Respiratory Medicine (2012) **106**, 875–882

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Pulmonary hypertension in interstitial lung disease: Prevalence, prognosis and 6 min walk test

Charlotte U. Andersen [a,*], Søren Mellemkjær [b], Ole Hilberg [c], Jens Erik Nielsen-Kudsk [b], Ulf Simonsen [a], Elisabeth Bendstrup [c]

[a] *Department of Biomedicine, Aarhus University, Wilhelm Meyers Alle 4, 8000 Aarhus C, Denmark*
[b] *Department of Cardiology, Aarhus University Hospital, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark*
[c] *Department of Pulmonary Diseases, Aarhus University Hospital, Nørrebrogade 44, 8000 Aarhus C, Denmark*

Received 11 November 2011; accepted 22 February 2012
Available online 15 March 2012

KEYWORDS
Exercise capacity;
Interstitial lung disease;
Lung fibrosis;
Prognosis;
Pulmonary circulation;
Pulmonary hypertension

Summary
Background: Pulmonary hypertension (PH) is an important complication to interstitial lung disease (ILD). The aim of the present study was to investigate the prevalence and impact of PH on prognosis and exercise capacity in ILD patients.
Methods: 212 ILD patients were screened for PH by echocardiography. Criteria for PH were either a tricuspid pressure regurgitation gradient >40 mmHg, a tricuspid annular plane systolic excursion <1.8 cm or right ventricular dilatation. If possible, PH was confirmed by right heart catheterisation. Pulmonary function tests and 6 min walk tests (6MWT) were performed.
Results: 29 patients (14%) had PH, 16 (8%) had mild and 13 (6%) had severe PH (mean pulmonary artery pressure $\geq$ 35 mmHg). Compared to patients without PH, lung function parameters were lower in PH patients, a larger proportion had idiopathic pulmonary fibrosis (IPF) (41 vs 21%, $p = 0.006$), and the hazard ratio for death was 8.5 (95% CI: 4–17). After correction for lung function parameters and the presence of IPF, 6MWT was significantly lower in patients with PH compared to non-PH patients (difference $\pm$ SEM: 58 $\pm$ 22 m, $p = 0.01$).
Conclusions: PH occurred in 14% of a cohort of patients with ILD and was associated to IPF and lower lung function parameters. Mortality was markedly higher in PH patients, and the presence of PH reduced 6MWT independently of lung function and the presence of IPF. The present results emphasize the need for intensified treatment of patients with ILD and PH.

* Corresponding author. Tel.: +45 87 16 76 92.
E-mail address: cua@farm.au.dk (C.U. Andersen).

0954-6111/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2012.02.015

Introduction

Pulmonary hypertension (PH), defined by a mean pulmonary artery pressure (MPAP) >25 mmHg, is an important complication to interstitial lung disease (ILD). The gold standard for diagnosis of PH is right heart catheterisation (RHC). Echocardiography remains the best non-invasive screening modality for PH,[1] although it is subjected to inaccuracies.[2,3]

So far, studies investigating the occurrence of PH in ILD have focused on lung transplant candidates with idiopathic pulmonary fibrosis (IPF),[4,5] patients with sarcoidosis,[6,7] or scleroderma-related ILD.[8,9] The results have shown a great variation with regard to prevalence, while PH has been shown to worsen the prognosis in both patients with IPF[4] and scleroderma-related ILD.[10] However, at tertiary referral centres, physicians are faced with a broad and heterogeneous group of patients with ILD, of which several subtypes are rare.[11] At present, very few data describe the occurrence and impact on prognosis of PH in such populations. Furthermore, it is unclear whether PH per se reduces exercise capacity in ILD, or if it simply reflects more advanced lung disease.

The aim of the present study was to estimate the prevalence, the prognostic effect and the impact of PH on exercise capacity measured by the 6 min walk test (6MWT) in ILD patients at a tertiary referral centre in Denmark.

Methods

The study was approved by The Danish Research Ethics Committee, Region Central Jutland (Issue nr: M-20080219) and conducted in accordance with the Helsinki Declaration.

Study subjects

Consecutive patients were recruited during 16 months at a tertiary referral centre for evaluation and treatment of ILD in Denmark. Potential participants included all prevalent and incident cases during the study period with any subtype of ILD, including patients with sarcoidosis stage II–IV. All patients had an echocardiography performed as part of their initial evaluation.

Inclusion criteria were: age >18 years, written consent and a diagnosis of ILD according to ATS/ERS guidelines[12] based on an overall assessment of high-resolution computer tomography (HR-CT) scan, lung function tests, bronchoscopy and biopsy, if available.

Time of inclusion was the date, when echocardiography was performed.

Diagnoses

Patients were divided into eight diagnostic groups (IPF, Non specific interstitial pneumonia, desquamative interstitial pneumonia, hypersensitivity pneumonitis, ILD associated to rheumatologic disorders, sarcoidosis stage II–IV, end-stage fibrosis (manifest end-stage fibrotic changes and indeterminable underlying ILD) and other (including patients with unclassified ILD)).

37 patients had a clinical working diagnosis of "unclassified ILD" at the time of inclusion. 21 of these were reclassified into one of the other diagnostic groups after re-evaluation of clinical course, HR-CT scans and biopsies. It was not possible to reclassify 16 patients, who were put in the category "other" types of ILD.

Use of medication and presence of concomitant cardiovascular disease were assessed by interviews and patients' records.

Echocardiography

The tricuspid regurgitation jet was measured by Doppler echocardiography in multiple projections, and the tricuspid pressure regurgitation gradient (TR) was calculated from the modified Bernoulli equation: $4v^2$ (v = peak velocity of tricuspid regurgitation, m/s). Dimensions of the ventricles were evaluated from standard projections. The tricuspid annular plane systolic excursion (TAPSE) was assessed in the four chamber apical window with the M-mode cursor through the lateral tricuspid annulus ring. Respiratory compression of the caval vein was evaluated, and left ventricular systolic function was assessed by shortening fraction and wall motion index.

Criteria for a positive screen for PH on echocardiography were: TR >40 mmHg, right ventricular dilatation or decreased TAPSE (<1.8 cm).[13] If the acoustic windows were too poor to measure at least one of these parameters, patients were excluded from the analysis.

RHC

Patients screened positive for PH on echocardiography were asked to undergo RHC performed with a Swan–Ganz catheter.[14] For patients on oxygen therapy, this treatment was continued during RHC. Otherwise, oxygen was not used. If patients were formerly diagnosed with PH by RHC, and signs of PH on echocardiography were still obvious at inclusion, results from the former RHC were used.

Patient groups

The non-PH group comprised patients screened negative for PH by echocardiography, and patients who were screened positive by echocardiography but had an MPAP <25 mmHg at RHC. Patients with $25 \leq$ MPAP < 35 mmHg or a $40 <$ TR ≤ 60 mmHg in the absence of RHC constituted the mild PH group, and severe PH encompassed patients with MPAP ≥35 mmHg or TR >60 mmHg in the absence of RHC. The PH group included patients with mild or severe PH.

Mortality

Survival status was assessed using the electronic system at Aarhus University Hospital in which deaths are registered on a week-to-week basis.

Lung function

Lung function tests included spirometry, body plethysmography and determination of diffusion capacity for