Concise report

Pulmonary arterial hypertension associated with systemic sclerosis in patients with functional class II dyspnoea: mild symptoms but severe outcome

Eric Hachulla¹, David Launay¹, Azzedine Yaici²,³, Alice Berezne⁵, Pascal de Groot⁴,⁶, Olivier Sitbon²,³,⁴, Luc Mouthon⁵, Loïc Guillemin⁵, Pierre-Yves Hatron¹, Gérald Simonneau²,³,⁴, Pierre Clerson⁷ and Marc Humbert²,³,⁴ on behalf of the French PAH-SSc Network*

Abstract

Objective. To describe the history of SSc-associated pulmonary arterial hypertension (SSc-PAH) in patients with New York Heart Association (NYHA) functional class (FC) II dyspnoea at diagnosis.

Methods. Data at the time of diagnosis were collected and analysed retrospectively for 77 consecutive patients with SSc-PAH.

Results. Twelve patients (15.6%) presented with PAH and NYHA FC II dyspnoea. After a mean follow-up of 44 months, only 4 out of the 12 PAH patients remained stable in FC II, while 8 showed worsening to FC III or IV. Three patients died during the observation period; two from PAH and one from rectal cancer. Survival in patients in FC II at diagnosis was 100, 91 and 80% at 1, 2 and 3 years, respectively.

Conclusions. A majority of patients with mildly symptomatic SSc-PAH in NYHA FC II at diagnosis have a severe disease with poor prognosis.

Key words: Pulmonary arterial hypertension, Systemic sclerosis.

Introduction

Breathlessness is a common symptom in patients with SSc-associated pulmonary arterial hypertension (SSc-PAH). A majority of patients with SSc-PAH are in New York Heart Association (NYHA) functional class (FC) III or IV at diagnosis [1, 2]. Recent data indicate that patients with severe disease in NYHA FC III or IV exhibit poorer survival as compared with patients with mildly symptomatic disease in NYHA FC II [3–5]. Until recently, little data have been published on the history and outcomes of patients with SSc-PAH who were in NYHA FC II at diagnosis. In this study, we present the functional and haemodynamic characteristics, evolution and 5-year survival observed among patients with SSc-PAH in NYHA FC II at PAH diagnosis from three expert reference centres in France.

Patients and methods

Patients from three reference centres, with expertise in the management of SSc-PAH (Béclère Hospital, Université Paris-Sud 11, Clamart; Huriez Hospital, Université de Lille 2, Lille; and Cochin Hospital, Université Paris Descartes, Paris; France), were enrolled in this study.
Patients were classified as having SSC according to Masi et al. [6] and lcSSc or dcSSc according to LeRoy et al. [7]. All consecutive SSC patients diagnosed with PAH from January 2000 were retrospectively included in the study. Patients with other causes of pulmonary hypertension (PH) were excluded (particularly patients with severe interstitial lung disease based on pulmonary functional tests and high-resolution CT scan, or those with post-capillary PH).

Diagnosis of PAH was confirmed using right heart catheterization (RHC), and defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest with a mean pulmonary arterial wedge pressure (mPAWP) ≤15 mmHg. In patients with mild mPAP increase (<35 mmHg) and normal mPAWP at rest, a loading test was done during RHC to exclude post-capillary PH due to left ventricular diastolic dysfunction, which is at least as frequent as PAH in patients with SSC [8].

Evaluation of dyspnoea was based on NYHA FC, as previously described [9]. NYHA FC was defined by the senior cardiologist or pneumologist at the time of the RHC. History and characteristics of patients at PAH diagnosis, including 6-min walk distance (6MWD), Doppler echocardiography and pulmonary function test results and haemodynamic parameters, were described according to NYHA FC. Survival data were right-censored at 5 years and survival was estimated using the Kaplan–Meier method. Comparisons of survival curves were conducted using the log-rank test. Analysis of variance (ANOVA) was used for comparisons of continuous variables and χ² testing for comparisons of categorical variables. Results of ANOVA were confirmed by non-parametric tests (Kruskall–Wallis’ test). As the non-parametric tests gave results that were consistent with those from ANOVA, only ANOVA results are presented here. This study was approved by the French ‘Informatique et Libertés’ institution in accordance with the current French legislation.

**Results**

Data from 77 consecutive patients with SSC-PAH were obtained from Béclère Hospital, Clamart (n = 43), Hôpital Huriez, Lille (n = 23) and Cochin Hospital, Paris (n = 11). As RHC (the recognized gold standard for PAH diagnosis) was used, all cases of post-capillary PH were excluded from the study. Twelve patients (15.6%) presented in NYHA FC II at PAH diagnosis. Clinical and haemodynamic data, stratified according to NYHA FC, are presented in Table 1. No difference was seen between centres (data not shown).

Patients in NYHA FC II were typically younger, with less severe haemodynamic parameters than patients in FCs III and IV; however, their duration of SSC prior to PAH diagnosis was comparable. The diffusing capacity for carbon monoxide (DLCO) was less impaired in patients in NYHA FC II, although these differences were not significant. No differences were observed between immunological status and lung volumes were subnormal (data not shown). All haemodynamic parameters were significantly less impaired in patients in NYHA FC II with lower pulmonary vascular resistance and higher cardiac index. The 6MWD was also significantly greater among patients in NYHA FC II, compared with the other patient subgroups.

Individual data at PAH diagnosis for the 12 patients in NYHA FC II are displayed in Table 2. Six patients had an mPAP <30 mmHg, further suggesting mild PAH; however, six patients exhibited higher levels of mPAP, ranging from 38 to 60 mmHg. Moreover, 5 out of these 12 patients had a cardiac index <3 l/min/m².

All patients were treated according to the current recommendations [9] at the time of diagnosis (Table 2). After

| Table 1 Characteristics of SSC-PAH patients at the time of PAH diagnosis according to NYHA FC |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Males, n (%) | NYHA II, n = 12 | NYHA III, n = 49 | NYHA IV, n = 16 | P-value |
| BMI, mean (s.d.), kg/m² | 24 (3) | 25 (7) | 23 (3) | 0.73 |
| Bibasal fibrosis on HRCT scan, n (%) | 4 (33) | 25 (52) | 13 (30) | 0.10 |
| Diffuse SSC, n (%) | 1 (8) | 11 (22) | 5 (31) | 0.34 |
| Age at SSC onset, mean (s.d.), years | 49 (16) | 52 (13) | 60 (12) | 0.06 |
| Duration between SSC onset and PAH diagnosis, mean (s.d.), years | 5 (5) | 6 (7) | 6 (7) | 0.85 |
| Age at PAH diagnosis, mean (s.d.), years | 54 (16) | 58 (12) | 66 (10) | 0.03 |
| DLCO, mean (s.d.), % predicted | 50 (10) | 44 (12) | 40 (13) | 0.12 |
| PaO2, mean (s.d.), mmHg | 76 (12) | 67 (15) | 70 (14) | 0.24 |
| PaCO2, mean (s.d.), mmHg | 35 (3) | 33 (6) | 34 (6) | 0.60 |
| 6MWD, mean (s.d.), m | 341 (135) | 286 (102) | 204 (119) | 0.0009 |
| mPAP, mean (s.d.), mmHg | 37 (12) | 47 (10) | 46 (12) | 0.02 |
| mPAWP, mean (s.d.), mmHg | 9 (3) | 8 (3) | 7 (3) | 0.16 |
| Cardiac index, mean (s.d.), l/min/m² | 3.2 (0.6) | 2.5 (0.6) | 2.2 (0.4) | 0.0001 |
| PVR, mean (s.d.), dyn/cm² | 423 (209) | 800 (366) | 922 (344) | 0.002 |

HRCT: high-resolution CT; PVR: pulmonary vascular resistance; *Bonferroni corrected for multiple comparisons.*
In this retrospective review of data from 77 patients with SSc-PAH, we observed that 12 patients (15.6%) were mildly symptomatic at the time of PAH diagnosis (NYHA FC II). Overall, mean haemodynamic parameters were less impaired among these patients vs those in FCs III and IV. Nevertheless, six patients in NYHA FC II exhibited mPAP > 35 mmHg and five patients exhibited a cardiac index < 3 l/min/m², confirming that mildly symptomatic patients with SSc-PAH frequently exhibit severe haemodynamic compromises at diagnosis.

Clinical worsening (defined as deterioration in NYHA FC) was observed in approximately two-thirds of SSc-PAH patients in NYHA FC II in our cohort, after a mean follow-up of almost 4 years. This observation is comparable with the rate of disease progression of 39% observed among SSc-PAH patients in FC II in the UK PH service [4]. Three-year survival of patients with SSc-PAH in NYHA FC II was 80% in this study, compared with 65% in patients from the UK PH service [4]. This high 3-year mortality rate questions the supposedly good prognosis of patients with mildly symptomatic disease.

It should be noted that all patients in this study were treated in accordance with PAH current guidelines, emphasizing that patients with mildly symptomatic PAH are treated with the dual endothelin receptor antagonist bosentan, in patients with mildly symptomatic (NYHA FC II) PAH, placebo-treated patients in this study were observed in a recent trial of the dual endothelin receptor antagonist bosentan in patients with mildly symptomatic (NYHA FC II) PAH to have a greater disease progression at 6 months vs bosentan-treated patients. This finding, along with the results of the UK PH service [4], suggests that PAH patients in NYHA FC II might benefit from treatment with an endothelin receptor antagonist, even in the modern management era. In a study of patients from the UK PH service [4], the 3-year mortality rate was 80% in patients with mildly symptomatic PAH, compared with 65% in patients from the UK PH service [4]. This finding, along with the results of the UK PH service [4], suggests that patients with mildly symptomatic PAH benefit from treatment with an endothelin receptor antagonist, even in the modern management era.

**Discussion**

In this retrospective review of data from 77 patients with SSc-PAH, we observed that 12 patients (15.6%) were mildly symptomatic at the time of PAH diagnosis (NYHA FC II). Overall, mean haemodynamic parameters were less impaired among these patients vs those in FCs III and IV. Nevertheless, six patients in NYHA FC II exhibited mPAP > 35 mmHg and five patients exhibited a cardiac index < 3 l/min/m², confirming that mildly symptomatic patients with SSc-PAH frequently exhibit severe haemodynamic compromises at diagnosis.

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All patients were treated with bosentan, an endothelin receptor antagonist. In patients with mild symptoms, bosentan was well tolerated and no significant adverse events were reported. In patients with more severe symptoms, bosentan was effective in improving haemodynamic parameters, with high pulmonary vascular resistance parameters, with high pulmonary vascular resistance (P 0.006) among patients in NYHA FC II (80%) vs those in NYHA FCs III (72%) and IV (30%) [Fig. 1].
by clinical practice guidelines [11]. In two different screening programmes, SSc-PAH patients in NYHA FCs I and II represented 50 and 71%, respectively, of newly diagnosed patients [12, 13]. As in our study, the reported duration from SSc onset to PAH diagnosis did not differ between patients in NYHA FC II vs those in FCs III and IV. We, therefore, consider that the better clinical and haemodynamic presentation in patients in NYHA FC II is not only due to a lead time bias. Whether better management of mildly symptomatic patients in NYHA FC II will translate into better survival in future remains to be firmly demonstrated. However, the significant clinical and haemodynamic effects of targeted therapies, such as bosentan, in patients with PAH in FC II [10], suggests that these patients may benefit from PAH specific treatment.

A possible limitation of this study is that some patients categorized in NYHA FC II at diagnosis may have underestimated their degree of dyspnoea, due to a subconscious adaption of their daily activities to their capabilities. Such an occurrence may have led to an inappropriate classification into a lower FC.

In conclusion, patients with mildly symptomatic SSc-PAH in NYHA FC II frequently present with significant marked haemodynamic compromise and poor prognosis. We observed within a 5-year period that approximately two-thirds of such patients can deteriorate to NYHA FCs III or IV and some will die, which suggests that more aggressive management may be of benefit to this patient population. Further studies are needed, however, to determine predictors of outcome in these patients. These results highlight the importance of a systematic screening strategy for SSc-PAH, even among patients who are mildly symptomatic.

### Rheumatology key messages

- More than half of SSc-PAH patients with NYHA FC II at PAH diagnosis worsened to FC III/IV after nearly 4 years.
- The estimated 3-year survival of SSc-PAH patients with NYHA FC II at diagnosis is 80%.
- Patients with mildly symptomatic SSc-PAH in NYHA FC II frequently present with severe haemodynamic parameters and poor prognosis.

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### Disclosure statement

L.G. is a consultant for Actelion Pharmaceuticals and has received lecture fees. All other authors have declared no conflicts of interest.

### References


Appendix 1