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"IPF Updates" Monograph Series

MANAGING COMORBIDITIES IN IPF

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CME INFORMATION

Needs Statement/Intended Audience

This activity has been planned in accordance with the need to provide pulmonologists and other health care providers with a continuing medical education activity that addresses the best practices for management of patients with IPF.

Educational Activity Learning Objective

Upon completion of this activity, the participants should be able to:

- Discuss recent evidence for treatments in the management of IPF

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Release/Expiration Dates

This activity is eligible for CME credit from **December 2009 through December 31, 2010.**

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Steven A. Sahn, MD, has received grant and research support from Centocor, Gilead, and InterMune. He has served as a consultant for InterMune, LAM Foundation, and Merck, and has received honoraria from Boehringer Ingelheim. He has received other financial or material support from UpToDate and PCCU.

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MANAGING COMORBIDITIES IN IPF

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and debilitating condition characterized by scarring of the lung tissue in the absence of a known cause.[1] The most prominent symptoms include exertional dyspnea and a chronic dry cough. IPF is the most common form of interstitial lung disease, affecting up to 42.7 per 100,000 adults in the United States (US).[2] Onset is usually between the fifth and seventh decades of life, and the mean age at presentation is 66 years.[1] Median survival from time of diagnosis is 2 to 5 years.

IPF leads to significant impairment in health-related quality of life (HRQOL). A meta-analysis of 7 studies, including 512 IPF patients, examined the impact of IPF on HRQOL.[3] These studies employed 1 respiratory-specific scale, the St. George's Respiratory Questionnaire (SGRQ), and 2 generic instruments, the Short Form-36 (SF-36) and the World Health Organization Quality of Life 100-Item Instrument (WHOQOL-100). IPF particularly affected physical health and level of independence. The degree of impairment in HRQOL was similar in patients with IPF and chronic obstructive pulmonary disease (COPD). Overall, dyspnea measures correlated moderately with scores from domains that measured physical health and energy/fatigue/pep, but measures of pulmonary function and gas exchange correlated less strongly with these and other domains.

IPF is associated with a number of comorbidities, including pulmonary hypertension, COPD, lung cancer, coronary artery disease (CAD), diastolic dysfunction, gastroesophageal reflux disease (GERD), sleep disorders, endocrine disorders, and psychiatric disturbances.[4-11] These comorbid conditions may significantly impact patient outcomes and impair HRQOL.[6,10,12-14] Although there is currently no approved therapy for IPF, addressing these comorbidities may improve patients' HRQOL and increase longevity. This monograph reviews common comorbidities associated with IPF and explores implications for the management of IPF in patients with coexisting conditions.

Comorbid Conditions

Pulmonary Hypertension

Pulmonary hypertension (PH) in IPF is more common among patients with severe fibrosis but may occur at any stage of the disease.[15] Right-heart catheterization (RHC) remains the gold standard for diagnosing resting PH.[6] Pulmonary arterial hypertension is usually defined as a mean pulmonary artery pressure (PAP) greater than 25 mm Hg at rest with normal pulmonary capillary wedge pressure (PCWP) measured by RHC. There are currently no generally accepted criteria for defining exertional PH in IPF. PH is present at rest in about 20% to 40% of patients with IPF who are evaluated for or are awaiting lung transplantation.[6]

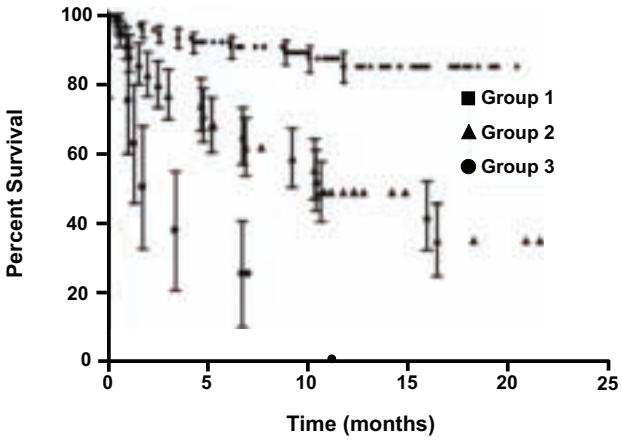
Pulmonary arterial hypertension (PAH) denotes idiopathic PH. In patients with IPF, PAH is associated with reduced exercise capacity and worse survival.[6,12,16] Among 79 patients with IPF undergoing pretransplantation RHC, PAH was associated with a lower mean diffusing capacity of the lung for carbon monoxide (DL_{CO}), increased requirement of supplemental oxygen, and lower mean distance walked and mean pulse oximetric saturation nadir during the 6-minute walk test (6MWT).[12] One-year mortality rates were significantly higher for patients with PAH compared with those without it (28.0% versus 5.5%, $P = 0.002$). Higher mPAP was linearly associated with a greater risk of mortality. While a reduced DL_{CO}, supplemental oxygen requirement, or poor 6MWT

performance should raise suspicion of PH in patients with IPF, such criteria are insufficient to rule out PH.[6,12]

Because RHC is invasive and difficult to perform routinely in clinical practice, noninvasive markers of PH have recently been explored in patients with IPF. Measurement of brain natriuretic peptide (BNP) appears to be more clinically useful than right ventricular systolic pressure (RVSP) by echocardiography (used as a surrogate for systolic PAP [sPAP] in the absence of right ventricular outflow obstruction) as a prognostic marker for PH in IPF. Song and colleagues retrospectively reviewed 131 IPF patients who underwent both echocardiography and BNP measurement (mean follow-up 10.1 months; range, 0.1–30.0 months).[16] When echocardiography was used to detect PH, using a sPAP of 40 mm Hg as the threshold, patients with PH had worse survival than those without PH (mean survival 10.8 months versus 23.7 months, $P < 0.001$). Similarly, patients with elevated BNP levels (normalized ratio > 1) had a significantly shorter median survival than those with normal BNP levels (11.0 months versus 22.5 months, $P < 0.001$). However, on multivariate analysis, only BNP levels independently predicted prognosis, suggesting that BNP is a better prognostic marker than PH via echo. The authors also looked at the BNP ratio and the echo estimate of the RVSP/systolic pulmonary artery pressure in parallel to determine whether this approach could be used to determine risk. As seen in Figure 1, survival was greatest among patients with sPAP < 40 and normal BNP levels (Group 1, 1-year mortality rate 15.2%), intermediate among patients with either sPAP ≥ 40 or elevated BNP (Group 2, 1-year mortality rate 51.2%), and lowest among those with both sPAP ≥ 40 and elevated BNP (Group 3, 1-year mortality rate 100%).[16] Thus, measurement of BNP levels and sPAP by echocardiography can be used in a complementary fashion to diagnose PH and stratify risk of patients with IPF.

Patients with IPF may develop PH as a consequence of the disease or may be disproportionate to the underlying fibrotic disease.[15] Vascular ablation and chronic hypoxia play important roles in the development of secondary PH.[6,15] However, increased capillary density and angiogenesis have been demonstrated in areas of normal lung adjacent to fibrotic regions, suggesting that other mechanisms may be critical.[6] In particular, vascular ablation and chronic hypoxia do not adequately explain the development of disproportionate PH.[6] Vascular remodeling in the setting of hypoxia may contribute to the pathogenesis of PH in IPF. Platelet-derived growth factor, transforming growth factor-ß, and fibroblast growth factor have all been implicated in the pathogenesis of IPF, idiopathic PAH, and hypoxia-induced PAH, suggesting common underlying mechanisms. The early development of PH in patients with disproportionate PH may be related to increased fibrotic cell mediators, abnormal vasculature, or response to hypoxia.[15] Nocturnal desaturation is common among patients with idiopathic interstitial pneumonia and does not appear to be related to the severity of underlying pulmonary disease. Chronic intermittent nocturnal hypoxia may play an important role in the development of disproportionate PH.[15]

Figure 1. Survival curves of subjects by sPAP and BNP levels.[16]



Group 1: sPAP < 40 mm Hg and BNP ratio < 1
Group 2: either sPAP ≥ 40 mm Hg or BNP ratio ≥ 1
Group 3: sPAP ≥ 40 mm Hg and BNP ratio ≥ 1

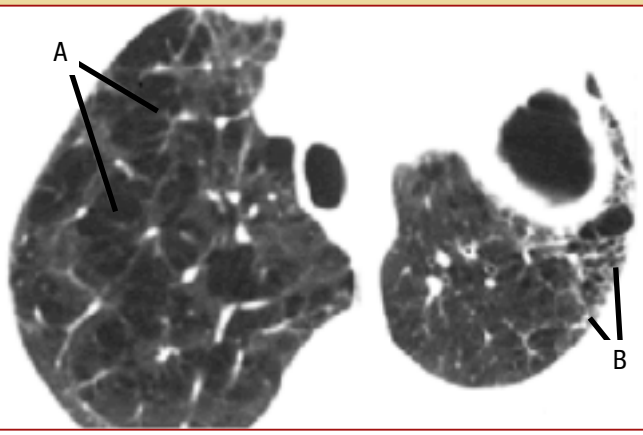
Rational approaches to treatment of PH would target hypoxemia, vascular remodeling, and/or destruction of lung parenchyma.[6] Although supplemental oxygen would be a logical choice for the prevention or treatment of PH, data do not support beneficial effects of oxygen on survival in patients with IPF and PH.[6] Classes of targeted therapies used in other forms of PH include calcium channel blockers, endothelin-1 (ET-1) receptor antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors. Calcium channel blockade does not play a role in the treatment of the majority of patients with PH. Ongoing trials are examining the efficacy and safety of ET-1 antagonists (bosentan and ambrisentan), inhaled prostacyclin analogs (iloprost and treprostinil), and the phosphodiesterase-5 inhibitor sildenafil in patients with IPF and PH.[17]

COPD (Emphysema)

IPF is associated with an elevated risk of emphysema. The prevalence of emphysema, confirmed with high-resolution CT (HRCT), in a cohort of 110 patients with IPF was 28%.[10] Among patients with IPF, emphysema was significantly associated with male gender and with smoking. Echocardiographic features of severe PH were seen in 21/29 patients (72%) with IPF and emphysema. Compared with IPF patients without emphysema, those with emphysema had a significantly higher mean decrease in oxygen saturation during rest and exercise, a significantly higher mean fibrosis HRCT scan score, a significantly higher eSPAP, and significantly lower median survival time (25 versus 34 months). The 2 most important variables associated with mortality were FVC < 50% predicted and eSPAP ≥ 75 mm Hg. Thus, higher mortality among IPF patients with emphysema appears at least partially associated with the development of severe PAH.

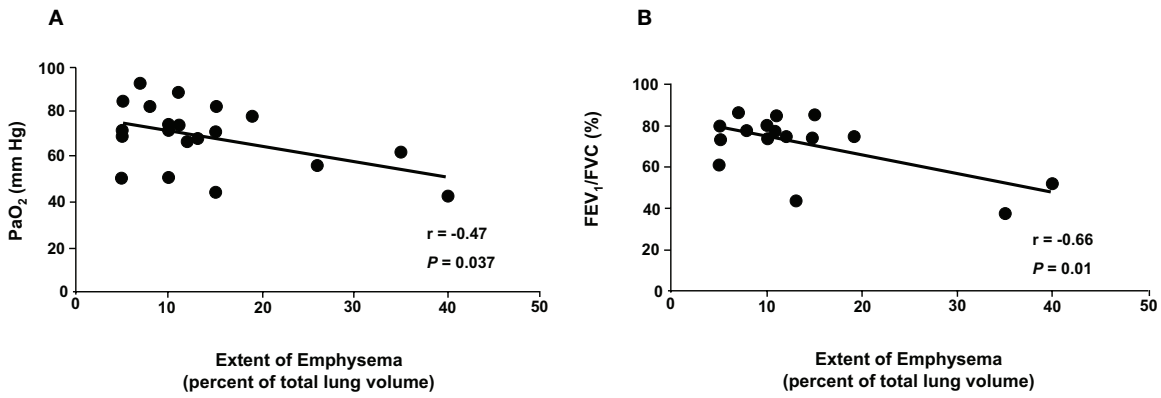
PFTs may be misleading in IPF patients with emphysema because lung volumes may be preserved and FEV_1 and FEV_1/FVC may be normal.[18,19] This may occur because the fibrosis prevents the early airway closure which is characteristic of emphysema, leading to normal ventilation of emphysematous areas, including bullae. Emphysema in the setting of IPF confounds PFT results but also significantly and independently contributes to functional impairment and exertional dyspnea.[19] Mura and colleagues compared 21 IPF patients with emphysema with 21 IPF patients without emphysema matched for age, sex, race, BMI, treatment, and radiographic extent of total disease.[19] All enrolled subjects were former smokers and had no clinical, radiographic, or electrocardiographic evidence of heart failure, PH, or acute inflammation. Patients had a high frequency of emphysema in the upper lobes with fibrosis in the lower lobes (Figure 2).[19]

Figure 2. Severe emphysema (A) and honeycombing (B) in a patient with IPF and emphysema.[19]



As expected, IPF patients with emphysema demonstrated significantly higher residual volume and total lung capacity (TLC) compared with those without emphysema. Among IPF patients with emphysema, extent of emphysema was significantly correlated with PaO_2 (r = -0.47, P = -0.037) and FEV_1/FVC (r = -0.66, P = 0.010) (Figure 3).[19] This study demonstrated that having half the total lung volume affected by IPF and emphysema causes as much physiological impairment as having the same amount of lung volume affected by IPF alone. Emphysema caused a similar degree of impairment in diffusing capacity and gas exchange (ie, 2 of the central features of lung impairment in PF) as IPF.

Figure 3. A: Relationship between extent of emphysema (percent of total lung volume) and PaO_2 in Group 1 (n = 21). B: Relationship between extent of emphysema (percent of total lung volume) and the ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) in Group I (n = 21).[19]



Cottin and Cortier recently suggested that PF with emphysema be considered a unique clinical syndrome resulting from the association of distinct features (ie, tobacco smoking, severe dyspnea, unexpected subnormal spirometry findings, severely impaired transfer capacity for carbon monoxide, hypoxemia at exercise), characteristic imaging features (ie, centrilobular and/or paraseptal emphysema, and diffuse interstitial opacities suggestive of pulmonary fibrosis of the lower lobes), and an elevated risk for severe PH.[20] Recognition of IPF with emphysema is important for the following reasons: (1) the risk of PH is elevated and is associated with worse survival; (2) lung volumes are likely to be relatively preserved and thus not relevant for follow-up; (3) responses to clinical interventions may differ in IPF patients with versus without emphysema, confounding clinical trials results; (4) interstitial patterns not characteristic of IPF or emphysema have been observed in patients with IPF plus emphysema and may contribute to pathophysiology; and (5) diagnostic criteria for IPF may not apply to all IPF patients with emphysema since these patients may have normal lung volumes despite advanced disease and a requirement for long-term nasal oxygen therapy.[20]

Lung Cancer

Most data suggest that lung cancer occurs in 10% to 30% of patients with IPF.[5] The increased risk of lung cancer in IPF may be explained by IPF contributing to the development of lung cancer, lung cancer playing a role in the development of IPF, and/or by common mediators causing both lung cancer and IPF. Proposed pathogenetic mechanisms are summarized in Table 1.[5]

Tuberculosis should be considered in the differential diagnosis of lung cancer in patients with IPF. The incidence of tuberculosis in patients with IPF is about 6.3%, more than 5 times that of the general population.[21] Atypical manifestation of pulmonary tuberculosis is relatively common in IPF and may mimic lung cancer or bacterial pneumonia. The most common thin section findings consistent with tuberculosis in patients with IPF are subpleural nodules and a lobar or segmental consolidation.

Table 1. Proposed pathogenetic mechanisms to explain increased risk of lung cancer in IPF.[5]

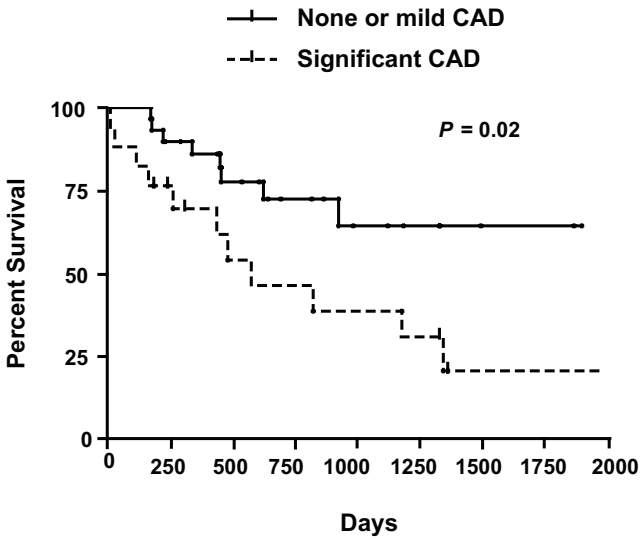
Mechanism	Pathogenesis
IPF causes lung cancer	• Chronic inflammation • Cytokine mediation • Cellular injury and genetic damage due to recurrent inflammation and repair
Lung cancer causes IPF	• Chemotherapy- and radiation therapy-induced toxicity • Surgery • Focal atelectasis "scar carcinoma" • Inhaled carcinogens (cigarette smoke, asbestos, silica, beryllium)
Common mediators cause lung cancer and IPF	• Increased imaging surveillance ("overdiagnosis bias")

Questions have been raised regarding whether IPF should be a contraindication for lung cancer surgery. In 870 patients undergoing surgery for lung cancer, IPF was associated with a significantly increased risk of surgery-related hospital mortality.[22] Postoperative 5-year survival for patients with stage I lung cancer was 61.6% for patients with IPF versus 83.0% for patients without IPF ($P = 0.019$). Thus, although IPF is associated with increased mortality following pulmonary resection for lung cancer and with poor long-term survival, a substantial proportion of patients (39.4%) with both IPF and stage I lung cancer survive for at least 5 years following surgery. These findings suggest that IPF should not be a contraindication to lung resection for stage I lung cancer in selected patients.

Coronary Artery Disease

Accumulating evidence suggests that coronary artery disease (CAD) is common among patients with IPF. A cross-sectional study of 630 patients referred for lung transplantation evaluation demonstrated that CAD is more prevalent among patients with fibrotic lung disease compared with nonfibrotic disease.[4] IPF was significantly associated with CAD (odds ratio 2.3) after multivariable adjustment. Coronary angiography was performed in 49 patients with pulmonary fibrosis (PF) and 51 with emphysema who were candidates for lung transplantation surgery.[23] CAD, defined as at least one 50% stenotic coronary artery, was diagnosed in a significantly greater proportion of patients with PF (28.6%) than with emphysema (9.8%), despite the fact that 98% of emphysema patients versus only 31% of PF patients were heavy smokers. Age, gender, and other CV risk factors were similar between patient groups. Patients with emphysema were significantly more likely to have received corticosteroids. These findings

Figure 4. Survival of IPF patients with and without CAD (Kaplan-Meier analysis).[14]



suggest that systemic inflammation may play a role in the development of both IPF and CAD.

Basavaraj and colleagues recently confirmed the association of IPF with CAD and examined the prognostic impact of CAD in this patient population.[14] Among the 61 patients with unknown CAD status, 36 (59%) were found to have CAD, demonstrating that CAD is often present even when not suspected in patients with IPF. Overall, 18% of IPF patients (N = 73) undergoing left-heart catheterization (LHC) during evaluation for lung transplant had significant CAD. When transplant recipients were excluded from analysis, IPF patients with significant CAD had significantly increased mortality compared with those with mild or no CAD (Figure 4).[14] Results of this study underscore the importance of evaluating patients with IPF for CAD and treating patients as appropriate to minimize cardiovascular risk.

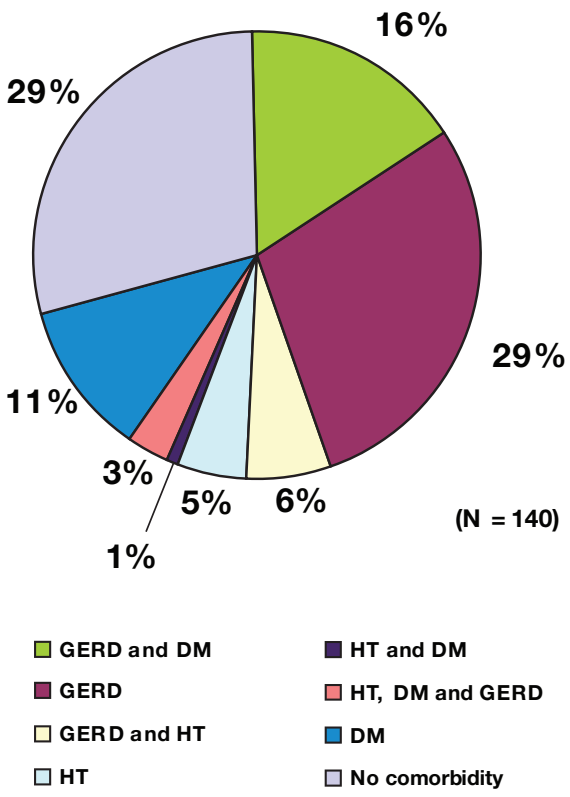
Diastolic Dysfunction

In patients with IPF, right ventricular (RV) diastolic dysfunction has been well described and is closely associated with exercise capacity and prognosis.[8,24] A recent study used conventional and tissue Doppler echocardiography to study right and left diastolic and systolic function in 22 IPF patients with mild-to-moderate PH and 22 healthy individuals.[8] Compared with controls, IPF patients demonstrated significant impairment of both systolic and diastolic RV function. Furthermore, all IPF patients exhibited a characteristic reversal of left ventricular (LV) diastolic filling to late diastole. Patients with IPF showed additional findings indicative of LV diastolic dysfunction. LV propagation velocity was also significantly lower among IPF patients versus controls. LV systolic function was preserved in IPF patients. Significant negative correlations were seen between indices of LV diastolic function and sPAP. In addition to evaluating IPF patients for RV dysfunction, physicians should be aware of the possibility of early impairment of LV diastolic function in patients with IPF. It is unclear whether treating diastolic dysfunction in IPF patients will improve function or longevity.

GERD

GERD is a common gastrointestinal disorder that typically manifests as heartburn, regurgitation, indigestion, and chest pain.[25] Less common symptoms of GERD include laryngitis, sinusitis, cough, asthma-like symptoms, and recurrent pneumonias. Epidemiologic studies demonstrate a high frequency of GERD in patients with IPF. Raghu and colleagues reported abnormal esophageal reflux in 87% of 65 IPF patients by esophageal pH monitoring and manometry.[26] Notably, only 47% of patients with IPF exhibited classic GERD symptoms of heartburn and regurgitation, while 78% of subjects reported at least 1 symptom suggestive of GERD. Manometry testing was normal, and most patients had normal peristaltic activity. Similarly, a survey of 140 patients from the Interstitial Lung Disease (ILD) database at the University of Chicago found a relatively high prevalence of GERD symptoms in patients with IPF (54%, Figure 5) compared with the general

Figure 5. Prevalence of selected comorbidities in IPF patients.[11]



population (20%).[11] In both studies, there was no correlation between GERD symptoms and PFT results.[11,26] Analysis of 18 IPF patients found that 66% had GERD based on pH monitoring.[27] Reflux was silent in one-third of IPF patients with GERD, and patients with or without GERD could not be distinguished by symptoms of heartburn and regurgitation. Furthermore, 67% of patients had supine (nocturnal) reflux; nocturnal reflux is cleared more slowly and thus has a greater potential for causing damage. Together, these studies suggest that patients with IPF should be routinely monitored for GERD.

A mechanistic relationship between GERD and IPF has been considered for many decades.[25] In addition to IPF, GERD has been associated with other pulmonary diseases such as asthma, COPD, and cystic fibrosis. Accumulating evidence from animal studies suggests that aspiration of acid into the lungs can cause pulmonary damage, including parenchymal damage, pneumonitis, increased epithelial permeability and damage, edema, and fibrotic proliferation.[25] Consistent with these findings, pulmonary evaluations and esophageal pH monitoring of 95 elderly patients with suspected GERD revealed that patients with regurgitation or large hiatal hernias were significantly more likely than those without to have bilateral pleural adhesions, thickenings, and scars.[28] Scarring and pleural thickening was more pronounced in patients with more severe GERD. The odds ratio of having respiratory symptoms was 8.7 among patients with total reflux time greater than 10% compared with those who had a total reflux time of less than 10%.

Although most prescribed therapy for IPF involves systemic corticosteroids, no definitive evidence exists for the efficacy of this treatment in IPF.[29] Oral corticosteroids have been shown to exacerbate GERD in patients with asthma, and this side effect (in addition to other corticosteroid side effects, such as reduced bone density and weight gain) is likely to occur in patients with IPF as well.[30,31] Given the growing body of evidence for the role of GERD in IPF, corticosteroids should be reconsidered as a treatment for IPF.[31] Conversely, treatment of GERD in patients with IPF may improve pulmonary function. A retrospective review examined clinical outcomes over a period of 2 to 6 years in 4 patients with newly diagnosed IPF and GERD treated solely with PPI therapy and fundoplication, if needed.[32] All 4 patients achieved long-term stabilization or improvement in pulmonary function with adequate treatment for GERD. Larger studies are needed to investigate the safety and efficacy of PPI therapy in this patient population.

Laryngopharyngeal reflux (LPR) is a variant of GERD involving the larynx and pharynx.[33] In most cases, LPR is believed to be due to retrograde flow of stomach contents into the laryngopharynx. PPIs are the mainstay of treatment for LPR and may be most effective in patients with typical GERD symptoms. In a study of 30 COPD patients diagnosed with LPR, symptoms of LPR and COPD were improved after 2 months treatment with a PPI.[34] Future research is needed to determine the incidence of LPR in IPF and evaluate whether PPI therapy improves pulmonary function in IPF patients with LPR.

Hiatal Hernia

Hiatal hernia has been identified as a risk factor for GERD. A retrospective cohort study in 85 patients with IPF examined whether the presence and extent of hiatal hernia (determined by HRCT) predicts survival over time.[35] Overall, 96% of IPF patients had a hiatal hernia (Figure 6), and 25% had a craniocaudal hiatal hernia of 5 cm or larger.[35] Surprisingly, the presence of a craniocaudal hiatal hernia was associated with improved survival ($P = 0.05$). While the presence of a craniocaudal hiatal hernia ≥ 5 cm was associated with improved median survival (1597 vs 931 days), the difference was not statistically significant. There was a trend toward increased survival in patients with GERD symptoms (HR = 0.33, $P = 0.08$). A retrospective analysis of 50 patients undergoing procedures for paraesophageal hiatal hernia, 7 of whom had pulmonary manifestations as the only GERD symptoms, found that surgical repair of hiatal hernia, along with an antireflux procedure, resulted in total resolution of respiratory complaints for up to 160 months.[36]

Figure 6. High-resolution computed tomography (HCRT) image with a mediastinal window setting shows a moderately-sized hiatal hernia containing a small amount of air (see arrows).[35]

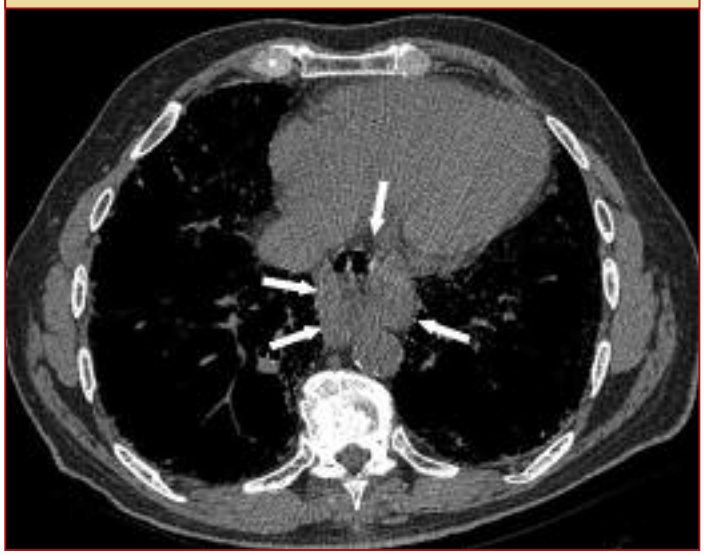
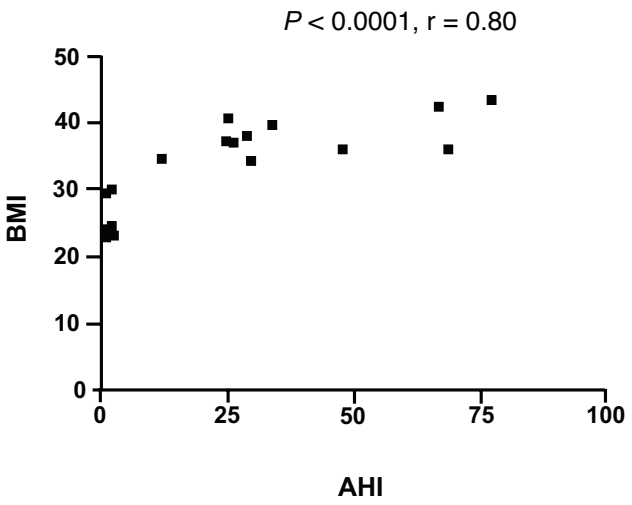


Image Courtesy of Joyce Lee, MD.

Sleep Disorders

Sleep disturbances, including obstructive sleep apnea (OSA), are common in IPF.[9,37,38] In the first study to describe sleep-related breathing disorders in IPF, nocturnal polysomnography (NPSG) was performed in 18 IPF patients to investigate complaints consistent with sleep-disordered breathing.[37] These complaints included excessive daytime sleepiness, snoring, witnessed apneas, and daytime fatigue. Patients demonstrated decreases in sleep efficiency, slow-wave sleep, and rapid eye movement (REM) sleep as well as moderate apnea and an increased mean arousal index. Overall, 11 patients (61%) met diagnostic criteria for OSA (1 mild, 5 moderate, 5 severe), 4 patients were diagnosed with primary snoring, and 3 patients had NPSG features suggesting upper airway resistance syndrome. Apnea-hypopnea index (AHI) correlated positively with BMI (Figure 7).[37] In this study, AHI was negatively correlated with FEV_1 values ($r = -0.49$, $P = 0.04$) and FVC% ($r = -0.42$, $P = 0.08$), and REM AHI was negatively correlated with FEV_1% ($r = -0.59$, $P = 0.008$) and FVC% ($r = -0.50$, $P = 0.03$). Reduced lung volumes in restrictive airway disease can decrease upper airway stability and increase resistance associated with a reduced traction on the upper airway. These changes can lead to collapse of the upper airway, especially during REM sleep when functional residual capacity is lower due to inactivity of intercostal muscles. The authors suggest that obese IPF patients with significantly

Figure 7. Correlation of AHI and BMI values.[37]



decreased pulmonary function may have an increased risk for OSA, especially during REM sleep.

Findings from a recent study in which NPSG was performed in 50 patients with IPF suggest that up to 88% of IPF patients may have OSA as defined by an AHI of more than 5 events per hour.[9] OSA was mild in 20% of patients and moderate-to-severe in 68%. Hypopneas were more prevalent than apneas. Mean BMI was lowest in patients with no OSA (26 kg/m^2) but did not differ between patients with mild versus moderate-to-severe OSA (33 kg/m^2 for both groups). GERD was common, but differences between groups in GERD prevalence were not statistically significant. Surprisingly, PFTs did not inversely correlate with the severity of sleep apnea. The FVC % was greater in the moderate-to-severe OSA group than in the no OSA group (73 ± 13.7 vs 58 ± 10.5, $P = 0.03$); the FEV_1 was also greater (2.4 ± 0.6 L vs 1.77 ± 0.7 L, respectively, $P = 0.006$). In this study the PFTs were performed in an upright or standing position. The authors suggested that forced vital capacity (FVC) measured with the patient in the supine position may better illustrate the relationship between upper airway and lung volumes during sleep. Subjects without a previous diagnosis of OSA were asked to complete the Epworth Sleepiness Scale (ESS) questionnaire and the Sleep Apnea Scale of Sleep Disorders Questionnaire (SA-SDQ) prior to NPSG.[9] Both instruments have been validated and are commonly used to measure daytime sleepiness and assess the risk for sleep apnea, respectively. Excessive daytime sleepiness on the ESS (score ≥ 10) or increased risk for OSA on the SA-SDQ (> 29 for men and > 26 for women) are considered to be risk indicators for sleep-disordered breathing. Of the 35 patients who completed the ESS and/or SA-SDQ, 31 scored as being at risk for sleep apnea; 26 of these 31 patients (84%) were determined by NPSG to have OSA. Three of the 4 patients (75%) whose questionnaire scores suggested no risk for OSA actually had this disorder based on NPSG findings. SA-SQD scores correlated with OSA severity ($r = 0.45$, $P = 0.01$), whereas ESS scores did not. The positive predictive value of the ESS was 21%, and the negative predictive value was 67%. Corresponding values for the SA-SDQ were 88% and 50%, respectively.

A study in 15 patients with IPF and 15 controls matched for age and anthropometric variables demonstrated significant impairment in sleep quality, with consequent impairment of physical and social functioning, in patients with IPF.[38] Compared to controls, IPF patients had a decrease in sleep efficiency and slow wave sleep as well as an increase in stage 1 sleep and arousal index. Tachypnea persisted during sleep, and oxygen saturation below 90% occurred during 34% of total sleep time. Clinical interviews with the Pittsburgh Sleep Quality Index (PSQI) and the Functional Outcomes in Sleep Questionnaire (FOSQ) revealed moderate-to-significant impairment in quality of sleep and daytime function. FOSQ scores correlated negatively with total sleep time with oxygen saturation below 90%. Improvement of sleep quality should be a primary therapeutic goal in patients with IPF who experience sleep disturbance, especially considering the recent finding that poor sleep

quality is associated with impaired HRQOL in patients with IPF.[13] Given the high prevalence of OSA in IPF and the relatively poor utility for sleep questionnaires in predicting OSA risk, physicians should consider formal evaluation and NPSG for all patients with IPF.

Endocrine Disorders

Disorders such as diabetes mellitus (DM) and hypothyroidism coexist with IPF and may contribute to the pathophysiology of this disease. Review of medical records of 155 IPF patients from the ILD database at the University of Chicago found that 31% had DM, and 16% had hypothyroidism, including 28% of women and 10% of men (Figure 5).[11] IPF was thus associated with elevated rates of these conditions. The prevalence of DM in the general population is about 7.8% (18.8% in adults over 60 years of age) and that of hypothyroidism is 4.6% (15% in older women).

A case-control study in Japan compared 52 patients with IPF with 184 controls.[39] Patients with a history of corticosteroid therapy were excluded due to potential negative effects of corticosteroids on glucose tolerance. Analysis of medical records resulted in a diagnosis of DM in 32.7% of IPF patients versus 11.4% of controls (adjusted OR, 4.06; $P < 0.001$). IPF patients were significantly more likely than controls to have a history of smoking (84.6% versus 50.5%, respectively). Patients and controls had similar prevalences of obesity, hyperlipidemia, hypertension, and hyperuricemia. When IPF patients with DM were compared with IPF patients without DM, the only differences observed were in diabetic parameters of fasting blood glucose (FBG) and HbA1c, although groups were not compared with respect to smoking history. Patients with DM and IPF had mild DM (mean FBG, 145.6 g/dL; mean HbA1c, 6.26%). The authors suggested that DM may increase the risk of IPF via hyperglycemia-mediated lung damage, but studies are needed to elucidate the relationship between DM and IPF.

A large case-control study (N = 920 IPF patients over 40 years of age and 3593 controls) in the United Kingdom confirmed the association of IPF with diabetes and GERD but found no association between IPF and smoking status, hypercholesterolemia, gout, or socioeconomic status.[40] The effects of DM prevention and therapy on the course of IPF have not been studied, but physicians should be alert to the possibility of DM in patients with IPF given the relatively high rate of DM in this patient population.

Psychiatric Disorders

When a patient has a chronic illness such as IPF, psychiatric issues should be considered as part of comprehensive care. It is not uncommon for patients with chronic illness to become anxious or depressed. A study of 41 IPF patients found that approximately 25% had significant depressive symptoms.[41] Subjective breathlessness correlated with depressive symptoms. In another small study, patients with IPF had significantly greater anxiety and depression scores than healthy controls, although scores were not high enough to suggest clinically significant emotional dysfunction.[42]

Psychiatric symptoms may be due to medications used to treat pulmonary illness.[7] Systemic corticosteroids in particular may cause mood disturbances (eg, mania, depression, and mood lability), which tend to occur most frequently within the first 2 weeks of treatment and to be dose-related.[7]

Patients may experience dyspnea or fatigue as manifestations of anxiety or depression, and it is important to consider whether a psychiatric disorder exists in patients with IPF.[7] Furthermore, depression is a risk factor for nonadherence in patients with chronic disease.[43] Patients with depression are 3 times more likely than nondepressed patients to be nonadherent with medical treatment. A quick way to screen IPF patients for depression is to ask if, during the past month, they have often been bothered by feeling down, depressed, or hopeless and also if they have often

been bothered by having little interest or pleasure in doing things.[44] Patients who respond "yes" to either question should be further evaluated for depression.

Role of Lifestyle Modification

For IPF and its comorbidities, lifestyle modification comprises diet, exercise, and smoking cessation. A high body-mass index increases the risk of GERD as well as hiatal hernia.[45,46] For patients who are overweight, weight loss may effectively alleviate symptoms of GERD and reduce the risk and health impact of diabetes and CAD.[47,48] A diet high in fiber, fruits, and vegetables; low in highly processed foods; and favoring lean protein as well as nuts, olive oil, and fish oil over other forms of protein and fat, is recommended to reduce inflammation and cardiovascular risk.[47] In addition to improving lung and muscle function and contributing to a healthy weight, exercise improves insulin sensitivity and acutely lowers glucose and triglyceride levels. Exercise has also been shown to improve depressive symptoms in older adults.[49]

Smoking cessation is recommended for all patients. First-line treatments for smoking cessation include counseling, nicotine replacement therapy, and pharmacotherapy (ie, bupropion, nortriptyline, and varenicline).[50] Medications used for smoking cessation should always be used as an element of a supportive program rather than on their own.

Pulmonary Rehabilitation

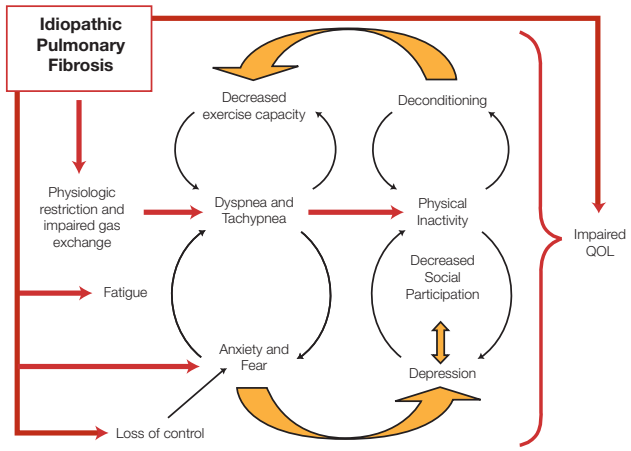
IPF and its comorbidities may lead to a number of health sequelae (eg, dyspnea, fatigue, exercise limitation, anxiety and depression, impaired HRQOL) that dramatically impact the lives of patients with this disease.[51] Specific goals of pulmonary rehabilitation (PR) in lung disease are to improve HRQOL by:

- Alleviating respiratory symptoms and complications
- Allowing a return to work or leisure activities
- Increasing control over daily functioning
- Improving physical conditioning and exercise capacity
- Improving emotional well-being
- Reducing hospitalizations[52]

Pulmonary rehabilitation is a comprehensive, multidisciplinary program that incorporates patient education, counseling, and behavioral modification to address these sequelae by improving self-management, reducing symptoms, optimizing functional capacity, and increasing patient participation.[51] Typical PR programs include a short, intensive component followed by a maintenance program. Following a comprehensive patient assessment, the rehabilitation staff tailors an exercise and overall intervention (eg, psychosocial, nutritional) program to the individual. Studies of PR in IPF have been limited but have demonstrated improvements in exercise capacity, dyspnea, and HRQOL.[51]

In addition to addressing the clinical consequences of IPF, PR has the potential to improve comorbid conditions that may be present, such as depression and CAD. PR may benefit patients with IPF by interrupting various pathways leading to

Figure 8. Pathways to sequelae or comorbidities in IPF.[51]



sequelae or comorbidities (Figure 8).[51] It has been suggested that improved walking distance after PR in patients with IPF may result from better overall cardiovascular fitness derived from the aerobic exercise regimen. Exertional dyspnea may improve when patients increase their self-exposure to the "dyspneic state," possibly by desensitizing their perception of dyspnea. Resistance training would also be expected to improve general muscle strength and tone in patients with IPF. Swigris and colleagues reported anecdotes of patients who returned to the clinic following PR with an improved sense of well-being, a greater sense of control, more energy, and a better general outlook on life.[51]

Conclusions

IPF is associated with a variety of comorbidities such as GERD, hiatal hernia, OSA, and cardiovascular disease or dysfunction. Many IPF patients suffer from multiple comorbid conditions. A comprehensive approach to the management of IPF should include routine screening for comorbid conditions. When screening suggests the presence of a comorbid condition, patients should be referred to an appropriate specialist (eg, gastroenterologist, cardiologist, psychiatrist, endocrinologist) for further evaluation and treatment. Referral to a nutritionist and a PR program may also offer benefits with respect to IPF and comorbidities. Participation in support groups may be helpful since IPF profoundly affects patients' psychological well-being and functional capacity. Given the paucity of effective treatments for this disease, it is worthwhile to explore whether treatment of comorbid conditions improves pulmonary symptoms, improves HRQOL, and/or increases longevity in patients with IPF.

IPF Resources

- The PILOT Patient Counseling Tools include patient-oriented brochures on conditions associated with IPF, pulmonary rehabilitation, and emotional well-being: http://www.pilotforipf.org/patient_tools.php.

- The Coalition for Pulmonary Fibrosis offers educational resources for physicians and patients as well as links to support groups and clinical trials information: http://www.coalitionforpf.org/.

- The Pulmonary Fibrosis Foundation similarly provides educational materials, links to support groups, and clinical trials information: http://www.pulmonaryfibrosis.org/

- *Idiopathic Pulmonary Fibrosis and You* is a comprehensive patient education guide published by the American College of Chest Physicians: http://www.chestnet.org/downloads/patients/guides/IPF.pdf.

- The American Lung Association provides information on IPF as well as other pulmonary conditions, offers smoking cessation support, and a toll-free lung help line: http://www.lungusa.org/.

- The American Gastroenterological Association Patient Center offers patient education on GERD and its treatment as well as a gastroenterologist locator: http://www.gastro.org/wmspage.cfm?parm1=848.

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BIAS, FAIR BALANCE

Was this activity fair, balanced, objective, and free from commercial bias? ❑ Yes ❑ No

If no, please state reason(s) _____

PRACTICAL APPLICATION

4 = strongly agree 3 = agree 2 = disagree 1 = strongly disagree

(a) _____ What I learned at this activity has increased my confidence in managing patients with IPF

(b) _____ What I learned at this activity will improve my patients with IPF

(c) _____ What I learned at this activity will result in an improvement in my patients' IPF management

(d) Do you intend to make changes or apply new information to your practice as a result of this activity?

_____ Yes, I plan to make changes*
_____ I'm not sure, but I'm considering changes*
_____ No, I already practice these recommendations

*If yes or considering changes, please check off what you intend to do differently or incorporate into your clinical management of patients with IPF as a result of this educational activity.

_____ Monitor patients for GERD and pulmonary hypertension
_____ Evaluate patients for lung cancer, emphysema, and CAD
_____ Incorporate pulmonary rehabilitation into the management plan
_____ Evaluate and manage sleep quality
_____ Use a quality of life instrument as a monitoring tool
_____ Provide patients with counseling tools and resources
_____ Other, please specify

_____

BARRIERS

What are the top 3 barriers that might inhibit your ability to incorporate any of the above changes into your clinical practice?

1. _____ 2. _____ 3. _____

DEMOGRAPHIC QUESTIONS

How did you hear about this CME activity?

❑ Web Search ❑ Colleague ❑ Direct Mail

Number of years in practice: ❑ ≤ 5 ❑ 6–10 ❑ 11–15 ❑ 16–20 ❑ 21–25 ❑ > 25

How many of your patients are being managed for IPF?

❑ ≤ 5% ❑ 6–20% ❑ 21–40% ❑ 41–60% ❑ > 60%

May we contact you in the future with a brief survey to assess how you have used the information presented in this activity or to assess other educational needs? ❑ Yes ❑ No

ACTIVITY EVALUATION

4 = strongly agree *3 = agree* *2 = disagree* *1 = strongly disagree*

Upon completion of this activity, I will be able to:
_____ Discuss recent evidence for treatments in the management of IPF

Please rate the overall content presented in this activity: ❑ Too basic ❑ Appropriate ❑ Too complex

ONGOING UNMET EDUCATIONAL NEEDS

Recommendations for future CME topics in this disease area: _____

_____

_____

_____

POSTTEST ANSWERS

Record your Posttest answers by filling in the blank with the correct letter from the corresponding question:

1. ❑ a ❑ b ❑ c ❑ d ❑ e ❑ f

_____

2. ❑ a ❑ b

_____

3. ❑ a ❑ b ❑ c ❑ d ❑ e

_____

4. ❑ a ❑ b ❑ c ❑ d ❑ e

_____

5. ❑ a ❑ b ❑ c ❑ d

POSTTEST

1. Which of the following disorders is *not* known to be a comorbidity of IPF?

a. Pulmonary hypertension
b. Lung cancer
c. Crohn's disease
d. Coronary artery disease (CAD)
e. Gastroesophageal reflux disease (GERD)
f. Sleep disorders

2. The endothelin-1 antagonists bosentan and ambrisentan have been shown to extend progression-free survival in patients with IPF and pulmonary hypertension.

a. True
b. False

3. Which of the following statements about IPF and GERD is true?

a. GERD occurs twice as frequently in patients with IPF as in an age-matched comparator group
b. The prevalence of abnormal reflux by esophageal pH monitoring and manometry is twice that of classic GERD symptoms in patients with IPF
c. There is a positive correlation between GERD symptoms and PFT results
d. Nocturnal aspiration of reflux acid is a major causative factor in IPF
e. None of these statements is true

4. Which of the following is not a validated quality of life instrument useful for monitoring patients with IPF?

a. St. Martin's Respiratory Questionnaire (SMRQ)
b. Epworth Sleepiness Scale (ESS)
c. St. George's Respiratory Questionnaire (SGRQ)
d. World Health Organization Quality of Life 100-Item Instrument (WHOQOL-100)
e. Sleep Apnea Scale of Sleep Disorders Questionnaire (SA-SDQ)

5. How should the issue of depression be managed in the context of IPF?

a. Family members are the best source of information about changes in affect and mood
b. Patients should be screened for depression as part of their 3 to 6-month follow-up visit, and be further evaluated if the screen is positive
c. Anxiety is no more common in patients with IPF than in the general population, and should be managed by the PCP or psychiatrist
d. Psychiatric issues should be addressed before referral for pulmonary rehabilitation, otherwise compliance is usually poor

NOTES

NOTES

Sponsored by
The France Foundation
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Supported by an
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