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# Pulmonary hypertension in idiopathic pulmonary fibrosis: a review

*T.J. Corte[1], S.J. Wort[1, 2], A.U. Wells[1, 2]*

[1] Department of Thoracic Medicine Royal Brompton Hospital, London, UK; [2] Imperial College, London, UK

**Abstract.** Pulmonary hypertension (PH) is a common in patients with idiopathic pulmonary fibrosis (IPF) referred for transplantation. When present, PH is associated with increased mortality, and may explain the deterioration of some patients with preserved pulmonary function. PH in IPF may develop as a consequence of, or disproportionate to the underlying fibrotic lung disease. The distinction between these two 'stages' of PH is essential as there are key differences in their pathophysiology, identification, and potential treatment options. Treatment advances in idiopathic pulmonary artery hypertension have focused attention on PH associated with underlying lung disease. We focus on pathogenetic mechanisms, identification of PH, and the potential for therapeutic intervention for PH in IPF. Although vascular ablation, and chronic hypoxia are both important in the aetiology of secondary PH, these mechanisms do not explain the development of disproportionate PH. In these patients, the early development of PH may be associated with increased fibrotic cell mediators, abnormal vasculature or response to hypoxia, seen in IPF. Nocturnal and exercise desaturation are common in IPF, and may precede and contribute to the development PH. Therapeutic options for PH in IPF are limited, and there have been no controlled trials. Successful therapeutic intervention in pulmonary arterial hypertension, has led to suggestions that therapeutic intervention with PH specific therapy may be useful. However, controlled trials are warranted before therapy can be recommended. In the design of such trials, the distinction between secondary and disproportionate PH is essential. *(Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 7-19)*

**Key words:** Interstitial lung disease, idiopathic pulmonary fibrosis, pulmonary hypertension, pathogenesis, right heart catheter, echocardiogram, six minute walk test, brain natriuretic peptide, nocturnal desaturation, prognosis; mortality

## Introduction

In idiopathic pulmonary fibrosis (IPF), variations in disease course and survival limit the accuracy of prognostic evaluation. Disease severity and serial declines in pulmonary function tests are independent predictors of subsequent progression (1-4), but clinical deterioration is not always associated with overt changes in the severity of interstitial lung disease. Pulmonary vascular limitation is increasingly recognised as a major complication of the disease.

The reported prevalence of pulmonary hypertension (PH) ranges from 31% to 85% (5-10). The presence of PH in IPF is associated with higher mortality (7, 11, 12), and its development con-

Received: 11 February 2009
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Correspondence: Prof. Athol. U. Wells,
Royal Brompton Hospital, Sydney st,
London SW3 6NP, United Kingdom
Tel. +44 207 3528121
Fax + 44207 3497769
E-mail: athol.wells@rbht.nhs.uk

tributes to the deterioration of IPF patients. PH is more frequent when underlying fibrosis is severe, but may occur at any stage of the disease process (7, 13, 14). In the context of advanced fibrosis, PH may be 'secondary' to the underlying disease. In milder disease, the pathogenesis, and clinical implications of PH may differ from PH in advanced fibrosis. Therefore, we consider PH in IPF in two 'stages': PH secondary to underlying lung disease, and disproportionate PH.

Historically, the importance of PH in IPF has been under-recognised. However, treatment advances in idiopathic pulmonary artery hypertension (PAH) have focused attention on PH associated with underlying lung disease. We focus on pathogenetic mechanisms, identification of PH, and the potential for therapeutic intervention for PH in IPF.

## Definition and Classification of Pulmonary Hypertension

PH is defined by the following hemodynamic parameters: sustained mean pulmonary arterial pressure (mPAP) ≥25mmHg at rest or ≥30mmHg during exercise, pulmonary capillary wedge pressure ≥15mmHg and pulmonary vascular resistance (PVR) ≥3Wood units.m$^2$.

In the reclassification of PH at the 2003 World Symposium in Venice (Table 1) (15-17), PH associated with lung disease was unified as a single group, based on a perception that it results from chronic hypoxia. The prevailing view, based on chronic obstructive pulmonary disease (COPD) data, has been that secondary PH is usually mild (18-21) with mortality determined by the severity of the underlying lung disease. Importantly, PH in some interstitial disorders (including sarcoidosis, Langerhan's cell

**Table 1.** Venice Classification of Pulmonary Arterial Hypertension (15, 17)

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic
   - 1.2 Familial
   - 1.3 Associated with:
     - 1.3.1 Collagen vascular disease
     - 1.3.2 Congenital systemic-to-pulmonary shunts
     - 1.3.3 Portal hypertension
     - 1.3.4 HIV infection
     - 1.3.5 Drugs and toxins
     - 1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
   - 1.4 Associated with significant venous or capillary involvement
     - 1.4.1 Pulmonary veno-occlusive disease
     - 1.4.2 Pulmonary capillary hemangiomatosis
   - 1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease
   - 1.1 Left-sided atrial or ventricular heart disease
   - 2.2 Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of distal pulmonary arteries
   - 4.3 Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

histiocytosis) are included in a separate miscellaneous subgroup (17), as the link to hypoxemia is less certain in these conditions. As discussed in this review, the same consideration applies to an important sub-group of IPF patients, in whom PH is disproportionate to the severity of the underlying lung disease.

## Prevalence of PH in IPF

PH is frequent in IPF, especially in severe disease. Most studies of PH in IPF are in patients referred for lung transplantation, in which the reported prevalence of PH is 32% to 46% (7-9, 13, 22, 23). PH develops over time in these patients, as demonstrated by the rise in prevalence of PH in IPF patients awaiting transplantation from 33% at initial assessment to up to 85% immediately prior to transplantation (8, 10). However, it is likely that the overall prevalence of PH in IPF is lower than in patients referred for transplantation.

However, PH is not confined to patients with advanced lung disease. Even in IPF transplantation referral cohorts, there is no correlation between the presence or the severity of PH and the extent of disease on high resolution computed tomography (CT), the forced vital capacity (FVC) or the composite physiological index (7, 13, 14, 24). However, the exact prevalence of disproportionate PH is uncertain, despite its obvious pathogenetic importance. Selection bias imposes major constraints. Cross-sectional prevalence studies are needed in IPF, to further characterise the dichotomy between secondary and disproportionate PH. Current studies, which are confined to transplantation cohorts, necessarily fail to make this essential distinction.

## Prognostic Significance of PH in IPF

The presence of PH is a malignant prognostic determinant in IPF patients (7, 11, 12). Systolic pulmonary artery pressure (sPAP) >50mmHg on echocardiography is associated with a median survival of 0.7yrs, compared to 4.1yrs for a sPAP of 36-50mmHg, and 4.8yrs for a sPAP of ≤35mmHg (11). In another IPF study, five year survival was lower in patients with mPAP >17mHg (16.7%) than for patients with mPAP ≤17mmHg (62.2%) (12). PH has also been associated with a worse outcome in IPF patients following pulmonary transplantation (25). These findings have not been universally replicated. In one study of patients referred for transplant assessment, there was no correlation between hemodynamic variables and survival (26), although the short median survival time (5.7 months) in this cohort is an important limitation. It is also uncertain whether mild to moderate PH (as opposed to severe disease) has prognostic significance. No conclusions can be reached on this point, based on the echocardiographic study of Nadrous (11), as pulmonary pressures tend to be systematically over-estimated by echocardiography in IPF (23). False positive diagnoses of PH by echocardiography must necessarily dilute the prognostic significance of the echocardiographic definition of mild to moderate PH.

## Histopathologic findings in PH

Histopathologic changes classic for PAH have been observed in PH associated with hypoxia (27), although not specifically studied in IPF. Independent of the initial trigger, the structural changes of the pulmonary bed in PH are often uniform (28, 29). Pulmonary vascular remodelling is complex, involving all layers of the vessel wall (29). Eccentric intimal thickening occurs, with fibrotic, plexiform lesions developing at branch points of 'muscular' arterioles, containing 'onion-skin' layers of cells (both myofibroblasts and endothelial cells). Eventually, these lesions become concentric and encroach on the vessel lumen. With time, they become less cellular, with extracellular matrix deposition (30). Smooth muscle hypertrophy and extracellular matrix expansion are relatively early findings; with smooth muscle hyperplasia playing a more minor role (30). Adventitial thickness increases as fibroblasts deposit collagen, inflammatory cells are recruited, and the adventitial vasa-vasorum develops (31).

## Pathophysiology of PH in IPF

The pathophysiology of PH in the context of IPF is complex. Although multiple mechanisms are likely to coexist in many cases, a broad pathogenetic

distinction can be made between secondary and disproportionate PH. Fibrotic vascular ablation and chronic hypoxic vasoconstriction appear to account for PH secondary to advanced fibrosis but are less applicable to disproportionate PH, although likely to play an ancillary role in some cases. In patients with PH out of proportion to underlying lung disease, putative aetiological factors have included molecular mediators common to PH and IPF, perturbation of the balance between angiogenesis and angiostasis and intermittent hypoxia (especially during sleep and exercise).

*Secondary Pulmonary Hypertension*

Historically, PH secondary to IPF was partially explained by the fibrotic ablation of pulmonary vessels, and the subsequent elevation in PVR. Vascular ablation is likely to play a major part in the development of PH in end-stage IPF, accounting for a rise in the prevalence of PH from 33% to 85% over time in a transplantation referral cohort (10). Plainly, this mechanism is less relevant to the sub-group of patients with disproportionate PH.

Chronic hypoxia is important in the development of secondary PH in patients with slowly progressive chronic conditions such as COPD or systemic sclerosis-related fibrotic lung disease. However, it does not explain the presence of PH in IPF patients with limited fibrosis or normoxia (7, 12-14, 24). Even in advanced IPF, chronic resting hypoxia is a late finding and is, thus, unlikely to play a primary causative role for PH. However, hypoxia is a frequent consequence of PH, as shown by a moderate correlation between resting $PaO_2$ and mPAP in IPF ($r=-0.47$, $p<0.001$) (12), and may amplify disease severity in established PH. Furthermore, longer-standing intermittent nocturnal hypoxia may play a crucial role in the development of disproportionate PH. The mechanisms involved in the pulmonary vascular response to hypoxia are, therefore, discussed below.

*Disproportionate Pulmonary Hypertension*

*1. Molecular mechanisms common to PH and IPF*

Several cell mediators are involved in the pathogenesis of both lung fibrosis and PH, suggesting an overlap in the pathogenesis of these disorders. Production of pro-fibrogenic cytokines such as 5-lipoxygenase (5-LO) and transforming growth factor-β (TGF-β) are up regulated in both IPF and idiopathic PAH (32-34). Increased 5-LO leads, in turn, to increased production of tumour necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), and fibroblast growth factor, all of which are important mediators of pulmonary vascular remodelling and lung fibrosis.

Prostaglandin-E2 (PGE2) levels are reduced in the bronchoscopic lavage fluid of IPF patients (32) and in the pulmonary vessels of patients with idiopathic PAH. Reduced PGE2 levels lead to increased production of TNF-α and TGF-β both of which are important in interstitial collagen deposition, and pulmonary vascular remodelling.

Endothelin-1 (ET-1) is clearly important in the pathogenesis of PH, with several studies showing increased ET gene expression and ET-1 levels in endothelial cells and plexiform lesions of patients with idiopathic PAH (35). In idiopathic PAH, ET-1 plasma levels (36) correlate with hemodynamic indices of PH and inversely correlate with survival (37). ET-1 also acts as a pro-fibrotic mediator. ET-1 levels are elevated in the airway epithelium of rats with bleomycin-induced fibrosis (38). Plasma ET-1 levels are higher in IPF patients, than normal controls (39, 40). In IPF, ET-1 levels are also elevated in the airway epithelium, type-2 pneumocytes and pulmonary vascular endothelial cells (particularly in the presence of superimposed PH) (40), correlating directly with mPAP and indirectly with $PaO_2$ (40-42).

ET-1 is produced mainly by endothelial cells, but also by leukocytes, macrophages, and smooth muscle cells (43). ET-1 gene expression is induced by hypoxia, shear stress, and various growth factors and cytokines (44). ET-1 acts directly on smooth muscle cells, binding to $ET_A$ and $ET_B$ receptors, activating phospholipase C, with subsequent influx of calcium ions, and vasoconstriction (45). It also acts indirectly to stimulate cytokine and growth factor production, with resultant extracellular matrix deposition (43). ET-1 also stimulates inflammation and platelet aggregation (46). It also binds to $ET_B$ receptors on endothelial cells stimulating nitric oxide (NO) and prostacyclin release leading to endothelium-dependent vasodilation. ET-1 thus has a bimodal effect, with an initial mild vasodilation, followed by prolonged vasoconstriction (47).

The role of these cell-mediators in both PH and IPF suggests an underlying link in the pathogenesis of these disorders, and may offer opportunities for therapeutic interventions that are relevant to both conditions.

*2. Angiostasis and Angiogenesis*

There is evidence for both angiogenesis and angiostasis in the lungs of IPF patients. These conflicting observations have been difficult to reconcile (48, 49). Turner-Warwick first described new vessel formation in fibrotic lungs, with evidence of anastomoses between the pulmonary and systemic circulation (50). Both angiogenic and angiostatic chemokines are present, but despite a net pro-angiogenic environment (51, 52), there is an overall reduction in vessel density (53). Traditionally, this reduction in vasculature was explained by fibrotic vascular ablation. However, although total vessel density is markedly reduced, vessel redistribution is seen in areas of fibrosis. Vessels are absent within fibroblastic foci, and microvascular density is decreased in areas of extensive fibrosis, but increased in areas of minimal fibrosis, and adjacent to fibroblastic foci (53, 54). Phenotypically, the new vessels formed in fibrotic areas are abnormal with an absent elastin layer (51, 54).

It is unlikely that either angiogenesis or angiostasis alone are responsible for the development of PH in IPF patients. The angiostatic reduction in vessel density may contribute to elevation of the PVR. In isolation, angiogenesis should not increase PVR, as the newly formed thin-walled vessels are unlikely to vasoconstrict effectively. However, it appears likely that balance of angiogenesis and angiostasis is lost in the IPF lung, with regional imbalance leading to areas of angiogenesis (adjacent to fibroblastic foci) (53) and other areas of angiostasis. One intriguing unifying hypothesis is that widespread angiostasis may represent a homeostatic response to focal angiogenesis, amplifying the development of PH.

*3. Adaptive Response to Intermittent Hypoxia*

*a) Pulmonary Vascular Response to Hypoxia*

Chronic hypoxic pulmonary vasoconstriction largely occurs in the 'muscular' pre-capillary arterioles. This adaptive response allows redirection of blood flow to better-ventilated lung, minimising ventilation-perfusion mismatch, and subsequent arterial hypoxia. Significant vasoconstriction occurs at $P_AO_2$< 70mmHg within seconds of exposure to hypoxic conditions, and reverses completely when normoxia is restored (55). Multiple mechanisms underlie the acute hypoxic vasoconstrictive response. Initially, hypoxic conditions inhibit voltage-gated potassium ion channels resulting in an influx of calcium ions and subsequent vasoconstriction via calmodulin-mediated myosin activation (55). Mitochondria may play a role in sensing cellular hypoxia, although the precise mechanism remains uncertain (56). Hypoxic vasoconstriction is dependent on an intact pulmonary vascular endothelium (57), and endothelium-derived factors, such as ET-1 are important in its mediation (58). Thus, it is likely that alveolar hypoxia has both a direct effect on adjacent pulmonary arterioles, as well as an indirect effect modulated by endothelial vasoactive mediators.

Chronic alveolar hypoxia leads to a sustained vasospastic response, associated with pulmonary vascular remodelling (59). Animal studies have shown attenuation of hypoxia-induced PH by selective and non-selective ET-1 antagonists, suggesting a key role for the endothelin pathway in the pathogenesis of PH (60). Down-regulation of synthesis of the vasodilator nitric oxide occurs in chronic hypoxia. Serotonin, a potent pulmonary vasoconstrictor, worsens PH in animal models of hypoxic PH (61). Prolonged hypoxia is associated with an influx of alveolar macrophages, neutrophils and pro-inflammatory cytokines, suggesting inflammation may play a key role (62). When present, chronic hypoxia is an important driving mechanism for pulmonary vascular remodelling.

*b) The role of Intermittent Nocturnal Hypoxia*

The prevalence of nocturnal desaturation in IPF is not widely studied. However, nocturnal desaturation is common in idiopathic interstitial pneumonia, and is not related to the severity of underlying lung disease (63). Based on these data, it is likely that the prevalence of nocturnal hypoxia is high, and under-recognised in IPF patients.

In a study of interstitial lung disease, nocturnal desaturation was associated with a significant rise in arterial ET-1 levels (64). The acute vasospastic response to hypoxia occurs within seconds (55) and

ET-1 is an important mediator in vascular remodelling and fibrosis. These factors suggest that pulmonary vascular remodelling, and in turn, the development of PH, might be driven by nocturnal hypoxia.

We propose that intermittent nocturnal hypoxia may precede and contribute to the development of PH. Repetitive episodes of acute hypoxia result in an acute rise in PVR (65) and eventually lead to vascular remodelling (perhaps mediated by ET-1), the hallmark of PH. Additionally, intermittent hypoxia may result in the resetting of peripheral chemoreceptors, and lowering of patients' hypoxic drive, as seen in other nocturnal hypoventilation syndromes (66, 67). This 'desensitisation' to hypoxia may make patients more vulnerable to exposure to daytime and exercise-induced hypoxia, which in turn, may also contribute to pulmonary vascular remodelling.

*c) The role of Intermittent Exercise Induced Hypoxia*

Exercise desaturation is frequent in IPF, especially in severe disease, and is clearly associated with higher mortality, independent of pulmonary function (68, 69). IPF patients with six-minute walk test (6MWT) desaturation to 88% have a higher mortality, similar the increased mortality seen in IPF patients with PH (69). As exercise-induced hypoxia is a feature of established PH, its presence may reflect the development of PH, in some IPF patients.

However, we suggest that repetitive, exercise-induced hypoxia may also precede and contribute to the development of PH in IPF. In a recent study of IPF patients without resting hypoxia, pulmonary pressures increased during exercise. Although oxygen desaturation did occur during exercise, oxygen supplementation did not ameliorate the rise in pulmonary pressures, suggesting that exercise-induced hypoxia is not the only mechanism contributing to the acute rise in pulmonary arterial pressures during exercise (70). Plasma ET-1 levels rise acutely with exercise desaturation (71), and may play a role in the pathophysiology of PH in IPF. Current studies of transplant populations with severe disease are not able to accurately assess this process, in which larger prospective studies of the general IPF population are warranted, particularly as there are widespread implications for oxygen therapy and pulmonary rehabilitation.

## Identification of PH in IPF

Currently, the diagnosis of PH rests on the gold-standard right heart catheter (RHC). However, RHC is moderately invasive and resource-limited, therefore not acceptable as a regular screening tool for PH. With the potential for therapeutic intervention, 'screening' IPF patients for the early identification of PH is increasingly desirable and clinically relevant, as PH may develop at any stage of the underlying disease. Elevated mPAP reflects the underlying pathology of the pulmonary vasculature but may not accurately represent the pathophysiology of the smaller pulmonary vessels. A reliable investigation reflecting the calibre of the distal pulmonary vessels is desirable, but yet to be identified. Peacock and colleagues reviewed the current end-points available for detecting and monitoring PH, concluding that they were often inadequate (72).

*Pulmonary Function*

In IPF in the absence of PH, pulmonary function testing plays a key role in the assessment of severity, and monitoring of progression. The question remains, however, as to whether particular pulmonary function profiles predict the presence of PH in IPF. Routine markers indicative of disease severity (such as FVC) are not helpful in the assessment of PH in these patients. This poor association between FVC and mPAP highlights the uncoupling of disease severity and PH seen in IPF patients.

Diffusing capacity (DLco), a non-specific marker, is reduced in both vascular and fibrotic disease. In IPF, DLco is lower in patients with PH on RHC (7). The combination of DLco<40% and requirement of supplemental oxygen is more accurate at predicting PH than pulmonary function parameters alone (sensitivity 65%, specificity 94%). Hamada *et al* confirmed these findings, showing a negative correlation between DLco % predicted and mPAP and survival (12). However, Nathan *et al* demonstrated that DLco levels, measured in isolation, are not reliably indicative of PH (13). The additional diagnostic value of adjusting DLco for alveolar volume (KCO) or forced vital capacity (FVC/DLco), in order to identify disproportionate reduction in DLco, merits further study in IPF.

Patients with both IPF and PH have lower $PaO_2$ levels than patients with IPF alone. It has been suggested that hypoxemia disproportionate to the reduction in lung volumes is a useful predictor for the presence of PH in patients with ILD. Zisman *et al* established a model inversely relating mPAP to $SpO_2$ as well as to FVC%/DLco% (73), and have validated this model in a second IPF population (74). Models such as this require further elucidation and external validation, but may be useful in non-invasive screening for PH.

*Echocardiography*

Despite limitations in visualisation of the right heart, and operator dependence, trans-thoracic echocardiography (TTE) is a useful and readily available tool for evaluation of PH (75). Tricuspid peak Doppler flow velocity correlates well with hemodynamic parameters (75, 76) and systolic PAP is relatively sensitive (79-100%) and specific (60-98%) for the presence of PH (77, 78). Measurement of sPAP is not possible in the absence of tricuspid regurgitation, and while this is rarely a problem in severe PH (79) this limits the utility of TTE in the assessment of less severe PH. Despite these limitations, TTE is the recommended tool for screening and early detection of PH by the American College of Chest Physicians (80).

In chronic lung disease, the role of TTE for the identification of PH has been questioned. In patients awaiting pulmonary transplantation, one study showed similar median sPAP values by RHC and TTE. However, measurements differed by >20mmHg in 17.7%, and correlation between the two methods was non-significant, suggesting that echocardiography is unreliable in this patient cohort (81). In patients awaiting lung transplantation, RHC and TTE measures of sPAP correlated ($r^2$=0.50), but the relationship was insufficient to justify the use TTE alone to identify PH (82). Arcasoy *et al* studied patients with advanced lung disease evaluated for lung transplantation, and found a significant correlation (r=0.69) of sPAP measured by RHC and TTE. However, 52% of measurements differed by >10mmHg, and 48% of patients were misclassified as having PH by echocardiography. TTE tended to overestimate sPAP in patients with normal pressures, and underestimate sPAP in those with PH (23).

Novel echocardiographic parameters evaluated in PH include 'time to peak pulmonary artery flow acceleration' (PAT) which inversely correlates with PVR (83). RV isovolumic relaxation time (RV IVRT), negatively correlates with mPAP and can be used in the absence of tricuspid regurgitation (84). Measurement of peak tricuspid systolic velocity on tissue Doppler is simple and reproducible, and correlates with right ventricular dysfunction (85) and PVR (86). RV IVRT measured by tissue Doppler correlates better with mPAP than conventional echocardiography (84). In one study of patients with pulmonary fibrosis and mild PH, tissue Doppler parameters of right ventricular (RV) function (such as RV E/Em index) correlated better with survival than conventional TTE parameters in one study (87).

Stress echocardiography may be a further method for the identification of early PH in IPF patients. In patients with systemic sclerosis, stress echocardiography revealed that 46% had exercise-induced PH, and that this inversely correlated with maximal workload achieved (88). Exercise-induced PH may be a predictor for the development of overt PH. Stress echocardiography may be a novel screening tool for patients at risk for the development of resting PH.

*Cardiac Magnetic Resonance Imaging*

Cardiac magnetic resonance (CMR) imaging is an excellent technique for determining right ventricular structure and function (89), also providing 3-dimensional visualisation of the pulmonary artery. Furthermore, pressure-volume loops can be constructed to assess RV contractility. CMR is also more accurate and reproducible than TTE in assessing RV wall motion abnormalities and systolic function, although assessment of diastolic function is more difficult (90).

CMR has an established role in the diagnosis and monitoring of patients with PH. RV mass index correlates with mPAP (91), and RV impairment on CMR is associated with elevated NT-pro brain natriuretic peptide (NT-proBNP) levels (89). In one study of patients with connective tissue disease and mild lung fibrosis, early signs of right ventricular dysfunction on CMR were associated with the development of PH (92). There have been no specific CMR studies in patients with PH in the context of IPF. However, it is likely that CMR will become an

important tool for the identification of PH in IPF patients, in whom TTE is somewhat less reliable especially in mild PH.

*Computed Tomography*

Computed tomography is not commonly used to identify PH as it is neither sensitive nor specific for this purpose. However, CT does have the advantage of imaging the pulmonary vasculature as well as the pulmonary parenchyma and cardiac chambers. A correlation between the diameter of the main pulmonary artery on CT and mPAP has long been recognised (93) with a main pulmonary artery diameter >3.32cm being specific (95%), but not sensitive (59%) for PH (94). A closer correlation with mPAP was found using the ratio of 'Pulmonary artery diameter'/'Ascending aorta diameter' (95). Few studies have focused on more peripheral pulmonary arteries, however Tan *et al* demonstrated an elevation in the segmental pulmonary artery size compared to its corresponding bronchus in patients with PH compared to a control group (96).

There have been few CT studies focusing on the identification of PH in IPF patients. One study of 65 patients with advanced fibrosis did not show a difference between CT measured 'main pulmonary artery diameter'/'aorta diameter' in patients with or without PH as measured on RHC (24). In patients with interstitial lung disease, the main pulmonary artery diameter, and the 'main pulmonary artery diameter'/'aorta diameter' ratio correlate poorly with RHC parameters (97).

Right ventricular size can be assessed on contrast-enhanced CT. Deviation of the interventricular septum, and reflux of contrast into the hepatic veins or inferior vena cava is specific for tricuspid regurgitation in patients with PH (98). Patients with severe PH often have pericardial thickening or mild to moderate pericardial effusions (99) however, these changes are neither sensitive, nor specific for PH. Pulmonary parenchymal changes, such as mosaicism, present in PH, are difficult to visualise in the presence of lung fibrosis.

*Functional Exercise Capacity*

Exercise-induced hypoxia occurs commonly in both IPF and PH and is likely to be multi-factorial, reflecting ventilation-perfusion mismatching, low mixed-venous oxygen, oxygen diffusion limitation and intra-cardiac shunting (100). Exercise-induced hypoxia occurs in patients with overt PH but may also precede and contribute to the development of PH in IPF patients (101).

In IPF, the 6MWT is simple, reproducible (102) and can be performed in severe disease. Desaturation during 6MWT to 88% is common and associated with increased mortality, independent of pulmonary function and resting oxygen saturation (68). In IPF patients awaiting transplantation, greater desaturation on 6MWT was present in patients with PH on RHC (7). The adverse prognostic significance of 6MWT desaturation may reflect either advanced fibrotic disease or the presence of early pulmonary hypertension (or pulmonary hypertension on exercise which may precede resting PH (101).

The clinical utility of the six-minute walk distance (6MWD) in IPF is critically dependent upon underlying disease severity. In unselected IPF patients, the 6MWD appears to have little or no prognostic value (68, 102, 103). By contrast, as in idiopathic PAH (104, 105), the 6MWD may have an important role in severe disease, based upon data from IPF transplantation cohorts (106, 107). A 6MWD of less than 350m was associated with a higher mortality (106) and in another study, a 6MWD of less than 207m predicted more strongly than FVC % predicted (with an adjusted mortality rate ratio of 4.7) (107). A weak but significant correlation between 6MWD and mPAP was demonstrated in this transplant population (107).

*Natriuretic Peptides*

Atrial natriuretic and brain natriuretic peptide (BNP) are the two main peptides in the natriuretic system. BNP is secreted by the cardiomyocytes from both left and right ventricles in response to ventricular stretch (108). Ventricular wall stretch up-regulates BNP gene transcription leading to increased BNP secretion (109). BNP is the biologically active prohormone secreted by the cardiomyocytes into the bloodstream. It has a short half-life, as it is metabolised by serum endopeptidases releasing the more stable, but inactive NT-proBNP, which is, in turn, excreted by the kidneys.

In patients with idiopathic PAH, BNP correlates with right ventricular dysfunction, functional class, hemodynamic parameters and measures of exercise capacity (110). BNP levels are elevated PH secondary to congenital heart disease, systemic sclerosis (111), and chronic thromboembolic disease (112). BNP is useful in longer-term follow up of patients with PH, with changes in BNP levels correlating with changes in hemodynamic parameters and 6MWD (113, 114).

Instability of BNP in the bloodstream makes rapid processing of the samples imperative, and assays more complicated to perform, compared to the fully automated analysis of NT-proBNP levels. Earlier studies were done with BNP, however more recently, NT-proBNP has been found to correlate with echocardiographic and CMR measures of right ventricular impairment (89), hemodynamic indices and 6MWD (115). High initial NT-proBNP is an independent predictor of poor prognosis (116). NT-proBNP is renally excreted, and therefore affected by impaired renal function. Thus, it may be a more inclusive prognostic marker, incorporating poor renal function, known to be an independent predictor of poor prognosis. NT-proBNP does not correlate with hemodynamic parameters in the presence of renal impairment, and may not be as good as BNP as a follow-up marker in PH (117).

Limited data are available for the role of natriuretic peptides in the identification of PH in chronic lung disease. BNP may be secreted in small amounts by lung parenchyma (118), but this remains unconfirmed. Elevated BNP levels in patients with chronic lung disease are associated with poorer prognosis, and exercise tolerance (119). In this study, elevated BNP correlated with hemodynamic measures for PH, and identified significant PH (sensitivity 85%; specificity 88%). Elevated BNP also predicted mortality independent of pulmonary function, suggesting that the increased mortality was related to the development of PH, and that BNP may be a useful screening modality for PH in the context of chronic lung disease. In a study of 39 IPF patients, BNP correlated with hemodynamic indices of PH, but not pulmonary function (120). BNP of 33.3pg/ml was the identified threshold, distinguishing between moderate-high and no-mild PH with a sensitivity of 100% and specificity of 89%. This study suggests that plasma BNP is a useful non-invasive measure for the identification of PH in patients with IPF, but larger prospective studies in IPF patients (also assessing left ventricular function) are warranted before natriuretic peptides are used routinely in clinical practise.

## Treatment of PH in IPF

Few clinical trials have been performed specifically addressing treatment of PH in IPF. Historically, treatment has focused on reversal of hypoxia and treatment of the underlying respiratory condition. Supplemental oxygen is recommended for the treatment of PH at large (17), with no specific data available in IPF. In light of its likely pathogenetic role, correction of chronic resting hypoxia with supplemental oxygen is important. The benefit of reversing intermittent hypoxia (at night, or on exercise) is unknown, and needs further study.

Vasodilators have been used cautiously in IPF patients, due to the potential risk of worsened gas exchange and hypoxemia (121). Shunt fraction and hypoxemia are increased with intravenous prostaglandin I2, but not with sildenafil (122, 123). Nitric oxide and sildenafil appear to cause selective pulmonary vasodilation, with maintained ventilation perfusion matching and arterial oxygenation.

Limited data in IPF and PH suggest a clinical and hemodynamic benefit of sildenafil. A single dose of sildenafil (50mg) acutely improves pulmonary hemodynamics and gas exchange (122). Furthermore, echocardiographic parameters and 6MWD improved in three IPF patients treated with sildenafil for three months (124). A study of 11 IPF patients, treated with sildenafil for three months demonstrated a mean improvement in 6MWD of 49m, with 57% patients showing a significant response (125). Sildenafil was well tolerated with only a single patient experiencing transient hypotension. Clearly, larger studies are required to clarify the role of sildenafil in this patient group.

The role of endothelin receptor antagonists (ETRA)s in IPF associated PH has not been widely studied. As ET-1 thought to be instrumental in the pathogenesis of IPF and PH, ETRAs may well be a helpful intervention. The “Bosentan use in Interstitial Lung Disease” (BUILD)-1 study demonstrated no benefit of bosentan over placebo in IPF patients (126). However, there was a non-significant trend

**Summary of Current Uncertainties**

1. PH is common in IPF patients referred for transplantation. However, studies in transplant populations do not capture the prevalence in IPF overall. Larger studies of the greater IPF population are needed to define the prevalence of PH in IPF, and to determine the best method(s) for identification of PH in these patients.

2. PH in IPF may develop as a consequence of, or disproportionate to the underlying fibrotic lung disease. The distinction between these two 'stages' of PH is essential as there are key differences in their pathophysiology, identification, and potential treatment options. When present, PH is associated with increased mortality, and may explain the deterioration of some patients with preserved pulmonary function.

3. Although vascular ablation, and chronic hypoxia are both important in the aetiology of secondary PH, these mechanisms do not adequately explain the development of disproportionate PH in IPF. In these patients, the early development of PH may be associated with increased fibrotic cell mediators, abnormal vasculature or response to intermittent hypoxia.

4. It appears likely that angiogenesis and angiostasis occur in balance in the IPF lung. It is possible that widespread angiostasis may represent a homeostatic response to focal angiogenesis, so contributing to the development of PH.

5. Nocturnal and exercise desaturation are common in IPF, and may precede and contribute to the development PH. Repetitive episodes of acute hypoxia result in acute rises in PVR, and eventually lead to vascular remodelling. Intermittent hypoxia may also lead to the resetting of peripheral chemoreceptors, and a reduction in hypoxic drive, as seen in nocturnal hypoventilation syndromes, amplifying PH.

6. Therapeutic options for PH in IPF are limited, and there have been no controlled trials. Successful therapeutic intervention in PAH, as well as encouraging case-series in patients with fibrotic lung disease, have led to suggestions that therapeutic intervention with PH specific therapy may be useful. However, controlled trials are warranted before therapy can be recommended. In the design of such trials, the distinction between secondary and disproportionate PH is essential.

towards improvement for patients taking bosentan. This may reflect the presence of a responsive subgroup, perhaps those with underlying vascular decompensation. The use of bosentan in IPF is currently being further evaluated in the BUILD-3 study. In a small study of open-label bosentan in 12 IPF patients (some with PH), bosentan was well-tolerated, but not associated with changes in clinical or physiological parameters at three months (127). No controlled studies have addressed the effect of ETRAs in IPF and PH.

We hypothesise that IPF patients may benefit from early identification and treatment of PH. It is clear that markers associated with pulmonary vascular disease such as exercise desaturation, also predict mortality. This suggests that vascular decompensation on exercise may precede the development of PH on RHC. An algorithm for the identification of patients at higher risk of developing PH, based on exercise data and other markers, is required to facilitate early intervention. In the same way that angiotensin converting enzyme inhibitors, when given following myocardial events, reduce the long-term development of cardiac failure (128); early treatment of patients at higher risk may prevent or retard the development of established pulmonary hypertension.

## Conclusion

PH is a common complication of IPF. It is associated with considerable additional morbidity and mortality. Pathogenetic mechanisms are incompletely understood although it is likely that both fibrosis and vascular remodelling share key mediators, such as ET-1. Whilst RHC remains the gold standard for diagnosis of PH at present, it is clear that non-invasive measures are desperately needed. Furthermore, detection of the early development of PH may be of clinical benefit. Importantly, the development of agents such as ETRAs for the treatment of idiopathic PAH, has raised the possibility of therapy for patients with both IPF and PH. Clinical trials to test this hypothesis are clearly warranted.

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