Respiratory Medicine (2010) **104**, 1035–1041

available at www.sciencedirect.com

ScienceDirect

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

Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis☆

Steven D. Nathan [a,*], Ashwin Basavaraj [b], Cristina Reichner [b], Oksana A. Shlobin [a], Shahzad Ahmad [a], Joseph Kiernan [a], Nelson Burton [a], Scott D. Barnett [a]

[a] *Inova Transplant Center, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22042, USA*
[b] *Georgetown University Medical Center, Washington, DC, USA*

Received 27 October 2009; accepted 9 February 2010
Available online 2 March 2010

KEYWORDS
Pulmonary fibrosis;
Coronary artery disease;
Pulmonary disease;
Chronic obstructive;
Heart catheterization

Summary
Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease with a poor prognosis for which there is no effective medical therapy. An awareness of comorbidities that are treatable and might impact outcomes in these patients is therefore very important. We sought to determine the prevalence of coronary artery disease (CAD) in IPF patients in comparison to a control group of patients with chronic obstructive pulmonary disease (COPD). We also sought to assess the impact of CAD on IPF patient outcomes.
Patients and methods: IPF and COPD transplant candidates whose work-up included left heart catheterization were categorized as having significant CAD, non-significant CAD or no disease. The risk factor profile and prevalence of CAD in both groups was compared.
Results: There were 73 IPF and 56 COPD patients. The prevalence of CAD was 65.8% in the IPF group compared to 46.1% in the COPD patients ($p < 0.028$). Significant disease was present in 28.8% of IPF patients vs.16.1% of the COPD patients ($p < 0.081$). Unsuspected significant CAD was found in 18% of IPF patients versus 10.9% of COPD patients ($p < 0.004$). Outcomes of IPF patients with significant CAD was worse than those with no or non-significant disease ($p < 0.003$) with a median survival of 572 days from the time of left heart catheterization.
Conclusion: There is a higher prevalence of CAD in IPF patients compared to a similarly matched COPD group. This increased association appeared to be independent of common coronary artery risk factors. IPF patients with significant CAD appear to have worse outcomes.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; LHC, left heart catheterization.

☆ This study was unfunded. None of the authors have any financial conflicts of interest relevant to the subject of this manuscript.

* Corresponding author. Tel.: +1 (703) 776 3610; fax: +1 (703) 776 3515.
E-mail address: steven.nathan@inova.org (S.D. Nathan).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.02.008

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disorder of the lungs with an estimated prevalence between 14 and 42.7 per 100,000 in the USA.[1] Recent evidence suggests that the incidence and overall mortality from IPF is increasing.[1–3] The peak incidence was formerly thought to be in the 5th or 6th decade of life, but there is a growing appreciation that IPF is a disease of the elderly with the highest incidence in those older than 75.[1,4] Whereas previously IPF was regarded as having an inflammatory pathogenesis, it is now commonly held to be a disease of disordered repair with the main progenitors of the disease being activated fibroblasts and myofibroblasts.[5] The unbridled proliferation of these cells is seen in conjunction with derangements in cytokine and chemokine expression. Whether these constituents of the disease have local effects only or whether they might result in systemic sequelae has led to speculation of a link between IPF and coronary artery disease (CAD).[6–9]

The clinical course of IPF is one of progressive deterioration with significant mortality and a median survival of 2.5–3.5 years.[10] It is possible that co-existing morbidities contribute to some of this mortality. Older patients have been shown to have a significantly worse prognosis with a worse survival.[2,11] Whether this is a function of the disease or a higher prevalence of comorbid conditions is uncertain.

We have previously noted that patients with IPF being evaluated for lung transplantation have a higher prevalence of CAD than patients with chronic obstructive pulmonary disease (COPD) being similarly evaluated.[12] We therefore sought to validate this finding from prospectively collected data in subsequent patients with IPF and COPD. We also sought to establish whether IPF was an independent risk factor for CAD and whether underlying CAD impacted the outcomes of patients with IPF.

Methods

Our previously performed retrospective analysis included all IPF transplant candidates who had undergone left heart catheterization (LHC) as part of their pretransplant evaluation for the period October 1996 to August 2003. For the current study we analyzed data from IPF and COPD (control group) patients who were seen and evaluated for lung transplantation for the subsequent period from September 2003 to July 2008. IPF patients were diagnosed as per the American Thoracic Society/European Respiratory Society guidelines.[13] Commonly recognized risk factors for coronary artery disease were also collated. These included a history of smoking, hypertension, diabetes mellitus, hypercholesterolemia and a family history of CAD. In addition, it was noted whether patients had a history of CAD prior to their routine pretransplant LHC. Based on the results of the LHC, patients were categorized as having significant CAD (need for an intervention or major vessel with >50% lesion), non-significant CAD (< 50% occlusion of major vessel or disease of smaller vessels) or no disease. Lastly, we determined the mortality of those IPF patients with significant CAD versus those with no or non-significant CAD. This study was approved by the Inova Institutional Review Board.

Statistics

Continuous data are presented as mean and range or standard deviation. Categorical data are presented as frequency and percent. Continuous data were tested for statistical significance via Students' *t*-test or One-Way Anova, where appropriate. Categorical data were tested via chi-square. Unconditional logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (CI). Kaplan–Meier survival curves were used to explore associations between disease status and significant CAD with the log-rank test used to determine statistical significance. Cumulative probability of death after cardiac catheterization was calculated using Cox proportional hazards models to allow for the adjustment of potential confounders such as age, body mass index, gender, forced vital capacity percent predicted, and single breath diffusing capacity for carbon monoxide percent predicted. Hazard ratios (HR) are presented along with 95% CI. Statistical significance was set at $p < 0.05$ All statistical analyses were conducted using GraphPad Prism (Version 4.0, San Diego CA) and SAS (Version 9.2, Cary NC).

Results

There were 73 IPF patients and 56 COPD patients who qualified for the analysis. The demographics of the two groups are shown in Table 1. The diagnosis of IPF was confirmed in 41/73 (56.2%) of patients by surgical lung biopsy. Of the 73 IPF patients, 27 subsequently underwent lung transplantation. The diagnosis of IPF was confirmed in all of these with no alternate diagnosis suggested by histopathologic examination of the explants. Seventeen of these patients were in the group that had not had prior surgical lung biopsies. Therefore there was histopathologic evidence of IPF in 80.8% (59/73) IPF patients. In all cases where there was no tissue confirmation of the diagnosis, the ATS/ERS diagnostic criteria for IPF were fulfilled, including having CT scans showing changes typical of the disease. The diagnosis of COPD was made by a combination of clinical presentation and pulmonary function data. In addition, in all cases CT scans were obtained which showed changes consistent with emphysema.

The prevalence of CAD was 65.8% in the IPF group compared to 46.1% of COPD patients ($p < 0.028$) (Fig. 1). Significant disease was present in 21 (28.8%) IPF patients

Table 1 Demographics of the IPF and COPD patients.

	IPF ($N = 73$)	COPD ($N = 56$)	*P*
Age (mean ± SD)	60.1 ± 6.1	59.3 ± 5.9	0.453
Male Sex (%)	55 (75.3)	26 (45.6)	0.001
Caucasian	58 (79.5)	36 (63.2)	0.049
Body Mass Index, kg/m^2	28.6 ± 4.4	26.1 ± 5.1	0.003
FVC%	60.2 ± 15.0	54.3 ± 16.3	0.034
FEV_1%	63.5 ± 14.5	27.4 ± 11.6	0.001
DL_{CO}%	33.9 ± 14.9	33.8 ± 15.6	0.970

DL_{CO} = carbon monoxide diffusion capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume.

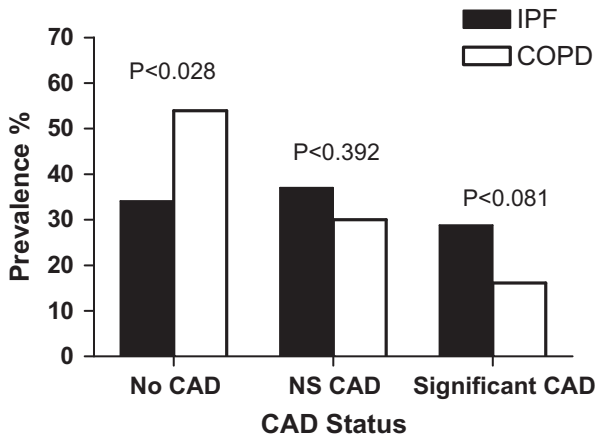

Figure 1 Coronary artery disease status of IPF ($N = 73$) and COPD ($N = 56$) patients as defined by left heart catheterization. Abbreviations: CAD = coronary artery disease, NS = non-significant.

compared to 9 (16.1%) of the COPD patients ($p < 0.081$). Non-significant disease was present in 27 (37%) of the IPF patients and 17 (30%) of the COPD patients ($p < 0.392$). The demographics of the IPF subgroups with no CAD, non-significant CAD and significant CAD are shown in Table 2. Patients with significant CAD were older and all the patients with non-significant disease were Caucasian. Of the 73 IPF patients, 12 (16.4%) had LHC prior to being evaluated for lung transplantation. Of these 12 patients, 1 had significant disease, 5 had non-significant disease and 6 had no disease. A further 9 IPF patients were known to have CAD. Therefore, prior to transplant evaluation, 20.5% (15/73) of IPF patients as compared to 17.9% (10/56) of COPD patients were known to have CAD. In patients with unknown CAD status, 63.5% (33/52) of the IPF patients were found to have some form of CAD at LHC, compared to 34.8% (16/46) of the COPD cases ($p < 0.005$, Fig. 2). Significant CAD was found in 21.2% (11/52) of these IPF patients compared to 10.9% (5/46) of the COPD patients ($p < 0.169$). For patients >60 years of age, the prevalence of CAD was 70% (28/40) and 56.5% (13/23) in the IPF and COPD patients, respectively ($p < 0.280$). Significant CAD accounted for 54% (15/28) and 21.7% (5/23) of these cases in the two groups ($p < 0.021$). Significant CAD was present in 5/14 (35.7%) of IPF patients who were diagnosed clinically versus 16/59 (27.1%) of patients in whom there was tissue confirmation of the diagnosis ($p < 0.527$).

Significant between group demographic differences were observed for male gender (IPF, 75.3% vs. COPD, 45.6%, $p < 0.001$), Caucasian (79.5% vs. 63.2%, $p < 0.049$), BMI (28.6 vs. 26.1, $p < 0.003$), and FEV_1% (63.5% vs. 27.4%, $p < 0.001$). A logistic regression model predicting CAD with adjustment for potential cofounders demonstrated that they did not significantly alter the influence of IPF status in the prediction of CAD. For the IPF patients, there were 10 patients with 3 or more risk factors for CAD, 24 with 2 risk factors, 25 with one risk factor and 14 with no risk factors. The prevalence of CAD amongst these groups is shown in Table 3. Compared to COPD, the diagnosis of IPF was predictive of CAD status (OR: 2.21; 95% CI: 1.09—4.53) prior to adjustment and nearly significant after adjustment (OR: 1.67; 95% CI: 0.59—4.78) for age, male gender, hypertension, hypercholesterolemia, diabetes, history of smoking, and a family history of CAD (C-statistic = 0.69) (Table 4). It is noteworthy that no adjusted demographic or clinical comorbidity was statistically significant in this final model.

Of the 11 IPF patients with unknown significant CAD prior to evaluation, surgery or stent placement was performed or recommended in 4 patients while the rest were managed medically. Of the 10 patients with known significant CAD, 3 had prior coronary artery bypass grafting and 2 had previously had coronary stents placed. Despite these interventions, Kaplan—Meier survival analyses revealed worse outcomes for those patients with IPF and significant CAD compared to those with no or non-significant CAD. The first analysis included 26 patients who received lung transplants with these patients censored as alive at the time of transplant ($p < 0.003$, Fig. 3). A second survival analysis was performed with transplant recipients excluded and this still showed a significant difference in outcomes in favor of those with non-significant or no CAD ($p < 0.026$).

Unadjusted Cox proportional hazard models suggested that from among modeled parameters including age, gender, body mass index, pulmonary function parameters (forced vital capacity (FVC) and diffusing capacity percent

Table 2 Demographics of IPF patients with unknown coronary artery disease status prior to left heart catheterization ($N = 52$).

	CAD Classification			
	None ($N = 19$)	Non-significant[a] ($N = 22$)	Significant[b] ($N = 11$)	P
Age (mean ± SD)	59.7 ± 5.9	58.7 ± 5.7	65.0 ± 5.2	0.013
Male (%)	14 (73.7)	16 (72.7)	10 (90.9)	0.462
Caucasian	14 (73.7)	22 (100)	7 (63.6)	0.015
Body Mass Index, kg/m^2	27.9 ± 5.2	29.5 ± 3.6	27.9 ± 4.5	0.443
FVC%	57.6 ± 13.3	64.6 ± 15.3	57.8 ± 19.9	0.299
FEV_1%	61.7 ± 12.1	67.8 ± 15.6	59.9 ± 14.4	0.232
DL_{CO}%	31.4 ± 9.4	36.0 ± 18.0	35.1 ± 15.2	0.596

CAD = coronary artery disease; DL_{CO} = carbon monoxide diffusion capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume; SD = standard deviation.

[a] Non-significant CAD = <50% occlusion of major vessel or disease of smaller vessels.

[b] Significant CAD = need for an intervention or major vessel with >50% lesion.

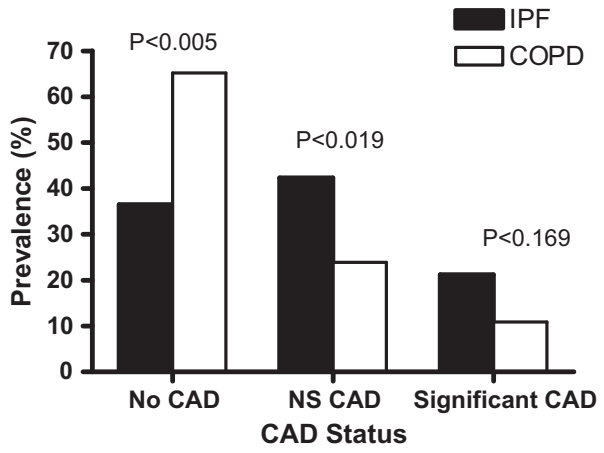

Figure 2 Coronary artery disease (CAD) status as defined by left heart catheterization in those IPF ($N = 61$) and COPD ($N = 46$) patients in whom CAD status was unknown at the time of the catheterization. Abbreviations: CAD = coronary artery disease, NS = non-significant.

predicted (DL_{CO})), mean pulmonary artery pressure, significant CAD and IPF status, only significant CAD (HR: 3.30; 95% CI: 1.11–9.83) and IPF (HR: 7.45; 95% CI: 2.19–25.51) status were predictive of mortality (Table 5). After adjustment for aforementioned potential confounders, male, age, FVC% predicted, DL_{CO} % predicted, only IPF status remained a significant predictor of death (HR: 20.22; 95% CI: 2.41–169.32). Although CAD status lost statistical significance after adjustment, there was still a trend towards significance (HR: 4.49; 95% CI: 0.95–21.36). No interaction between IPF status and significant CAD was evident (Fig. 4).

Discussion

In our study, we confirm the association of IPF with CAD by comparing a well characterized group of IPF patients with a control cohort of COPD subjects. We sought to explore this relationship in greater depth by collating and assessing the influence of traditional CAD risk factors. From amongst these, the only difference between the two groups was in cigarette smoking which was more prevalent in the COPD subjects. Therefore, one might have expected a greater prevalence of CAD in this group rather than the IPF patients, which serves to underscore the significance of our findings. In addition, our multivariate analysis accounting for the more commonly recognized CAD risk factors, still suggested that IPF was an independent risk factor. We further demonstrate that the presence of significant CAD in IPF patients might be associated with an increased mortality with a strong trend towards significance after accounting for other recognized important prognostic factors through our multivariate analysis.

There have been many advances in the understanding of the pathogenesis of IPF in recent years. These have not as yet translated into any effective therapies and the prognosis of this condition remains quite poor. The fibrotic process that characterizes IPF is confined to the lungs, but there is an increasing recognition that IPF may be associated with a higher propensity for certain comorbidities, including a greater predilection for CAD.[6–9,14–17] The explanation for the association between IPF and CAD is open to conjecture. Kizer and associates hypothesized three possible mechanisms: a common offending agent, a shared proclivity to fibrosis or a direct causal relationship between the two entities.[6] The first of these appears unlikely while the second might be possible, since IPF and CAD are both diseases associated with excessive fibrosis.[6] The pathogenesis of arteriosclerosis has similarities to that of IPF as it may be initiated by a denuded endothelium similar to the alveolar epithelial disruption described in IPF. The ensuing chronic inflammation may result in a complicated lesion and ultimately fibrosis of the artery.[18] A direct causal relationship between the two entities is also an appealing hypothesis. Both diseases ''share'' common cytokines that are upregulated and might be important in priming the milieu, thereby fostering the co-development of each disease. Also, intermittent hypoxemia represents a form of oxidative stress which may injure the endothelium and trigger atherogenesis.[19]

To our knowledge, there is no data looking at the prevalence of CAD in the general population as defined by left heart catheterization. However, estimates of the prevalence of CAD in patients age 55–64 in the US population as a whole, are 13.1% in men and 8.4% in women.[20] This is much lower than the prevalence found in our IPF patients. Since it was not feasible to have normal controls for comparison, we elected to use COPD patients for our comparative arm. This group appeared to most closely approximate our IPF patients in their demographic profile. In addition, one might have expected a higher prevalence of CAD in these patients by virtue of their greater exposure to cigarette smoking and the previously documented association of this disease with atherosclerosis.[21,22] On the other hand, the greater proportion of males in the IPF

Table 3 Number of risk factors in relation to the prior known presence and unknown coronary artery disease status in IPF patients ($N = 73$).

Risk factors	No. patients	Known CAD	Unknown CAD status, CAD classification		
			None	Non-significant	Significant
≥3	10	5 (50%)	1 (10%)	2 (20%)	2 (20%)
2	24	5 (20.8%)	5 (20.8%)	8 (33.3%)	6 (25%)
1	25	2 (8.0%)	8 (32.0%)	13 (52.0%)	2 (8.0%)
0	14	3 (21.4%)	4 (28.6%)	6 (42.9%)	1 (7.1%)

Abbreviations: CAD = coronary artery disease; No. = number of.

Table 4 Unadjusted and adjusted logistic regression models of factors predictive of coronary artery Disease in IPF and COPD patients.

	Unadjusted	Adjusted
Age	1.05 (0.99–1.19)	1.05 (0.98–1.12)
Male	1.85 (0.90–3.81)	1.74 (0.78–3.94)
BMI (kg/m^2)	1.05 (0.97–1.14)	1.01 (0.93–1.10)
Hypertension	1.65 (0.82–3.39)	1.84 (0.82–4.08)
Hypercholesterolemia	2.36 (0.92–6.12)	2.03 (0.71–5.76)
Diabetes	3.67 (0.76–17.72)	2.61 (0.48–14.22)
History of smoking	1.82 (0.85–3.86)	1.02 (0.36–2.91)
Family history of CAD	4.76 (0.55–40.75)	1.74 (0.18–16.77)
IPF status[a]	2.21 (1.09–4.53)	1.67 (0.59–4.78)

CAD = coronary artery disease; OR = odds ratio; and CI = confidence interval.
[a] IPF status relative to COPD.

Table 5 Unadjusted and adjusted proportional hazard models for the prediction of mortality.

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Age (years)	1.02 (0.95–1.09)	0.99 (0.92–1.06)
BMI	1.01 (0.92–1.12)	0.94 (.083–1.06)
FVC % predicted	1.02 (0.98–1.04)	0.99 (0.96–1.03)
Mean PA pressure (mmHg)	1.02 (0.97–1.07)	1.04 (0.97–1.12)
DL_{CO} % predicted	1.00 (0.97–1.03)	0.98 (0.93–1.04)
Male gender	1.74 (0.68–4.49)	1.90 (0.46–7.94)
Significant CAD	3.30 (1.11–9.83)	4.83 (0.90–26.03)
IPF	7.45 (2.19–25.51)	22.74 (2.54–203.17)

BMI = body mass index; CAD = coronary artery disease; DL_{CO} = carbon monoxide diffusion capacity; FVC = forced vital capacity; PA = pulmonary artery; and HR = hazard ratio.
[a] Adjusted for all other terms in the table.

cohort might have contributed to the greater prevalence of CAD in this group. However, the inclusion of gender within our Cox models demonstrated little impact on the IPF estimates.

It has previously been shown that cardiovascular disease does account for some of the mortality of patients with IPF. Indeed, CAD along with other cardiovascular comorbidities such as congestive heart failure and stroke has been reported to account for 27% of deaths in IPF patients.[14] However, our study is the first to suggest that IPF patients with significant CAD documented via left heart catheterization might have worse outcomes.Although it might be expected that patients with significant CAD would have worse outcomes than those without, in the context of a deadly disease which is more likely to drive mortality, this is somewhat of a surprise. The heightened mortality risk might be related to the interplay and negative cascade of the two diseases; specifically, it is possible that patients with pre-existing CAD are less likely to tolerate hypoxic episodes and therefore might be at greater risk for cardiac events. Those patients who were discovered to have significant CAD were treated medically and in some cases with further interventions, including stent placement or coronary artery bypass grafting. Despite these interventions, the presence of CAD still appeared to adversely

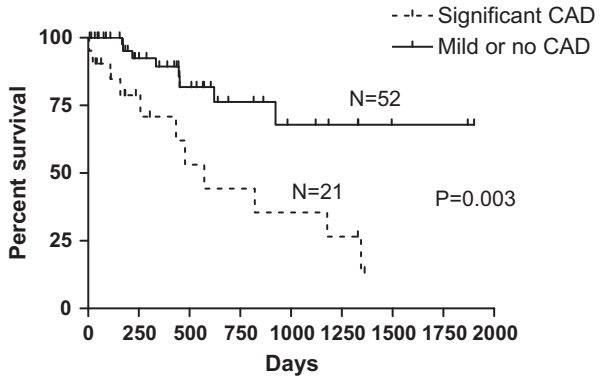

Figure 3 IPF survival comparison of patients with significant coronary artery disease to those with non-significant or no coronary artery disease.

impact outcomes. It is likely that undiagnosed significant CAD, which represented 18% of our population, would have an even more profound impact on outcomes if left untreated. It is noteworthy that the prognosis of our cohort with mild or no CAD was significantly better than the historical reported survival of patients with IPF. A possible explanation contributing to this is that some of the patients in these prior studies had unrecognized CAD that may have placed them at higher risk of mortality.[2,11]

Our findings might have important implications for the management of patients with IPF. In the context of a deadly disease without known, proven effective therapy, the ability to potentially impact the course of nearly 20% of the patients by ruling out and treating significant CAD is an important consideration. Most of our patients were relatively young since the majority of the LHCs were obtained as part of a lung transplant evaluation. The mean age of our cohort was 60 years with 98.6% (72/73) age $\leq$70. We speculate that the prevalence of CAD would be even higher in older patients with IPF. Whether the worse outcomes of older patients with IPF is due to a delay in the diagnosis, more aggressive disease, reduced pulmonary reserve or

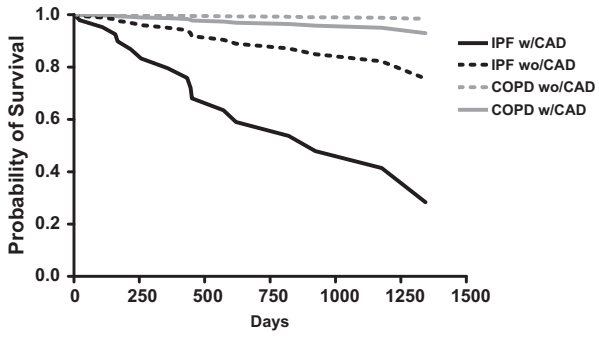

Figure 4 Results of Cox proportional hazards model adjusting for IPF ($p < 0.008$), CAD ($p < 0.059$), male ($p < 0.479$), age ($p < 0.565$), FVC% predicted ($p < 0.744$), and DL_{CO}% predicted ($p < 0.358$). Abbreviations: IPF = idiopathic pulmonary fibrosis; CAD = coronary artery disease; FVC = forced vital capacity; and DL_{CO} = single breath diffusing capacity for carbon monoxide.

a result of comorbidities is uncertain. Our findings with regards to CAD in IPF, and the likely higher incidence in elderly IPF patients, suggest that CAD might contribute to this noted worse prognosis.

Despite demonstrating worse survivals for those patients with significant CAD, we did not prove that its detection and treatment impacted survival. However, it does make intuitive sense that this might be the case. We therefore contend that there should a high index of suspicion for CAD in patients with IPF, especially elderly patients in whom episodes of shortness of breath could represent anginal equivalents. Although we assessed our patient population by left heart catheterization, it is possible that a less invasive cardiac stress test might suffice as a screen.[23–25]

There are several limitations to our study. Our relative small sample size and select nature of our patient population makes it difficult to extrapolate these findings to all IPF patients. Strengths of our study include our well-characterized IPF population and the fact that we did account for other common cardiac risk factors and risk factors for death through our multivariate analyses. Our choice of COPD patients as a comparative group could also be criticized if one were to argue that the higher prevalence of CAD in IPF might be due to COPD somehow being ''protective'' of CAD. This scenario is highly unlikely since, in addition to our COPD patients having a higher prevalence of smoking, there is also emerging data that COPD itself is associated with a heightened risk of cardiovascular complications.[21,22,26] Therefore, comparison to a normal population might have resulted in an even greater difference. There were some differences in the baseline characteristics of the two groups and we cannot categorically exclude these could have accounted for some of the differences in the prevalence of CAD described. However, our multivariate modeling suggests that this was not the case, although our study was not powered to explore these relationships.

In summary, our study confirms an association between CAD and IPF which appears to be independent of commonly recognized coronary risk factors. Co-existing CAD appears to be associated with increased mortality in IPF patients, despite appropriate therapeutic intervention. Screening for occult CAD, not only in potential lung transplant candidates, but also in other patients with IPF appears to be an important consideration. We speculate that aggressive therapeutic intervention for documented CAD could have a significant impact on the survival of IPF patients with this accompanying co-morbidity.

Conflict of interest

The authors have no conflict of interest.

Acknowledgements

Study concept and design: Nathan; *Acquisition of data:* Reichner, Basavaraj, Kiernan; *Analysis and interpretation of data:* Nathan, Basavaraj, Barnett, Kiernan; *Drafting of the manuscript:* Nathan; *Critical revision of the manuscript for important intellectual content:* Shlobin, Barnett, Ahmad, Burton, Kiernan; *Statistical analysis:* Barnett.

References

1. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;**174**:810–6.
2. Olson AL, Swigris JJ, Lezotte DC, Norris KM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med* 2007;**176**:277–84.
3. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. The incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006;**61**:980–5.
4. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;**150**:967–72.
5. Hunninghake GW, Schwarz MI. Does current knowledge explain the pathogenesis of idiopathic pulmonary fibrosis? A perspective. *Proc Am Thorac Soc* 2007;**4**:449–52.
6. Kizer JR, Zisman DA, Blumenthal NP, et al. Association between pulmonary fibrosis and coronary artery disease. *Arch Intern Med* 2004;**164**:551–6.
7. Hubbard RB, Smith C, Le Jeune I, Gribbin J, Fogarty AW. The association between idiopathic pulmonary fibrosis and vascular disease. *Am J Respir Crit Care Med* 2008;**178**:1257–61.
8. Ponnuswamy A, Manikandan R, Sabetpour A, Keeping IM, Finnerty JP. Association between ischaemic heart disease and interstitial lung disease: a case–control study. *Resp Med* 2009;**103**:503–7.
9. Izbicki G, Ben-Dor I, Shitrit D, et al. The prevalence of coronary artery disease in end-stage pulmonary disease: is pulmonary fibrosis a risk factor? *Resp Med* 2009;**103**(9):1346–9.
10. American Thoracic Society/European Respiratory Society International multidisciplinary consensus classifications of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;**165**:277–304.
11. King TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;**164**:1171–81.
12. Reichner CA, Nathan SD, Barnett SD, Keller A, Ahmad S, Burton N. Prevalence and impact on outcomes of coronary artery disease in patients with IPF. *Am J Respir Crit Care Med* 2004;**169**:A108.
13. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;**161**:646–64.
14. Panos RJ, Mortenson RL, Niccoli SA, King TE. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. *Am J Med* 1990;**88**:396–404.
15. Tobin RW, Pope CE, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;**158**:1804–8.
16. Mermigkis C, Chapman J, Golish J, et al. Sleep-related breathing disorders in patients with idiopathic pulmonary fibrosis. *Lung* 2007;**185**:173–8.
17. Caplan-Shaw CE, Arcasoy SM, Shane E, et al. Osteoporosis in diffuse parenchymal lung disease. *Chest* 2006;**129**:140–6.
18. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;**340**:115–26.
19. Hayashi M, Fujimoto K, Urushibata K, Uchikawa S, Imamura H, Kubo K. Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease. *Chest* 2003;**124**:936–41.
20. Heart disease and stroke statistics-2004 update. Coronary heart disease, acute coronary syndrome and angina pectoris. *Am Heart Assoc* 2004;**6**:9–12.

21. Iwamoto H, Yokoyama A, Kitahara Y, et al. Airflow limitation in smokers is associated with subclinical atherosclerosis. *Am J Respir Crit Care Med* 2009;**179**:35—40.
22. Maclay JD, McAllister DA, Macnee W. Cardiovascular risk in chronic obstructive pulmonary disease. *Respirology* 2007;**12**:634—41.
23. Leibowitz DW, Caputo AL, Shapiro GC, et al. Coronary angiography in smokers undergoing evaluation for lung transplantation: is routine use justified? *J Heart Lung Transplant* 1994;**13**:701—3.
24. Henzlova MJ, Padilla ML, Freilich A, et al. Dobutamine thallium 201 perfusion imaging in candidates for lung transplantation. *J Heart Lung Transplant* 1995;**14**:251—6.
25. Thaik CM, Semigran MJ, Ginns L, Wain JC. Evaluation of ischemic heart disease in potential lung transplant recipients. *J Heart Lung Transplant* 1995;**14**:257—66.
26. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;**32**:962—9.