.6$  years. Two of them died (pulmonary cancer: n=1, surgery complication: n=1, and unknown: n=1) and none was transplanted.

The probability of survival of patients was significantly poorer than that of controls (84.8 % *versus* 100 %, 73.5 % *versus* 96.4 % and 59.0 % *versus* 96.4 % respectively at 1, 2 and 5 years, p=0.003)

**Univariate analysis.** Univariate analysis was used to examine the relationship between survival and selected variables measured at initial right-heart catheterization. Mortality was not associated with patient age, gender, radiographic stage IV, any pulmonary function test including FEV<sub>1</sub> % of predicted, FEV<sub>1</sub>/FVC %, FVC % of predicted, TLC % of predicted, DLCO % of predicted, KCO % of predicted and PaO<sub>2</sub>, six-minute walk test and any hemodynamic parameters including mRAP, mPAP, CI and PVRI. Only NYHA functional class IV was significantly related with an increased risk of death [15.15 (2.77-83.33), p = 0.002].

### **Histopathology**

Native lungs were obtained from the 5 transplanted patients. Pulmonary explants were examined after endobronchial formalin fixation. Twenty two to 30 tissue blocks were processed. Paraffin sections were studied with hematoxylin eosin, elastic and iron stains. The

main histological findings are summarized in table and figure 2. In all cases sarcoid granulomas were fibrotic and scattered, not observed on each block. They were present in parenchyma in all cases and in the mediastinal lymph nodes in 3 out of the 5 cases. Vascular location of granuloma were predominantly veins (4 out of 5 cases) whereas arterial granulomas were seen in only 2 cases and neither venous nor arterial granuloma could be found in one patient. Besides granulomatous involvement, occlusive venopathy consisting of occlusive intimal fibrosis and recanalization was found in all cases (figure 2) while arterial lesions were minor with no plexiform neither thrombotic lesion. All cases had evidence of chronic hemosiderosis and iron deposit on elastic laminae. Parenchymal modifications were present in all cases and homogenous within all blocks: fibrosis was located in the sub-pleural space, interlobular septa and peri-bronchovascular sheets (figure 2).

## **DISCUSSION**

The current study reports a large series of patients with sarcoidosis-PH. It is the first to provide a comprehensive analysis of the underlying mechanisms of PH. The results suggest that (i) sarcoidosis-PH can take on two very different phenotypes depending on the presence or not of pulmonary fibrosis, (ii) specific mechanisms of PH can be multiple and vary from case to case particularly in the setting of fibrotic disease and (iii) sarcoidosis-PH confers a severe vital prognosis.

Surprisingly, 31.8 % of our patients developed PH in the absence of pulmonary fibrosis. In this patient group alterations in lung function were mild but mean DLCO was low and 2 patients had severe hypoxemia  $\leq 55$  mmHg. Mean PAP was significantly correlated with DLCO and PVRI with PaO<sub>2</sub>. Yet, PaO<sub>2</sub> and DLCO were preserved or only slightly decreased in controls without PH, which suggests that hypoxemia was rather the consequence than the cause of PH. In addition, no other cause of secondary PH was found. A fortuitous association between sarcoidosis and idiopathic PH cannot be definitively ruled out but seems unlikely with the low incidence of each disease. Even if there is no histological proof, our findings strongly support the role of specific pulmonary vasculopathy, which presumably also induces the severe reduction in DLCO. Only few similar cases are reported in the literature (7, 8, 10-13, 23), of whom two strikingly evidenced a histological pattern of granulomatous PVOD (11, 12). The two most typical HRCT features of PVOD are septal lines and ground glass attenuation (24, 25). Although these signs can also be seen in pulmonary sarcoidosis,

our patients with non fibrotic sarcoidosis-PH remarkably differed from controls without PH for the very high frequency of ground glass attenuation (85.7% *versus* 14.3%,  $p<0.01$ ), which may possibly reflect the presence of PVOD. Interestingly, 2 of our patients had a radiographic stage 0 at the time of PH diagnosis. In one previously reported case, comparisons of subsequent specimens obtained before and after established PH showed a clear progression of the pulmonary vascular involvement whereas parenchymal lesions of sarcoidosis remained relatively stable with corticosteroid therapy (10). Similarly, in our 2 stage 0 patients, we speculate that a preexistent parenchymal component either responded to corticosteroid therapy or improved spontaneously while the vascular involvement worsened.

The majority of patients with sarcoidosis-PH had radiographic stage IV (68.2%). Pulmonary function and particularly PaO<sub>2</sub> were significantly more altered in these patients than in controls without PH. A recent outstanding study by Shorr and colleagues on a large cohort of patients with advanced sarcoidosis listed for lung transplantation emphasizes that patients with PH have similar pulmonary function but require more supplemental oxygen than patients without PH (5). The discrepancy between these findings may result from the different selection methods. Anyhow, we failed to correlate mPAP or PVRI with pulmonary function or PaO<sub>2</sub>, except mPAP with DLCO. Furthermore, mPAP was over 35 mmHg in 53.3% of our patients, which was certainly out of proportion with the alterations in lung mechanics (26). Taken together these findings suggest that, at least in some stage IV cases, PH is not exclusively explained by the destruction of vascular bed or hypoxemia and that other mechanisms may also be involved. Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies was demonstrated in 21.4% of our patients with pulmonary fibrosis and may account for PH. Regarding HRCT findings, our patients with fibrotic sarcoidosis-PH significantly differed from controls without PH for the frequency of septal lines (78.6% *versus* 46.4%,  $p=0.047$ ), particularly when they drew a polygonal network (71.4% *versus* 25.0%,  $p=0.004$ ), which raised the possibility of PVOD.

Vascular involvement is very common in pulmonary sarcoidosis, reaching 69 to 100% of cases in pathologic studies (27, 28), and consists of occlusive or destructive lesions due to the invasion of vessel walls by granulomas or to the peri-vascular fibrosis. These changes can be observed at all levels, from large branches of pulmonary arteries to small veins but prevail in the venous side (27, 28). Yet, despite frequent vascular involvement, PH is rare (28). In our five transplanted patients with sarcoidosis-PH, lung examination revealed an original intrinsic

venopathy with marked lesions of intimal fibrosis (figure 2). The role of this venopathy and its relative part in the development of PH is difficult to affirm since all these patients had advanced pulmonary fibrosis. Nevertheless, this hypothesis is supported by the fact that venous lesions were occlusive, as demonstrated by the associated chronic hemosiderosis (figure 2) in the absence of another cause of venous hypertension including proximal venous obstruction and mitral stenosis (29).

PH is known to severely affect outcome and to be a predictor of mortality in patients with sarcoidosis listed for lung transplantation (16, 17). In our population, the survival was poor with a rate of 59.0 % at five years after PH diagnosis and may have been overestimated since transplanted patients were considered as censored at the date of transplantation. Survival was significantly worse than in controls without PH. PH was the cause of 57.1% of deaths, but hemodynamic measures were not found to be associated with mortality. NYHA functional class IV was the only predictor of mortality. Yet, the statistical analysis was limited by the small number of patients in our study.

These results support treating PH *per se* in patients with pulmonary sarcoidosis, but the appropriate management of such a complication is not well defined. There is not much written about the benefits of corticosteroids on sarcoidosis-PH and published data are somewhat discordant: PH can worsen despite corticosteroids (7, 10, 12, 13) as well as dramatically improve (9, 23). Gluskowski and colleagues studied the effects of 12 months corticosteroids on pulmonary hemodynamics in 24 patients with pulmonary sarcoidosis of which 3 had resting PH and 18 had abnormal increase in mPAP on exercise (30). A regression of radiological changes and improvement of lung function were observed in almost all patients but was accompanied by improvement of pulmonary hemodynamics in only half of them (30). In our experience, corticosteroids were never efficient in patients with pulmonary fibrosis but allowed a substantial and sustained improvement of PH in three out of the five cases without pulmonary fibrosis, alone or in association with methotrexate in one case. Interestingly, in one case with radiographic stage 0 PH recurred concomitantly with the reappearance of signs of sarcoidosis activity after corticosteroid therapy was stopped, and was reversible when it was reintroduced. Pulmonary vasodilator therapy, including novel agents, has been successfully considered in patients with PH secondary to pulmonary fibrosis (31, 32) but little is known about its usefulness in the context of sarcoidosis-PH (14, 33). In the small series of Preston and colleagues, five patients with sarcoidosis-PH received long-term inhaled

NO (in addition to intravenous epoprostenol in one case) and two patients received long-term oral calcium-channel blockers, but the results were not convincing (14).

In brief, our study allows identifying two very distinct phenotypes of sarcoidosis-PH depending on the presence or not of pulmonary fibrosis. Cases with pulmonary fibrosis are not preceded by a prior history of PH without pulmonary fibrosis. In opposition to fibrotic sarcoidosis-PH, specific vasculopathy seems the unique mechanism of non fibrotic sarcoidosis-PH but it gives rise to a higher level of mPAP and sometimes responds to corticosteroid therapy. Altogether with literature, these findings suggest that vasculopathy may be different between patients without or with pulmonary fibrosis. On the one hand PVOD may result from an active granulomatous involvement of venous walls and on the other from an authentic intrinsic venopathy. Interestingly, a pulmonary intrinsic venopathy has already been described in another granulomatous disorder, pulmonary histiocytosis X (34).

Limitations of our study are: (i) this is a retrospective analysis (ii) the two participant centers are highly specialized in sarcoidosis (Avicenne Hospital) and pulmonary vascular disease (Antoine Bécclère Hospital) which creates a selection bias and makes impossible the evaluation of PH prevalence among the general sarcoid population, (iii) the pathological material is limited and not available for patients with non fibrotic sarcoidosis-PH; however, we do think that it would have been unethical and risky to perform a lung biopsy in such cases.

We conclude that PH is a severe complication of sarcoidosis taking on two very different phenotypes. In the absence of pulmonary fibrosis a trial of oral corticosteroid therapy should be considered to treat PH complicating sarcoidosis since it may sometimes be efficient. In fibrotic disease, corticosteroids seem inefficient and physicians may choose to consider lung transplantation sooner than they would have otherwise solely on the basis of lung function. Systemic vasodilator therapy should be used with caution in patients with sarcoidosis-PH because of its potential risk of precipitating pulmonary edema in case of PVOD.

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## FIGURE LEGENDS

### **Figure 1: HRCT pattern of sarcoidosis-pulmonary hypertension with septal reticulations and ground glass attenuation.**

Patient with radiographic stage IV sarcoidosis. Computed tomography shows septal lines that are frequently deformed and draw a polygonal network in association with ground glass attenuation.

### **Figure 2: Pulmonary explant, peripheral specimen, paraffin section.**

Panel A (obj x 2.5, HE): homogenous fibrosis of visceral pleura, interlobular septa (arrow) and perivascular spaces.

Panel B (obj x 20, HE): interlobular septa vein with occlusive intimal fibrosis (arrow).

Panel C (obj x 20, iron stain): alveolar hemosiderosis (arrow 1) and iron deposits on elastic laminae (arrow 2).

## TABLES

**Table 1: Demographic, clinical and hemodynamic characteristics of the patients at the time of PH diagnosis.**

	<b>Group A</b> <b>(n = 7)</b>	<b>Group B</b> <b>(n = 15)</b>
Age, years	48 ± 13	45 ± 13
Male/Female, n	3/4	13/2
Caucasian/Black, n	4/3	13/2
Non/Ex/Current smokers, n	4/3/0	6/7/2
Time interval between sarcoidosis and PH, years *	3.7 ± 3.1	12.5 ± 6.2
NYHA functional class, n (%)	1 (14.3)	
II	4 (57.1)	2 (13.3)
III	2 (28.6)	8 (53.3)
IV		5 (33.3)
Right-heart failure, n (%)	1 (14.3)	4 (26.7)
Near-syncope, n (%)	0	3 (20)
Base-line hemodynamics		
mRAP mm Hg	7.3 ± 4.2	6.4 ± 6.7
mPAP mm Hg	51.7 ± 16.0	40.1 ± 11.6
PWP mmHg	8.8 ± 2.3	8.1 ± 3.6
CI l.min <sup>-1</sup> .m <sup>-2</sup>	2.45 ± 0.69	3.26 ± 0.09
PVRI IU.m <sup>-2</sup>	23.0 ± 10.4	14.6 ± 8.9
SvO <sub>2</sub> %	63 ± 16	68 ± 9
Acute vasodilator response n (%) ††	0 (0)	0 (0)

Group A includes patients without pulmonary fibrosis and group B patients with pulmonary fibrosis on chest X-ray. *Definition of abbreviation:* mRAP: mean right atrial pressure, mPAP: mean pulmonary artery pressure, PWP: pulmonary wedge pressure, CI: cardiac index, PVRI: pulmonary vascular resistance index and SvO<sub>2</sub>: mixed venous oxygen saturation.

\* Time interval between the first symptoms related to sarcoidosis and the diagnosis of PH. † Acute vasodilator response was tested with a short-term intravenous infusion of epoprostenol

or inhaled nitric oxide. A positive response was defined by a fall both in mPAP and PVRI  $\geq$  20 %.

‡ 9 patients of group B were not tested.

**Table 2: Functional ventilatory characteristics of patients at the time of PH diagnosis. Comparison with matched sarcoid controls without PH.**

	<b>Group A (n = 7)</b>	<b>Controls (n = 14)</b>	<b>p*</b>	<b>Group B (n = 15)</b>	<b>Controls (n = 30)</b>	<b>p<sup>†</sup></b>
PaO <sub>2</sub> mmHg	63 ± 17	78 ± 8	0.024	59 ± 11	79 ± 11	< 0.0001
FEV <sub>1</sub> ml	2141 ± 481	2504 ± 865	0.329	1233 ± 482	2030 ± 794	0.001
FEV <sub>1</sub> % pred	75 ± 20	84 ± 11	0.204	38 ± 18	56 ± 21	0.01
FEV <sub>1</sub> /FVC %	75 ± 8	72 ± 9	0.483	63 ± 14	67 ± 17	0.449
FVC ml	2851 ± 649	3648 ± 1269	0.143	2051 ± 659	3105 ± 1171	0.003
FVC % pred	82 ± 18	93 ± 9	0.07	50 ± 16	71 ± 23	0.004
TLC ml	4688 ± 1022	5247 ± 1312	0.348	4198 ± 1109	4827 ± 1465	0.165
TLC % pred	84 ± 13	92 ± 13	0.235	67 ± 13	73 ± 18	0.265
DLCO % pred <sup>‡</sup>	39 ± 28	86 ± 20	0.0009	38 ± 10	57 ± 19	0.002
KCO % pred <sup>‡</sup>	41 ± 29	88 ± 18	0.0005	58 ± 19	77 ± 22	0.01

Group A includes patients without pulmonary fibrosis and group B patients with pulmonary fibrosis on chest X-ray. Controls were matched for sex, age and radiographic stage.

*Definition of abbreviation:* PaO<sub>2</sub>: room air arterial partial pressure of oxygen, FEV<sub>1</sub>: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, DLCO: transfer coefficient of carbon monoxide, KCO: DLCO on alveolar volume and % pred: % of predicted value.

\* comparison between patients of group A and controls.

<sup>†</sup> comparison between patients of group B and controls.

<sup>‡</sup> DLCO and KCO were not available in 1 patient of group A and 2 patients of group B.



**Table 3: Patients treated with corticosteroids for sarcoidosis-PH\***

Sex/Age	Chest X-ray stage	Associated treatment	sPAP		
			Base-line	3-6 months	Last evaluation
F/55	0	methotrexate	66	35	< 30 mmHg at 12 months
H/61	II	O <sub>2</sub> , warfarin	121	125 †	dead at 11 months
F/52	II	-	60	40	30 mmHg at 14 months
H/28	II	-	77	60 †	30 mmHg at 36 months
H/63	II	-	80	82	dead at 18 months
H/55	IV	-	50	55	not reevaluated
F/62	IV	-	45	45 †	50 mmHg at 18 months †
H/57	IV	O <sub>2</sub>	80	85	transplanted at 14 months
H/47	IV	-	83	100	transplanted at 39 months
H/42	IV	O <sub>2</sub> , CYC	56	59	91 mmHg at 48 months †

*Definition of abbreviation:* M: male, F: female, sPAP: systolic pulmonary artery pressure estimated by Doppler-echocardiography, CYC: intravenous cyclophosphamide.

\* Whatever the treatment at the moment of PH diagnosis each patient received at least high doses of oral prednisone ranging from 0.5 to 1 mg.kg<sup>-1</sup>.

† In these patients the measure obtained by Doppler-echocardiography was confirmed by right-heart catheterization.

**Table 4: Histological findings on native lungs obtained from the 5 transplanted patients\*†**

Sex Age	Hemodynamics		Sarcoid granulomas				Vascular lesions					Hemosiderosis
							Arteries		Veins			
	mPAP mmHg	PVRI IU.m <sup>-2</sup>	Nodes	Parenchyma	Arteries	Veins	Intimal fibrosis and/or medial hypertrophy	Plexiform lesions	Obliteration	Intimal fibrosis	Perivascular fibrosis	
M 57	52	30.4	-	+	-	-	+	-	+	+	+	+
M 39	33	7.3	+	+	-	+	+	-	+	+	+	+
M 47	67	33.5	+	+	-	+	+	-	+	+	+	+
M 39	51	19.1	-	+	+	+	+	-	+	+	+	+
F 27	29	5	+	+	+	+	+	-	+	+	+	+

\* All the patients had radiographic stage IV and severe pulmonary fibrosis on HRCT.

† Histological vascular changes are recorded in a qualitative fashion: -: absent, +: present.

*Definition of abbreviation:* M: male, F: female, mPAP: mean pulmonary artery pressure, PVRI: pulmonary vascular resistance index.

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