Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension

T J Corte,¹ ² S J Wort,¹ M A Gatzoulis,¹ P Macdonald,² D M Hansell,¹ A U Wells¹

ABSTRACT

Background: Pulmonary hypertension (PH) is associated with a poor prognosis in diffuse lung disease (DLD). A study was undertaken to compare the prognostic significance of invasive and non-invasive parameters in patients with DLD and suspected PH.

Methods: Hospital records of consecutive patients with DLD undergoing right heart catheterisation (RHC) were reviewed (n = 66). Mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and non-invasive variables were examined against early (within 12 months) and overall mortality. A priori thresholds were examined against early mortality. Relationships between mPAP, PVR and non-invasive markers were assessed.

Results: Fifty patients had PH on RHC (mean (SD) mPAP 33.5 (11.8) mm Hg, PVR 5.9 (4.3) Wood units (WU)). Raised PVR was strongly associated with early mortality (odds ratio (OR) 1.30; 95% confidence interval (CI) 1.11 to 1.52, p = 0.001), with PVR > 6.23 WU being the optimal threshold for RHC in severe DLD should be low, enabling prioritisation of aggressive treatment including lung transplantation.

Conclusion: In severe DLD, early mortality is strongly linked to increased PVR but not to other RHC or non-invasive variables. These findings suggest that the threshold for RHC in severe DLD should be low, enabling prioritisation of aggressive treatment including lung transplantation.

In end-stage diffuse lung disease, prognosis is generally poor. Physicians require reliable prognostic markers for early death to refine the triage of patients for aggressive treatments and transplantation referral. On this basis, it has been recommended by an expert group that pulmonary hypertension (PH) is an indication for immediate listing for lung transplantation for interstitial lung disease at large.¹ PH is not uncommon in diffuse lung disease and is a malignant prognostic determinant, as shown in studies of idiopathic pulmonary fibrosis (IPF)¹² and advanced pulmonary sarcoidosis.⁹

In most studies, PH is quantified using the mean or systolic pulmonary artery pressure rather than pulmonary vascular resistance (PVR), and the systolic pulmonary artery pressure (sPAP) is a component of the Northern American Lung Allocation Score.¹⁰ The prognostic value of PVR has not been quantified in diffuse lung disease. However, in a recent study of patients with a variety of chronic lung diseases awaiting lung transplantation, raised PVR was strongly predictive of short-term mortality whereas a number of other variables, including mean pulmonary artery pressure (mPAP), were not.¹¹

In the current study we have compared PVR, mPAP and other variables as predictors of early mortality in patients with severe diffuse lung disease. A second goal of this study was to determine whether the prognostic role of right heart catheterisation (RHC) could be replicated by non-invasive surrogate markers. RHC is regarded as the reference standard in the evaluation of PH but is moderately invasive and resource-limited. We therefore studied the prognostic value of a non-invasive composite index modelled against measured PVR.

METHODS

Subjects
A retrospective review of consecutive patients with diffuse fibrotic lung disease undergoing RHC between February 1987 and April 2007 (n = 66) was undertaken. RHC was performed in cases of suspected PH based on clinical criteria or as part of a pretransplantation assessment. Clinical criteria for RHC included echocardiographic right ventricular systolic pressure (RVSP) > 40 mm Hg or right ventricular (RV) dilation and dyspnoea or hypoxaemia not explained by the underlying fibrosis. Multidisciplinary diagnoses were made using current guidelines for idiopathic interstitial pneumonia,¹² with retrospective reclassification (integrating biopsy data, high resolution computed tomography (HRCT) findings and observed longitudinal behaviour) in patients diagnosed before 2002. Twenty-two patients were also included in a radiology study addressing a separate hypothesis.¹³ Follow-up to death or to 1 June 2008 was complete in 62 of the 66 cases.

Measurements

Right heart catheterisation (RHC)
RHC measurements were performed at rest using standard techniques (Swan-Ganz catheters, Edwards Life Sciences, Irvine, California, USA). Cardiac output (CO) was calculated by the Fick equation: CO = (oxygen consumption)/(arterial oxygen saturation – mixed venous oxygen saturation) using standardised
reference tables to estimate oxygen consumption. PVR was calculated using the formula: PVR = (mPAP – mLAP)/CO, where mLAP = mean left atrial pressure. Left ventricular end diastolic pressure was used to estimate mLAP in patients with simultaneous left heart catheterisation (n = 51). Pulmonary capillary wedge pressure (n = 50) was used to estimate mLAP in the remaining 15 cases.

Non-invasive investigations
All patients had pulmonary function testing and two-dimensional echocardiography. Forty-two patients underwent the six minute walk test (6MWT). If patients had multiple tests, the test closest to the date of RHC was used. Full details of the echocardiography, pulmonary function and 6MWT methodology are available in the online supplement.

Rationale for a priori thresholds
A priori thresholds examined against early death using logistic regression included:

- RHC thresholds
  - mPAP: 17, 25, 35 and 40 mm Hg;
  - PVR: 5, 5.56 and 6.23 Wood units (WU);

- Non-invasive thresholds
  - RVSP: 30, 35, 40 and 50 mm Hg;
  - Transfer factor for carbon monoxide (TLCO): 30%, 35% and 40% predicted;
  - Forced vital capacity (FVC): 50% and 60% predicted;
  - Arterial oxygen tension (PaO2): 7, 7.5 and 8 kPa.

The rationale for mPAP thresholds was based on IFP studies in which mPAP of 17 and 25 mm Hg denoted poorer outcomes. Threshold mPAP values of 35 and 40 mm Hg were included as measures of moderate and severe PH. For PVR, current guidelines recommend ≥3 WU for the identification of pulmonary arterial hypertension (PAH), a threshold associated with a poorer prognosis in transplant candidates. Using linear regression, PVR values equivalent to mPAP of 25 and 35 mm Hg were calculated as 5.56 and 6.23 WU, and these threshold values were evaluated. The rationale for the remaining a priori thresholds is provided in the online supplement.

Statistical analysis
All analyses were performed using STATA statistical software Version 10.0 (Stata Corp, College Station, Texas, USA). Data are expressed as mean and standard deviation (SD) or median (range), as appropriate. Group comparisons were made using the Student t test or Wilcoxon rank-sum test. Outcome was evaluated for overall mortality (Cox regression, with satisfaction of the assumptions of proportional hazards analysis) and death within the first year (logistic regression): covariates included PVR, mPAP, RVSP, right atrial (RA) and RV dilation, TLCO, FVC, composite physiological index (CPI), PaO2, 6MWT desaturation ≤88%, diagnosis of IPF and male gender.

Univariate relationships were examined using Pearson or Spearman rank correlation tests as appropriate. Using stepwise analysis, a model was constructed to fit non-invasive variables to PVR. Covariates consisted of the CPI (included to adjust for the severity of interstitial lung disease) and the four variables found to be significantly linked to PVR on univariate analysis. The assumptions of multiple linear regression were satisfied, as judged by testing for heteroscedasticity and omitted variables. The prognostic value of this model was evaluated against overall mortality and against death in the first year. Analysis was repeated for the subgroup (n = 52) of patients with mLAP below 15 mm Hg and for individual diagnostic subgroups.

RESULTS
Baseline parameters
The baseline characteristics of the 66 patients (mean (SD) mPAP 33.6 (11.8) mm Hg, PVR 5.9 (4.3) WU) are summarised in table 1. Fifty patients (76%) had PH (≥25 mm Hg) and 28 (42%) had moderate to severe PH (≥35 mm Hg) on RHC and nine (14%) had significant coronary artery disease. Fifty (76%) had one or more echocardiographic findings compatible with PH (raised RVSP, n = 40; RA dilation, n = 24; RV dilation, n = 30; RV dysfunction, n = 23). Thirty-seven of the 66 patients (56%) had a TLCO ≤30% and 35 of 42 (79%) had significant oxygen desaturation on 6MWT to ≤88%.

Early mortality
During the study period there were 31 deaths, including 17 deaths within 12 months of RHC. As shown in table 2, patients dying within 12 months of RHC had significantly higher PVR (p < 0.001) and mPAP (p = 0.05) and lower pulmonary acceleration time (PAT) (p = 0.007). Age, gender, pulmonary function, RVSP and 6MWT desaturation did not differ between survivors and patients dying within 1 year.

Logistic regression for death within 1 year showed that PVR >6.23 WU was strongly linked to early mortality with an eightfold increase in death within the first year (odds Ratio (OR) 8.15; 95% confidence interval (95% CI) 2.58 to 27.37; p = 0.001). This finding remained robust following adjustment for age, gender, CPI and IPF diagnosis (OR 11.09; 95% CI 2.54 to 48.36; p = 0.001; table 3). These findings remained highly significant with the exclusion of each diagnostic subgroup (table 3). These trends remained strong for patients with mLAP <15 mm Hg (n = 52; OR 12.11; 95% CI 2.12 to 69.10; p = 0.005) but not for patients with mLAP ≥15 mm Hg (n = 14). Coronary artery disease was not linked to mortality or to raised left heart pressures. No mPAP or mean RAP threshold was predictive of early death.

On echocardiography, the presence of RV dilation was associated with a fourfold risk of early death (p = 0.02) whereas no RVSP threshold was helpful in the prediction of early death. No TLCO, FVC, CPI or PaO2 threshold was associated with early death. The diagnosis of IPF was only marginally associated with early death (p = 0.07).

Overall mortality
PVR was the strongest haemodynamic predictor of mortality (table 4, fig 1). Raised PVR was associated with higher mortality (hazards ratio (HR) 1.13; 95% CI 1.05 to 1.22; p = 0.001), remaining significant after adjustment for age, gender and disease severity (CPI). Mean PAF and CO were not predictive of overall mortality.

On echocardiography, RV dilation was associated with marginally higher mortality. One, two and three-year survival rates for those with RV dilation were 63.5%, 46.4% and 36.6% compared with 85.9%, 69.8% and 45.5% for those without RV dilation. Other echocardiographic parameters, including RVSP, were not significantly linked to outcome. Pulmonary function impairment (TLCO%, FVC%, PaO2 and CPI) was associated with higher mortality. CPI was strongly associated with higher mortality (HR 1.07, 95% CI 1.05 to 1.10, p < 0.001), remaining significant after adjustment for age, gender and PVR. No deaths occurred in patients without 6MWT desaturation.
Stepwise linear regression revealed that PaO2 (p = 0.02; 95% CI −1.40 to −0.16) and RVSP (p = 0.002; 95% CI 0.03 to 0.14) were independent determinants of PVR when adjusted for disease severity as determined by CPI (following correction for the five covariates assessed). The following equation predicted PVR with an equation r² of 0.57:

\[
\text{Predicted PVR} = 12.6 + 0.09 \times \text{RVSP} - 0.78 \times \text{PaO2} - 0.09 \times \text{CPI}
\]

However, predicted PVR values were not linked to overall mortality (p = 0.51) and were only of borderline significance for the prediction of death within the first 12 months (p = 0.06).

**DISCUSSION**

In diffuse lung disease, optimal therapeutic triage including prioritisation of transplantation requires accurate prognostic evaluation. We report for the first time that PVR provides discriminatory prognostic information not provided by mPAP levels or non-invasive evaluation. PVR was the strongest haemodynamic predictor for early mortality, independent of the severity of pulmonary fibrosis, as judged by CPI levels. We report an eightfold increase in early mortality above an a priori PVR threshold of 6.23 WU. Importantly, this finding was independent of the diagnosis of IPF, which was itself only marginally predictive of early mortality.

Lung biopsy provides invaluable prognostic guidance in less severe disease. However, in advanced disease, biopsy is often impracticable and less prognostically useful. In one study, survival did not differ between biopsy-proven IPF and non-specific interstitial pneumonia (NSIP) in severe disease. Patients with severe hypersensitivity pneumonitis have an outcome similar to that of IPF. In the current study, early mortality was not linked to diagnosis. It therefore appears that, in end-stage disease, the usefulness of diagnostic subclassification diminishes, justifying the amalgamation of diagnostic categories in transplantation studies of patients with diffuse lung disease. This consideration prompted us to evaluate determinants of early mortality in a mixed population with severe disease referred for RHC.

Our findings provide indirect support for the hypothesis that, in severe fibrotic lung disease, the severity of pulmonary vascular insufficiency rather than the severity of pulmonary fibrosis or a diagnosis of IPF or connective tissue disease determines short-term mortality. However, the selection bias inherent in the decision to perform RHC needs to be stressed. Throughout the study period RHC was performed in suspected or clinically overt PH rather than in consecutive unselected patients with severe pulmonary fibrosis. RHC was performed

### Table 5

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RVSP (mm Hg)</th>
<th>mPAP (mm Hg)</th>
<th>PVR (WU)</th>
<th>PVR index (WU/m²)</th>
<th>mPAP (mm Hg)</th>
<th>PVR (WU)</th>
<th>PVR index (WU/m²)</th>
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</thead>
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<tr>
<td>TLco (%) (n = 65)</td>
<td>29.6 (14.7)</td>
<td>33.6 (11.8)</td>
<td>5.9 (4.2)</td>
<td>10.4 (7.1)</td>
<td>33.6 (11.8)</td>
<td>5.9 (4.2)</td>
<td>10.4 (7.1)</td>
</tr>
<tr>
<td>FEV₁, forced expiratory volume in 1 s</td>
<td>52.0 (19.7)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
<td>52.0 (19.7)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
<td>52.0 (19.7)</td>
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<tr>
<td>TLC (n = 61)</td>
<td>72.5 (20.2)</td>
<td>67.8 (23.1)</td>
<td>8.4 (2.2)</td>
<td>67.8 (23.1)</td>
<td>8.4 (2.2)</td>
<td>67.8 (23.1)</td>
<td>8.4 (2.2)</td>
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<tr>
<td>FEV₁ % (n = 62)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
<td>62.4 (23.3)</td>
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<tr>
<td>PaO₂ (kPa, n = 61)</td>
<td>8.4 (2.2)</td>
<td>8.4 (2.2)</td>
<td>8.4 (2.2)</td>
<td>8.4 (2.2)</td>
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<tr>
<td>CPI (n = 62)</td>
<td>56.9 (14.6)</td>
<td>56.9 (14.6)</td>
<td>56.9 (14.6)</td>
<td>56.9 (14.6)</td>
<td>56.9 (14.6)</td>
<td>56.9 (14.6)</td>
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<tr>
<td>6MWT (n = 42)</td>
<td>81.4 (8.4)</td>
<td>81.4 (8.4)</td>
<td>81.4 (8.4)</td>
<td>81.4 (8.4)</td>
<td>81.4 (8.4)</td>
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<tr>
<td>6MWT distance (m)</td>
<td>254.6 (128.1)</td>
<td>254.6 (128.1)</td>
<td>254.6 (128.1)</td>
<td>254.6 (128.1)</td>
<td>254.6 (128.1)</td>
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</table>

*Student t test.

Values are mean (SD).

**Non-invasive estimates of mPAP and PVR**

Table 5 summarises the relationship between invasive (mPAP and PVR) and non-invasive variables as judged by non-parametric correlation. Significant but weak correlations were present between echocardiographic markers (RVSP and PAT) and both PVR and mPAP. An RVSP of ≥40 mm Hg correctly identified 79.2% of patients with PH on RHC (sensitivity 91.7%; specificity 41.7%; area under the curve 0.77, 95% CI 0.62 to 0.92). The specificity of RVSP improved (58.3%) with a higher RVSP threshold (≥50 mm Hg).
Echocardiography

Pulmonary function

RVSP 25 are linked to mortality. There are at least two possible severe disease were the focus of our study, with average TLCO linked to outcome in idiopathic PAH and chronic respiratory insufficiency such as serum brain natriuretic peptide, which is prognostic importance of pulmonary vasculopathy in an (median 3 years from presentation). Confirmation of the prognostic importance of pulmonary vasculopathy in an unselected group would require a large prospective study or a more accurate non-invasive marker of pulmonary vascular insufficiency such as serum brain natriuretic peptide, which is linked to outcome in idiopathic PAH and chronic respiratory disease* but has yet to be evaluated prospectively.

Our findings differ from those in IPF in which mPAP* and RVSP* are linked to mortality. There are at least two possible explanations for this apparent discrepancy. First, patients with severe disease were the focus of our study, with average TLCO levels less than 30%. In end-stage disease, pulmonary pressures may fall as the right ventricle fails, confounding relationships between pulmonary pressures and mortality reported in IPF populations of lesser average disease severity.** Second, the link between pulmonary pressures and mortality may vary with the

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rapidly of disease progression to end-stage disease and may therefore be stronger in IPF. Thus, our findings are applicable to patients with advanced disease but not to the full spectrum of disease severity in individual disorders.

The strikingly increased early mortality in patients with PVR >6.23 WU is consistent with a recent study in end-stage lung disease in which increased PVR independently predicted pretransplant mortality in a variety of chronic lung diseases. In addition, in idiopathic PAH, PVR may be a better prognostic marker than pulmonary artery pressure. As discussed above, mPAP may fall (relative to PVR) preterminally as the right ventricle fails. Indeed, in the current study there were five patients with increased PVR and normal mPAP. PVR is coupled to both pulmonary pressures and cardiac output, is a marker of the peripheral vasculature and may better reflect the pathophysiology of PH in fibrotic disease in which vascular ablation, chronic hypoxic vasoconstriction and vascular remodelling are seen histologically in peripheral vessels. Additionally, main pulmonary artery size on HRCT scanning does not correlate with pulmonary arterial pressures in interstitial lung disease, supporting the hypothesis that interstitial disease may be associated with a more aggressive vascular phenotype (whether due to fibrotic ablation or to the vasculopathic effect of cytokines generated in fibrotic lung tissue).

Our findings have direct relevance to the prioritisation of patients for lung transplantation. Since 2005 a transplant allocation score has been used in North America. PVR may be an important additional factor for consideration in this transplant allocation algorithm, which currently takes into account systolic PAP which our findings suggest has little value in predicting short-term prognosis.

The prognostic significance of RV dilation on echocardiography mirrors findings in idiopathic PAH. As RV dilation reflects uncoupling of the right ventricle—often a late finding—it is predictable that RV dilation is linked to early mortality. Our data suggest that RV dilation is a better prognostic indicator than RVSP alone. RV dilation is readily identifiable at echocardiography and may be an important marker in future outcome studies.

The relationship between baseline disease severity and overall mortality is not confined to studies of single disorders, as shown in studies of IPF and fibrotic NSIP. We demonstrate the prognostic importance of the CPI in advanced fibrotic lung disease across histological diagnoses. However, no pulmonary function parameter was predictive of early death. This suggests that early death is associated with PH rather than the severity of the underlying fibrotic lung disease. This is consistent with a study of patients with IPF assessed for transplantation in whom the presence of PH, but not lower pulmonary function, was associated with poorer outcomes at 1, 2 and 3 years.

No single non-invasive measurement correlated well with PVR or mPAP on RHC. No R² value was greater than 0.32 suggesting that, at best, only 30% of the variation in PVR was explained by these non-invasive variables. RVSP correlated best with mPAP and PVR. However, the sensitivity and specificity of RVSP for a diagnosis of PH on RHC was moderate, in keeping with previous studies highlighting the inadequacy of echocardiography in fibrotic lung disease. In our study, multiple linear regression was used to develop predictive equations for PVR using non-invasive measurements. PVR was independently determined by the combination of RVSP and PaO₂. However, predicted values were not as accurate in predicting prognosis as their RHC counterparts. Zisman et al reported an externally validated model predicting mPAP based on pulmonary function and oxygen saturation. Although a reliable non-invasive marker would be clinically useful, our results suggest that RHC remains an integral tool in diagnostic and prognostic assessment in selected patients with diffuse lung disease.

The limitations of a retrospective study design with respect to selection of patients for RHC are discussed above. Four other issues merit consideration. First, there was a risk of “chance fitting” due to the number of variables assessed, prompting us to examine candidate a priori thresholds identified in previous studies. Although FVR emerged as a striking prognostic marker, the possibility of chance fitting cannot be excluded. However, with adjustment for multiple comparisons (taking into account all 13 continuous variables), the association between PVR and early mortality remained significant (p = 0.01). In addition, this

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### Table 5: Correlation of right heart catheter measures (PVR and mPAP) with non-invasive clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>mPAP</th>
<th>PVR</th>
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<tbody>
<tr>
<td></td>
<td>R²</td>
<td>p Value</td>
</tr>
<tr>
<td>WHO class (n = 66)</td>
<td>0.23</td>
<td>0.06</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVSP (n = 48)</td>
<td>0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAT (n = 46)</td>
<td>−0.39</td>
<td>0.008</td>
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<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC % (n = 61)</td>
<td>0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>TCO₂ % (n = 65)</td>
<td>−0.01</td>
<td>0.88</td>
</tr>
<tr>
<td>Kco % (n = 65)</td>
<td>−0.26</td>
<td>0.04</td>
</tr>
<tr>
<td>FVC % (n = 62)</td>
<td>0.12</td>
<td>0.34</td>
</tr>
<tr>
<td>PaO₂ (n = 61)</td>
<td>−0.27</td>
<td>0.03</td>
</tr>
<tr>
<td>PaCO₂ (n = 61)</td>
<td>−0.05</td>
<td>0.71</td>
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<tr>
<td>CPI (n = 62)</td>
<td>−0.03</td>
<td>0.83</td>
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<tr>
<td>6MWT (n = 42)</td>
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<tr>
<td>6MWT end-test SpO₂</td>
<td>−0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>−0.02</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Pearson or Spearman correlation coefficient (R) as appropriate.
CPI, composite physiological index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Kco, transfer factor corrected for alveolar volume; mPAP, mean pulmonary artery pressure; 6MWT, six minute walk test; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; RVSP, right ventricular systolic pressure; SpO₂, oxygen saturation on pulse oximetry; TLC, total lung capacity; Tlco, transfer factor for carbon monoxide; WHO, World Health Authority.
finding is plausible on pathophysiologic grounds, as discussed earlier, and is consistent with studies in idiopathic PAH as well as in patients awaiting lung transplantation.11 Second, the wide confidence intervals for the prognostic value of PVR in our study should be acknowledged, underlying the need for further prospective evaluation. Third, our study cohort included 14 patients with raised left heart pressures. However, early death did not vary in prevalence with left heart pressures (data not shown), and the prognostic value of PVR was unchanged on exclusion of patients with raised left heart pressures. Moreover, the presence of coronary artery disease was not separately associated with early mortality and was therefore not a major confounding factor.

Oxygen desaturation below 88% at 6MWT has been reported as a malignant prognostic determinant in IPF and NSIP.45 46 In our study, mortality was confined to patients with desaturation at 6MWT to 88% or lower. However, no significant difference was seen for early death for patients with and without 6MWT oxygen desaturation (data not shown). In our study, 6MWT data were available for 42 patients (64%), including five who progressed to early death. The mean 6MWT distance was low at 254 m, in keeping with the severity of their underlying disease. However, patients with more severe functional impairment were unable to perform the 6MWT or were tested on supplemental oxygen (n = 7), limiting further prognostic evaluation.

We conclude that, in severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF. PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications (including prioritisation and referral for lung transplantation).

Funding: This research has been partly supported by an educational grant from Actelion Pharmaceuticals.

Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Thorax 2009 64: 883-888 originally published online June 21, 2009
doi: 10.1136/thx.2008.112847

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