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Management of idiopathic pulmonary fibrosis and pulmonary hypertension

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Abstract. Idiopathic pulmonary fibrosis (IPF) is an untreatable diffuse parenchymal lung disease with a median survival of approximately three years. Pulmonary hypertension (PH) is frequently seen in patients with IPF and is commonly attributed to hypoxic vasoconstriction and capillary destruction. Pathology findings include endothelial proliferation and medial hypertrophy that exceed those expected in the setting of hypoxia. Non-invasive evaluation has limited sensitivity and specificity for the diagnosis of PH in IPF; therefore, right-heart catheterisation remains the 'gold standard' diagnostic test. PH in patients with IPF is associated with decreased exercise capacity and worse survival. Given the grave consequences of this condition, treatment of PH could improve functional outcomes and survival. However, possible treatments such as long-term supplemental oxygen and targeted vascular therapy are either unstudied or remain unproven. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30 Suppl 1: 33-36)*

Key words: echocardiography, idiopathic pulmonary fibrosis; pulmonary hypertension, right heart catheterisation

Introduction

Idiopathic pulmonary fibrosis (IPF) is a life-threatening fibrotic lung disease of unknown aetiology that carries a poor prognosis with an estimated survival of between 2-5 years (1-3). There are multiple factors that impact on the prognosis and clinical course of patients with this disease (4). One well-recognised complication of IPF is the development of pulmonary hypertension (PH) that can occur at any stage of the disease and frequently complicates its course (5-7). This has been shown to impact upon patients' exercise and functional capacity and is associated with a worse survival (Figure 1) (6-8).

The reported incidence and prevalence of PH in the setting of IPF has not been well described in the literature, with a reported occurrence ranging between approximately 30 to 85% (4). This wide range may be due to several reasons such as the inclusion

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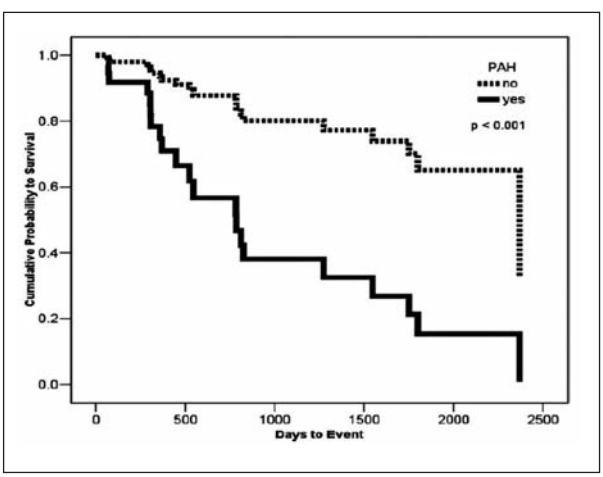

Fig. 1. Mortality in IPF with/without PH (6)

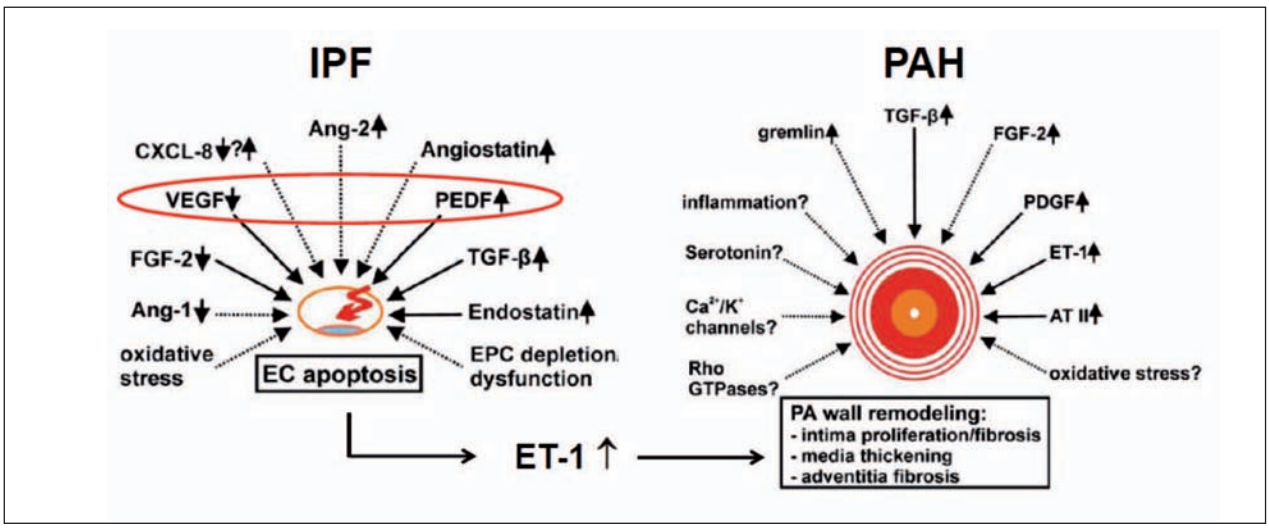

Fig. 2. Pathogenesis of IPF and PH (9)

of patients with different disease stages or transplant status being included in studies, and/or the application of different diagnostic methods for PH, particularly with the difficulties of obtaining accurate echocardiographic measurements in IPF patients. Possible pathogenic mechanisms of PH in IPF include vascular destruction, pulmonary hypoxic vasoconstriction and endothelial apoptosis and growth factor-induced remodelling of the pulmonary artery wall (Figure 2) (9). Thus, it seems likely that the same biological processes underlying fibrosis progression are also involved in the vascular remodelling and PH (10).

Considering the reduced functional status and prognosis, the identification of PH in IPF patients is crucial (4). However, as the symptoms of PH in IPF are relatively nonspecific, the development of PH in a patient with known IPF can be easily overlooked and a high degree of clinical suspicion is paramount. This case study describes the diagnosis and clinical management of a patient with IPF with co-existing PH.

Case report

Presentation

A 70-year-old, non-smoking male and former professional cyclist presented with progressive dyspnoea during exercise over the last 18 months. These symptoms had reportedly worsened significantly in the past six months. There was no history of any additional serious illnesses.

Diagnosis

Pulmonary function tests and electrocardiography (ECG) were reasonably typical except for abnormal maximum vital capacity (VC) and total lung capacity (TLC) (Table 1). Subsequent to therapy with intravenous pulse cyclophosphamide (CPX), capillary blood gas analysis (BGA) revealed a reduction of pO_2 from 69 mmHg at rest to 53 mmHg upon exercise. High resolution computed tomography (HRCT) showed evidence of honeycombing and traction-bronchiectasis. Standard and TAPSE (tricuspid annular plane systolic excursion) echocardiography were inconclusive. Right-heart catheter testing (RHT) revealed a pulmonary artery (PA) pressure of 82/49/12 mmHg, a Pulmonary Vascular Resistance (PVR) 600 $dyn \cdot s \cdot cm^{-5}$, a Transpulmonary Pressure Gradient (TPG) of 39 mmHg, and a CO of 5.2 $L \cdot min^{-1}$

Discussion

PH in IPF is frequent (it occurs in approximately one-third of all IPF patients) and compli-

Table 1. Pulmonary function test results

		Soll	1	%1/S	2	%2/S	D% (2/1)
VC MAX	[L]	4.23	0.98	23.1			
ERV	[L]	1.02	0.53	52.2			
IC	[L]	3.21	0.44	13.9			
FEV 1	[L]	3.08	0.98	31.8			
FEV 1 % VC MAX	[%]	73.71	100.00	135.7			
MEF 75	[L/s]	7.18	3.19	44.4			
MEF 50	[L/s]	4.15	3.07	74.0			
MEF 25	[L/s]	1.41	1.94	137.6			
PEF	[L/s]	7.98	3.51	44.1			
FIV1	[L]		0.84				
R tot	[kPa*s/L]	0.30	0.26	85.4			
SR tot	[kPa*s]	1.18	0.45	38.5			
ITGV	[L]	3.80	1.55	40.9			
RV	[L]	2.78	1.02	36.7			
TLC	[L]	7.30	2.00	27.3			
RV % TLC	[%]	43.21	51.08	118.2			
DLCO SB	[mmol/min/kPa]	9.02					
DLCO/VA	[mmol/min/kPa/L]	1.24					
RV-SB	[L]	2.78					
VIN	[L]	4.23					
VA	[L]	7.15					
TA	[s]						

cates the clinical course of patients with IPF. It has a significant impact on outcomes and increases mortality. It is therefore important to detect, but with common pathologic origins, it is easily overlooked. PH is generally defined by the presence of an increased normal mean PA pressure of ≥25 mmHg on right-heart catheterisation (RHC), and a decreased pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg (11). Diagnostically, recognising underlying PH in the setting of IPF remains challenging because of non-specific clinical symptoms and unrevealing ancillary testing. As yet, no non-invasive measurement has been shown to suffice as an adequate screening or diagnostic tool for the presence of PH in IPF (12). Non-invasive diagnostic methods provide clues for the diagnosis, but have limited sensitivity. For example, forced vital capacity (FVC) and exercise testing in IPF patients do not correlate with PH patients, although there does appear to be a correlation with gas-exchange parameters (DL_{CO}) and O_2 requirement (6).

Doppler echocardiography (ECHO) is commonly used to estimate systolic PA-pressure and to diagnose PH, and also provides additional accurate information regarding associated cardiac abnormalities, such as measurement of the right ventricular systolic pressure (RVSPecho) based on the estimated flow of the tricuspid regurgitant jet (13-15). However, it is frequently inaccurate in patients with advanced lung disease and leads to considerable over-diagnosis of PH and is therefore not considered an accurate tool for the assessment of PH in IPF (16, 17). The only reliable and 'gold standard' diagnostic tool for PH is RHT, but this is invasive with the inherent risk of complications (4).

There are also limited data on the treatment of PH in patients with IPF. The treatment of PH in patients with IPF is based on multiple factors, including disease severity, functional status and degree of hypoxaemia. Long-term O_2 administration for the correction of hypoxaemia should be recommended. Medications currently approved to treat PH have been administered in the setting of IPF, such as phosphodiesterase-5 inhibitors, non-selective endothelin receptor antagonists and prostacyclin analogues (18-22). Lung transplantation should be considered in patients refractory to pharmacological treatment. The availability of new pharmacological agents in the treatment of PH has raised the possibility of therapy in patients with IPF and associated

PH. Whether these PH-targeted therapies may be of benefit in this patient group, in terms of improving functional outcomes and survival, remains uncertain. (7, 23).

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Disclosures:
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