

TREATMENT OF SARCOIDOSIS-ASSOCIATED PULMONARY HYPERTENSION: A SINGLE CENTRE RETROSPECTIVE EXPERIENCE USING TARGETED THERAPIES

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ABSTRACT. *Background:* Pulmonary hypertension (PH), an increasingly recognised complication of pulmonary sarcoidosis, is associated with increased morbidity and mortality. Evidence of benefit with targeted therapies in sarcoidosis associated pulmonary hypertension (SAPH) is limited. *Methods:* We conducted a retrospective review of patients with sarcoidosis and right heart catheter proven PH who received treatment with targeted therapies (phosphodiesterase-5 inhibitors, endothelin receptor antagonists, or combination) at our hospital. Six minute walk test (6MWT), World Health Organisation (WHO) functional class, echocardiography, pulmonary function test (PFT) and serum brain natriuretic peptide (BNP) data were collected at baseline and during follow-up. *Results:* Thirty-three patients (16 men) with a mean age of 55.5 ± 10.7 years and mean pulmonary artery pressure of 44.0 ± 8.6 mm Hg received treatment with targeted PH therapies (sildenafil=29, bosentan=4). At six months, median six minute walk distance improved from 227 (88-526) meters to 240 (140-380) metres ($p=0.04$), median serum BNP levels improved from 35 (2-424) pmol/L to 26 (4-255) pmol/L ($p<0.01$), and at echocardiography, median tricuspid annular plane systolic excursion (TAPSE) improved from 17.5 (8.0-27.0) mm to 20.0 (15.0-27.0) mm ($p=0.03$). WHO functional class improved in 14 patients. Two patients developed side-effects attributed to sildenafil ($n=1$) or bosentan ($n=1$), requiring conversion to alternative PH therapies. Ten patients died, and one patient underwent lung transplantation, a median of 13.5 (3-37) months after commencing targeted therapies. *Conclusions:* Our results suggest that targeted therapies are safe in patients with SAPH. Controlled trials are warranted before therapeutic recommendations can be made. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 82-90)

KEY WORDS: sarcoidosis, pulmonary hypertension, treatment

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INTRODUCTION

Pulmonary hypertension (PH) is increasingly recognised as a major contributor to poorer outcomes in pulmonary sarcoidosis, including mortality (1, 2). Patients with sarcoidosis associated PH (SAPH) are more likely to experience persistent dys-

pnoea, the need for supplemental oxygen (3-5), and are more likely to be listed for lung transplantation (1, 2).

The prevalence of SAPH is not well defined, in part due to varying measurement technique and patient selection criteria. Prevalence estimates range from 5-6% in unselected sarcoidosis patient cohorts (6), with SAPH reported in up to 74% of patients referred for lung transplantation (5). In a recent series, PH at right heart catheter (RHC) was present in 54% of patients with sarcoidosis and persisting dyspnoea despite optimal treatment of pulmonary disease (7).

The pathophysiology of SAPH is complex, with multiple potential mechanisms contributing to elevated pulmonary vascular pressures. Destruction of the pulmonary vascular bed by parenchymal fibrosis is arguably the most frequent pathogenic mechanism, although 30-40% of patients with SAPH have no radiographic evidence of pulmonary fibrosis (8, 9). Granulomatous inflammation of the pulmonary vasculature, extrinsic compression from lymphadenopathy and/or mediastinal fibrosis, pulmonary veno-occlusive disease and left heart disease (including cardiac sarcoid involvement) are all recognised to be important in the pathogenesis of SAPH (7-11). In the 2013 Nice Pulmonary Hypertension classification, sarcoidosis is classified in category 5, along with disorders of unclear and/or multifactorial pathogenetic mechanisms (12).

Optimization of underlying sarcoid associated pulmonary disease, including the use of supplemental oxygen when hypoxaemia is present, is important in the management of SAPH. Although no randomised controlled treatment trials of targeted therapies for SAPH have been published, several series have reported functional and haemodynamic improvements with pulmonary vasodilators (13-17). We report our experience using targeted therapies in the treatment of SAPH.

METHODS

Patient selection

Review of our pulmonary hypertension database identified 33 consecutive patients with SAPH who received treatment with targeted therapies be-

tween 2006 and 2012. The diagnosis of sarcoidosis was confirmed in all patients based upon clinical, radiologic and/or pathologic data (in accordance with ATS/ERS/WASOG diagnostic criteria; 18). All patients underwent RHC, with PH defined as a resting mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg, and a normal pulmonary capillary wedge pressure (PCWP ≤ 15 mm Hg). Patients with additional pathology which may have contributed to PH (including pulmonary thrombo-embolic disease, congenital heart disease, and left heart disease) were excluded from this review.

Hospital records were reviewed, and six minute walk distance (6MWD), World Health Organisation (WHO) functional classification, serum brain natriuretic peptide (BNP), echocardiography and pulmonary function testing (PFT) data were collected at baseline, and during follow-up. Two-dimensional echocardiography using Doppler and colour flow imaging was performed, and tricuspid annular plane systolic excursion (TAPSE) was measured with the use of M-mode of the tricuspid lateral annulus motion. Six minute walk test (6MWT) was performed by senior trained personnel according to American Thoracic Society criteria (19). Local research ethics committee (Brompton, Harefield & NHLI REC reference 01-246) approval was in place for retrospective review of sarcoidosis patients.

Statistical Analysis

All analyses were performed using STATA statistical software (version 12.0; Stata Corp., College Station, TX, USA). Data were expressed as mean and standard deviation (SD) or as median and range as appropriate. Comparisons of BNP, echocardiography and 6MWT measurements were made using Wilcoxon's signed-rank test. For all analyses, a *P* value of <0.05 was considered statistically significant.

RESULTS

Demographics

The study population included 33 patients (16 men) with a mean age of 55.5 ± 10.7 years. Sarcoidosis was confirmed at biopsy in 26 patients, and at clinico-radiologic correlation in seven patients. At

the time of SAPH diagnosis, 31 patients were treated with prednisolone, with 18 patients receiving additional immunomodulatory therapy (methotrexate, azathioprine or hydroxychloroquine) for pulmonary or systemic sarcoidosis. The median duration from diagnosis of sarcoidosis until RHC confirmed SAPH was nine (1-33) years. Table 1 summarises demographic and baseline clinical information.

Baseline characteristics

All patients underwent RHC, with an average mPAP of 44.0 ± 8.6 mmHg, elevated pulmonary vascular resistance (PVR) of 10.0 ± 5.1 Wood Units, elevated right atrial pressure of 8.2 ± 4.3 mmHg, and reduced cardiac index of 2.1 ± 0.6 L/min/m².

Twenty-seven patients (81%) had echocardiographic features of right ventricular dysfunction and/or dilatation at the time of commencing targeted therapies, with a median right ventricular systolic pressure (RVSP) of 75.0 (38-120) mmHg. TAPSE was reduced at 17.5 (8.0-27.0) mm, and serum BNP levels were elevated in 32 patients (median BNP 35 pmol/L; range 3- 424) (normal range < 4 pmol/L). Baseline PFTs demonstrated severely reduced diffusing capacity for carbon monoxide (DLco% predicted 30.6 ± 14.3) and a moderately reduced forced vital capacity (FVC % predicted 64.8 ± 22.3). Patients were hypoxic at rest with a mean PaO₂ 8.0 ± 1.7 kPa. Twenty patients were receiving supplemental oxygen therapy (ambulatory or continuous oxygen) at flow rates of two to four litres/minute. Twenty-six patients had significant functional limitation (WHO functional class III or IV) at the time of SAPH diagnosis.

Twenty-five (76%) patients had fibrotic pulmonary sarcoidosis (stage IV) on chest radiograph. High resolution computed tomography (HRCT) was available in 31 patients, a median of 26 days (0-61) from RHC, with evidence of main pulmonary artery (mPA) dilation in the majority of patients. Electronic calliper measurement of the mPA (at the level of the mPA bifurcation) revealed a mean mPA diameter of 30.0 ± 4.8 mm, and in 23 patients, the ratio of the diameter of the mPA to ascending aorta (at the level of the mPA bifurcation) was greater than one. Cardiac magnetic resonance imaging (CMR) was performed in 25 patients, with post gadolinium delayed-enhancement sequences reveal-

Table 1. Demographic, clinical and haemodynamic characteristics of patients at the time of right heart catheterization.

n=33	
Age (years)	55.5 (10.7)
Males	16
Biopsy confirmed sarcoidosis	26
Scadding CXR stage	
Stage 2	1
Stage 3	7
Stage 4	25
Haemodynamic information	
mPAP (mmHg)	44.0 (8.6)
RA pressure (mmHg)	8.2 (4.3)
PVR (WU)	10.0 (5.1)
Cardiac index (L/min/m ²)	2.1 (0.6)
WHO functional class	
Class II	3
Class III	22
Class IV	4
Pulmonary function tests	
TLco%	30.6 (14.3)
Kco%	53.9 (14.7)
FVC %	64.8 (22.3)
FEV1 %	51.8 (18.3)
Echocardiography	
RVSP (mmHg) *	75.0 (38.0-120.0)
TAPSE (mm) *	17.5 (8.0-27.0)
RV dilatation/dysfunction	27 (81%)
Brain natriuretic peptide*	35 (3-424)
(pmol/L)	
* median (range)	

ing changes of active or previous cardiac sarcoid involvement in seven patients.

Response to therapy

Twenty-nine patients were commenced on sildenafil (20 mg three times daily), with bosentan (62.5 mg twice daily, increasing to 125 mg twice daily) in four patients. Three patients required combination therapy, with the addition of an endothelin receptor antagonist

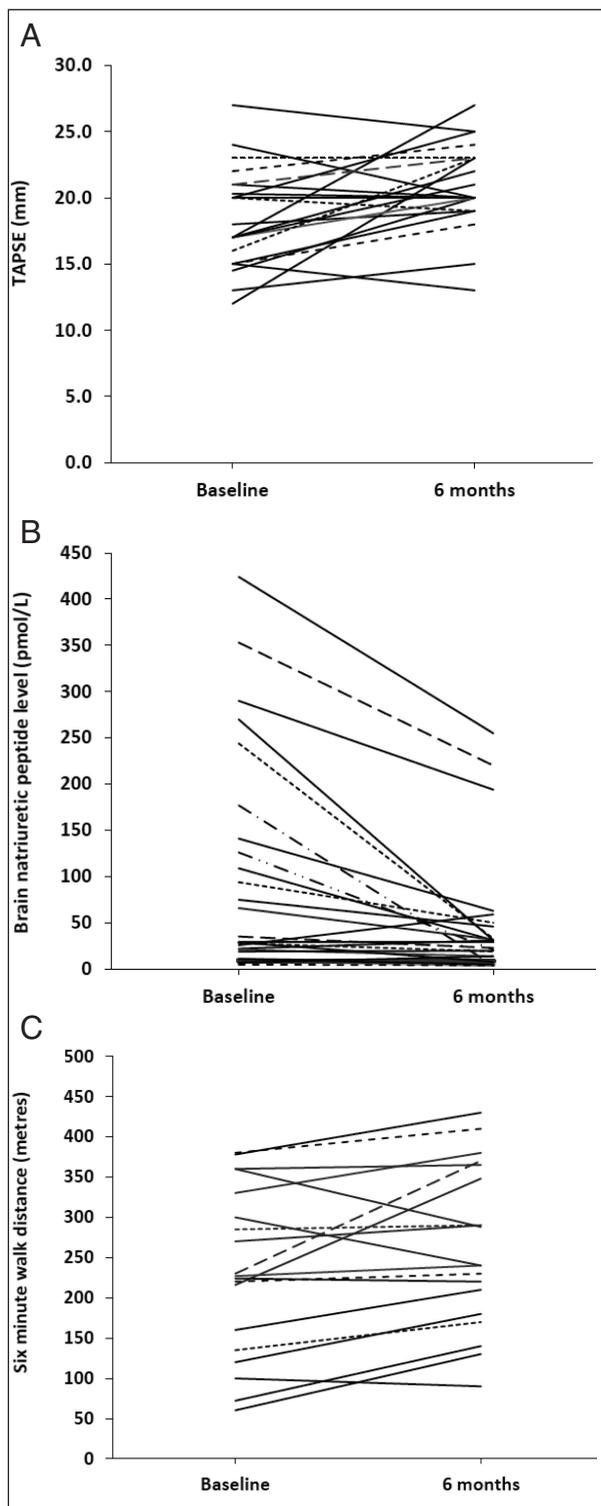


Fig. 1. Data before and after 6-months treatment with PH advanced therapies, for: (a) tricuspid annular plane systolic excursion (TAPSE); (b) brain natriuretic peptide (BNP); and (c) 6 minute walk distance.

(bosentan or ambrisentan) after an inadequate response to initial sildenafil monotherapy (defined as deteriorating one or more of the following: symptoms, falling 6MWT, rise in BNP, rise in RVSP or deterioration in right ventricular function (including TAPSE)). The median duration of follow-up after the commencement of targeted therapies was 15.3 (3–60) months.

Repeat clinical assessment was performed after six months of treatment. Follow-up echocardiography was available in 25 patients, with an improvement in median TAPSE from 17.5 (8.0–27.0) mm to 20.0 (15.0–27.0) mm ($p=0.03$) (figure 1a). Several other echo parameters did not change significantly (table 2). Repeat BNP levels were available in 29 patients, with an improvement in median BNP from 35 (3–424) pmol/L to 26 (4–255) pmol/L ($p<0.01$) (figure 1b), and in 19 patients with follow-up 6MWT, there was an improvement from 226 (35–396) metres to 240 (130–430) metres ($p=0.04$) (figure 1c). WHO functional class improved in 14 patients, remained stable in 12 patients, and deteriorated in eight. Two patients developed side-effects to initial PH specific therapy (visual side-effects on sildenafil, and deranged liver function tests on bosentan) and were successfully converted to alternative agents. Subgroup analysis of patients treated with sildenafil ($n=29$) was performed, and the statistically significant improvements in 6MWD, TAPSE and BNP remained unchanged (data not shown).

Follow-up

During follow-up, one patient underwent lung transplantation and ten patients died, a median of

Table 2. Echocardiographic parameters at baseline, and following 6 months of advanced therapies. Values are expressed as median and range.

	Baseline (n=33)	6 months (n=25)	p value
RVSP (mmHg)	73.0 (38.0–120.0)	66.0 (24.0–120.0)	NS
TAPSE (mm)	17.5 (8.0–27.0)	20.0 (13.0–25.0)	0.03
PacT (msec)	78.0 (44.0–133.0)	83.0 (37.0–148.0)	NS
RA area (cm ²)	19.2 (5.0–32.4)	19.5 (12.0–36.0)	NS
RV area (cm ²)	26.0 (12.0–30.0)	22.0 (11.0–33.3)	NS
Ecc Index	1.2 (0.9–1.7)	1.3 (1.0–1.7)	NS

RVSP=right ventricular systolic pressure; TAPSE=tricuspid annular plane systolic excursion; PacT=pulmonary acceleration time; RA=right atrium; RV=right ventricle; Ecc. Index=eccentricity index; NS=not statistically significant ($p>0.05$)

13.5 (3-37) months after commencing targeted therapies. Pre-treatment haemodynamic variables associated with a greater risk of death or transplantation included a higher PVR (15.7 vs 7.8 WU; $p=0.01$) and a lower cardiac index (1.6 vs 2.1 L/min/m²; $p=0.04$). On pulmonary function tests, a greater reduction in % predicted FVC (54.0 vs 71.0; $p=0.03$) and % predicted DLco (21.0 vs 33.0; $p=0.03$) were also associated with an increased risk of subsequent lung transplantation or death (Table 3).

DISCUSSION

Pulmonary hypertension associated with sarcoidosis presents a number of unique diagnostic and therapeutic challenges. With a multitude of potential pathophysiological mechanisms, and lack of controlled treatment trials with well-defined populations, treatment decisions in SAPH may be difficult. Nevertheless, an increasing number of observational studies have reported significant functional and haemodynamic improvements following pulmonary vasodilator therapy. Our results, the largest treated

SAPH cohort yet reported, further demonstrate the potential benefit of targeted PH therapies in these patients.

Following comprehensive evaluation, treatment with advanced therapies in our cohort resulted in statistically significant improvements in 6MWD, BNP levels and TAPSE at six months. Improvement or stabilisation in WHO functional class was achieved in 26 (78%) patients. The optimal method by which to gauge response to treatment in SAPH (as discussed in more detail below) is not known. At our institution, regular review with clinical, functional and echocardiographic assessments is performed, rather than routine repeat cardiac catheterization.

The improvement in 6MWD in our cohort, although modest, is of similar magnitude to that reported in several pulmonary arterial hypertension (PAH) controlled trials (20-23). In PAH, a minimal clinically important change in 6MWD of 33 metres has been proposed (24), although several confounders specific to sarcoidosis make the value of this threshold in SAPH less clear. Co-existent fibrosing lung disease, airflow obstruction, musculoskeletal disease and general deconditioning may all

Table 3. Echocardiographic parameters at baseline, and following 6 months of advanced therapies. Values are expressed as median and range.

	Survivors n=22	Deceased/Transplanted n=11	p value
Age (years)	53.5 (9.2)	57.1 (13.3)	NS
Follow-up duration (months)*	23.2 (6.0-66.4)	13.5 (2.0-37)	
Scadding CXR stage			
Stage 4	15	10	NS
non-Stage 4	6	2	NS
Haemodynamic information			
mPAP (mmHg)	44.4 (9.4)	42.7 (7.7)	NS
PVR (WU)	7.8 (3.5)	15.7 (7.0)	0.01
Cardiac index (L/min.m2)	2.6 (1.4)	1.6 (1.0)	0.04
Pulmonary function test			
DLco%	33.0 (14.7)	21.0 (8.0)	0.02
Kco%	57.3 (15.2)	46.3 (11.8)	NS
FVC %	71.0 (22.9)	54.0 (14.2)	0.03
FEV1 %	55.3 (19.6)	46.0 (14.3)	NS

* median (range)

CXR=chest radiograph; mPAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; WU=Wood units; DLco=diffusing capacity for carbon monoxide; Kco=transfer coefficient; FVC=forced vital capacity; FEV1=forced expiratory volume in 1 second; NS=not statistically significant ($p>0.05$)

limit functional capacity and create uncertainties when utilising 6MWD as a SAPH specific endpoint (25). In our cohort, further uncertainty is present due to the lack of follow-up 6MWD data in a significant proportion of patients. Three patients died within six months of commencing advanced therapies, and three patients deteriorated to the point that 6MWD was not possible. Three patients were followed up at another institution, and in the remaining five patients, 6MWD data was unable to be located. Such a significant proportion of missing data is a major methodological limitation.

We noted an improvement in TAPSE in our cohort, a finding that has not previously been reported following treatment of SAPH. TAPSE, a highly reproducible echocardiographic measure of right ventricular function, has been demonstrated to be a useful prognostic marker in idiopathic pulmonary hypertension (IPAH), systemic sclerosis-associated PH and Eisenmenger syndrome (26-28). Impairment in RV function results in a reduction in TAPSE, and given the prognostic importance of RV function in PH (29) and difficulty in accurately assessing RV function in clinical practice, TAPSE is increasingly recognised as a valuable prognostic determinant. In PAH, an increase in TAPSE of > 2 mm after initiation of PH specific therapy was associated with improvements in 6MWD, BNP levels and functional class (30). Furthermore, an improvement in TAPSE to ≥ 20 mm (following treatment) was associated with improved survival (31).

An improvement in serum BNP levels at six months was also noted in our cohort. While serum natriuretic peptide levels have been shown to improve in parallel with haemodynamic function following the initiation of advanced therapies (32, 33) it is not yet certain whether these biomarkers adequately track haemodynamic change in order to be a valid end point in clinical trials. The lack of validated treatment outcome measures in SAPH represents a major area of uncertainty. Despite this, demonstration of concordant trends in 6MWD, TAPSE and BNP in a subgroup of patients in our cohort suggests that we are observing a true treatment effect, rather than statistical chance. Furthermore, treatment response rates in our cohort are generally similar to those reported in other series of SAPH targeted therapies, including inhaled iloprost, sildenafil, bosentan and IV epoprostenol (13-16). Reassuring-

ly, targeted PH therapies were generally well tolerated, although two patients were converted to an alternative class of agent due to side-effects (deranged liver function tests on bosentan, ocular side-effects on sildenafil).

Despite overall favourable treatment responses, ten patients died during follow-up. Of these, only one patient demonstrated an improvement in objective measures (with an increase in 6MWD from 120 to 180 metres) at six months, suggesting that patients who fail achieve either functional or echocardiographic improvement following initiation of targeted therapies may benefit from early referral for lung transplantation evaluation.

A higher PVR and reduced cardiac index at RHC, and greater reduction in % predicted FVC and TLco were identified as the pre-treatment clinical variables most strongly associated with subsequent mortality. PVR (a derived value incorporating the mPAP, left heart pressure and cardiac output), when elevated, is a strong predictor of mortality in diffuse lung disease of varying aetiologies (including IPF and sarcoidosis) (34). PVR reflects disease affecting the small resistance pulmonary arterioles (35), such that a relatively minor reduction in vessel luminal calibre results in a large increase in flow resistance (as defined by Poiseuille's law). Whether the association between a higher pre-treatment PVR and subsequent mortality (despite therapy) represents a 'microvascular' SAPH phenotype with a poorer prognosis, or is a reflection of lower cardiac output, is not clear and warrants further evaluation.

Several pathophysiological mechanisms may contribute to elevated pulmonary vascular pressures in SAPH, and correctly identifying the underlying pathogenic pathway is vital in defining the optimal treatment regimen. In one series, PH associated with left ventricular dysfunction was identified in 15% of sarcoidosis patients referred for RHC, with this patient group experiencing higher mortality compared to patients without LV dysfunction (7). In our review, patients with significant left ventricular dysfunction (defined as a PCWP of ≥ 15 mmHg at RHC) were intentionally excluded in order to identify potential treatment benefit in a well defined population. Interestingly, in a subgroup of patients who underwent CMR (n=25), evidence of active or previous sarcoid cardiac involvement was present in approximately one third of patients, with the left

ventricle a frequent area of involvement. Whether all patients with elevated pulmonary vascular pressures should be screened for cardiac sarcoid involvement is unknown and warrants further evaluation.

A significant minority of patients in our cohort (25%) did not have radiographic evidence of pulmonary fibrosis, suggesting a mechanism other than fibrotic vascular ablation as the cause for elevated pulmonary vascular pressures (figure 2). Arterial granulomata in explanted lungs of sarcoid patients have been described (8), and in systemic lupus erythematosus-associated PH, improved pulmonary haemodynamics following immunosuppressive therapy has been reported (36, 37). It is intriguing to hypothesize a similar 'inflammatory vasculopathy' may contribute to the development and progression of SAPH in at least a subgroup of patients.

Consistent with several other retrospective series (13-17), SAPH in our cohort was not diagnosed until moderately severe. In early stage SAPH, symptoms and signs may be relatively non-specific, and difficulty in accessing PH therapies coupled with therapeutic nihilism may deter some clinicians from actively evaluating for SAPH. Furthermore, individual screening tests are often frustratingly imprecise. Current PH guidelines (12) recommend echocardiography as an initial screening test, although its utility in advanced lung disease has limitations (38). While several other screening measures (including serum BNP, PFT profile, CT vascular dimensions, and exercise desaturation) have also been assessed, no single test fulfils all criteria necessary for ideal screening tool. The majority of patients (74%) in our cohort had CT features of a dilated main pulmonary artery (defined as the ratio of the diameter of the mPA: ascending aorta of greater than one, at the level of the mPA bifurcation). An increased mPA: ascending aorta ratio is not only a useful screening measure for PH (39, 40), it has also been reported to predict excess mortality in patients with sarcoidosis, presumably due to the effect sarcoid associated pulmonary vascular disease (41). Bourbonnais and colleagues identified an oxygen saturation of <90% after 6 minute walk test as a strong predictor of SAPH (42), while Handa identified elevated plasma NT-pro BNP levels as a useful biomarker of cardiac sarcoid involvement, although it did not prove useful in identifying SAPH per se (43). The presence of a reduced DLco has also been reported as a useful predictor of

SAPH (42, 9). It is possible that an as yet undefined combination of these non-invasive measures will provide the most sensitive screening algorithm.

As discussed previously, the optimal method for judging response to therapy in SAPH represents a major area of uncertainty. Widely adopted in PAH, the 6MWT offers advantages of simplicity, low cost and reproducibility. However in sarcoidosis, the 6MWT may be affected by a variety of factors independent of PH, including musculoskeletal disease, cardiac dysfunction, parenchymal lung disease, depression and fatigue (25). In systemic sclerosis, where extra-pulmonary symptoms are also prominent, similar confounders have been described when using the 6MWD as an outcome measure in thera-

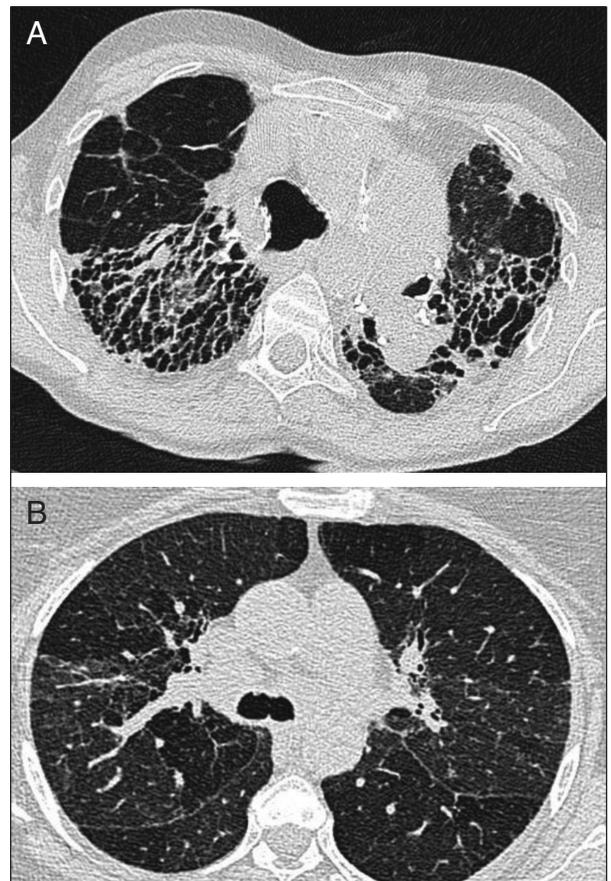


Fig. 2. High resolution computed tomography (HRCT) images from two patients with SAPH of similar haemodynamic severity. The differing extent of fibrotic pulmonary change suggests pathophysiologic mechanisms other than simple fibrotic vascular ablation may contribute to SAPH development.
2a. Extensive, predominantly upper lobe fibrotic changes are present.
2b. Limited peri-hilar reticular change and areas of mosaic attenuation (resulting from air trapping secondary to small airways disease).

pies for scleroderma associated lung disease (44). In the fibrotic idiopathic interstitial pneumonias, 6MWD has been shown to be highly reproducible over a short time period (i.e. one month or less) (45, 46), although marked variability exists when 6MWD is measured over a longer period (47, 48). Milman observed no significant change in 6MWD in SAPH patients treated with sildenafil, despite improvements in RHC measurements (14). We observed a reduction in serum BNP levels following treatment with advanced therapies. BNP, an important prognostic marker in PAH and PH associated with chronic lung diseases (including interstitial lung disease) (49-51), has been shown to parallel changes in pulmonary haemodynamics and functional capacity in PAH (49). A composite measure of time to clinical worsening (incorporating functional and haemodynamic assessment), if well defined and rigorously applied, may prove to be a more useful end point measure, particularly in a clinically heterogeneous disease such as sarcoidosis.

Limitations

Although encouraging, our results should be interpreted with caution given the methodological limitations inherent in retrospective observational studies. Lack of follow-up data (particularly 6MWT) was a major limitation, and the absence of a control group and small sample size were unavoidable limitations. The identification of optimal primary outcome measure (whether haemodynamic, functional or survival), remains an ongoing conundrum in PH therapeutic trials more generally. Nevertheless, we sought to limit confounders, including selection bias, by analysing response to treatment in consecutive patients, with well defined clinicopathologic characteristics, who had completed comprehensive assessment.

At the present time, there are no therapeutic guidelines for the management of SAPH. With all too frequent limitations on expensive pulmonary vasodilator therapies, adopting a treatment algorithm akin to PAH (including the use of combination therapies and prostanoids) is not always possible. Despite the limitations of our study, we believe that reporting uncontrolled pilot data such as these may help to catalyse controlled trials and the development of evidence based treatment strategies.

CONCLUSION

Untreated SAPH is increasingly recognised as a malignant prognostic determinant, and although no randomised controlled trials of PH specific therapies have been published, our results suggest that these therapies are safe in patients with SAPH. Prospective controlled studies are warranted to validate these findings before therapeutic recommendations can be made.

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