Increased epithelial permeability in pulmonary fibrosis in relation to disease progression

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Short title: Epithelial permeability and fibrosis

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Abstract

Objective: Epithelial injury contributes to pathogenesis in idiopathic pulmonary fibrosis (IPF) but its role in the interstitial lung disease of systemic sclerosis (SSc-ILD) is uncertain. We quantify the prognostic significance of inhaled technetium-labelled diethylene-triamine-pentacetate (99mTc-DTPA) pulmonary clearance, a marker of the extent of epithelial injury, in both diseases.

Methods: Baseline 99mTc-DTPA pulmonary clearance was evaluated retrospectively in patients with SSc-ILD (n=168) and IPF (n=97) against mortality and disease progression.

Results: In SSc-ILD, the rapidity of total clearance (HR=1.02; 95% CI 1.01, 1.03; p=0.001) and the presence of abnormally rapid clearance (HR=2.10; 95% CI 1.25, 3.53; p=0.005) predicted a shorter time to FVC decline, independent of disease severity. These associations were robust in both mild and severe disease. By contrast, in IPF, delayed clearance of the slow component, an expected consequence of honeycomb change, was an independent predictor of a shorter time to FVC decline (HR=1.01; 95% CI 1.00, 1.02; p<0.01).

Conclusions: Epithelial injury should be incorporated in pathogenetic models in SSc-ILD. By contrast, outcome is not linked to the overall extent of epithelial injury in IPF, apart from abnormalities ascribable to honeycombing, suggesting that core pathogenetic events may be more spatially focal in that disease.

Key words: DTPA clearance, epithelial permeability, fibrosis, progression, pathogenetic
Introduction

In the interstitial lung disease of systemic sclerosis (SSc-ILD), epithelial injury has been linked to the presence and progression of lung disease (1-3), but a pathogenetic contribution from epithelial injury has yet to be established. By contrast, in idiopathic pulmonary fibrosis (IPF), there is substantial evidence that epithelial cell dysfunction contributes to the fibrotic microenvironment (4;5), and markers of epithelial injury have been linked to outcome (1;6-8). Clearance of inhaled technetium-labelled diethylene-triamine-pentacetate (99mTc-DTPA) from the lung, a measure of epithelial permeability/injury (9), is abnormal in several interstitial lung diseases, including SSc-ILD (1;10) and IPF (1;8;11).

However, the possibility exists, with any prognostic marker, that relationships to a poor outcome might represent merely associations with more advanced disease. In a study of patients with SSc-ILD or idiopathic interstitial pneumonia, Wells et al (1) reported that rapid total 99mTc-DTPA clearance was associated with disease progression, but no adjustment was made for disease severity in this analysis. More rapid 99mTc-DTPA clearance has been associated with lower DLco levels in SSc (12) and with more extensive disease on HRCT in IPF (11). In IPF, a reported relationship between rapid clearance of the fast component of 99mTc-DTPA clearance and mortality was substantially weaker than the relationship between mortality and lower carbon monoxide diffusing capacity levels (8).

Therefore, the aim of the study was to examine relationship between the rapidity of 99mTc-DTPA clearance and outcome in IPF and SSc-ILD, with and without adjustment for disease severity (as judged by HRCT and pulmonary function tests).
Methods

Patients

Patients in both disease cohorts have been included in other published studies of outcome (13-15).

1) SSc-ILD

The cohort comprised 168 of 277 consecutive referred patients with systemic sclerosis and interstitial lung disease on HRCT (January 1990 to December 1999). Exclusion criteria are listed in the on-line depository. Serial PFT were available in 152 of 168 (90%) patients.

2) IPF

The cohort comprised 97 of 191 consecutive referred patients meeting ATS criteria for IPF (16), (December 1990 and December 1996). Exclusion criteria are listed in the on-line depository. Time to decline analyses were performed in 89 of 97 patients (serial PFT, n=73; death within six months of presentation, n=16).

Clinical data

Vital status (at 1st May 2006) and serial PFT (up to 1st May 2006) were recorded. Patients were categorised as former smokers (>one cigarette/day for >1 year) or lifelong non-smokers. Treatment was defined as corticosteroid and/or immunosuppressive (cyclophosphamide, azathioprine, mycophenolate mofetil) therapy at the time of 99mTc-DTPA clearance (see on-line depository for more details). Therapeutic status was defined as “intention to treat” (treatment from presentation or within three months of presentation) or “intention to observe” (no treatment
within three months of presentation).

PFTs (expressed as % predicted) and HRCT were performed as previously reported (14) (see online depository). The composite physiologic index (CPI) (17) was calculated: CPI = 91.0 – (0.65 x percent predicted DLco) – (0.53 x percent predicted FVC) + (0.34 x percent predicted FEV1).

All investigations were performed as part of a prospective routine clinical protocol.

**Staging status in SSc-ILD**

Disease severity was quantified as ‘mild’ [HRCT disease extent ≤10% or FVC ≥70% in ‘indeterminate’ disease (HRCT disease extent between 10% and 30%)] or ‘extensive’ [HRCT disease extent >30% or FVC <70% in ‘indeterminate’ disease’] (14).

**99mTc-DTPA pulmonary clearance**

Lung clearance of aerosolised 99mTc-DTPA was measured as a) total clearance; b) normal versus abnormally rapid clearance; c) the fast and slow components of clearance in the majority of patients with recorded raw data (18;19) (see on-line depository).

**Outcome**

Mortality and disease progression (time to decline in pulmonary function indices) were quantified from the date of 99mTc-DTPA clearance. Significant changes in PFT, using ATS and
ERS criteria (16), were defined as 1) $\geq 10\%$ decline in FVC and 2) $\geq 15\%$ decline in DLco on 2 consecutive occasions. When follow-up ended with functional deterioration on a single occasion, this was taken to indicate significant decline, with the proviso that there was symptomatic or radiographic evidence of deterioration. “Progression-free survival”, defined as the time to a progression event (decline in FVC, DLco or death) (20), was also evaluated.

The rate of change in FVC and DLco levels (mls/year), quantified as the difference between the last and first measurement over the total lung function follow up time, was also examined in relation to the speed of total DTPA clearance.

**Data analysis**

Analyses were performed using STATA software (Stata data analysis software; Computing Resource Centre, Santa Monica, CA). Data were expressed as means (SD) or medians (range), depending on distribution. Group comparisons were made using Student’s $t$ test, Wilcoxon rank sum, chi-squared statistics and Fisher’s exact test, as appropriate.

$^{99m}$Tc-DTPA clearance variables were examined in separate models against mortality and time to disease progression using proportional hazards analysis (see on line depository). Variables not contributing to equation explanatory power (p>$0.05$) were excluded, using a stepwise method.
RESULTS

As shown in Table 1, when compared to SSc-ILD patients, IPF patients were older, had more severe disease at presentation and exhibited a worse prognosis. IPF patients had markedly faster total clearance (p<0.00005) and a higher proportion of patients with abnormal total clearance (p=0.001) (Table 2).

\textit{99mTc-DTPA clearance in relation to disease severity (see on-line depository)}

In SSc-ILD (Table E1), clearance was increasingly rapid in increasingly severe disease [CPI (Figure E1): R_s = -0.37; p<0.00005; vs HRCT disease extent (Figure E2): R_s = -0.31, p=0.0001]. %FC was also associated with both measures of disease severity [CPI: R_s = 0.42; p<0.00005; HRCT disease extent: R_s = 0.25, p=0.005].

In IPF (Table E2), only the %FC was associated with the CPI (R_s = 0.22; p=0.05) and HRCT extent (R_s = 0.24; p=0.03).

A) Prognostic value of \textit{99mTc-DTPA clearance in SSc-ILD}

\textit{Mortality}

Mortality was associated with increasingly rapid total clearance (HR=1.02; 95% CI 1.00, 1.03; p=0.02) (Table 3) but this association was lost (p>0.10) with adjustment for age, gender, smoking status and disease severity (CPI levels and staging status in alternative models). Mortality was not linked to the presence of abnormally rapid clearance.
**Time to decline in pulmonary function variables**

A shorter time to FVC decline was predicted by increasing rapid total clearance (HR=1.02; 95% CI 1.01, 1.03; p=0.001) and the presence of abnormally rapid clearance (HR=2.10; 95% CI 1.25, 3.53; p=0.005) (Table 4). These variables were the only independent predictors of a shorter time to FVC decline in separate multivariate models (whether disease severity was quantified using CPI levels or staging status). By contrast, time to DLco decline was predicted by neither the rapidity of total clearance nor the presence of abnormally rapid clearance (Table 5).

Shorter progression-free survival (Table 3) was associated with increasing rapid total clearance (p=0.006), which was the only independent predictor on multivariate analysis (with severity quantified using CPI levels and staging status in separate models). Shorter progression free survival was also predicted by the presence of abnormally rapid clearance (p=0.02), but this association was lost on multivariate analysis.

**Correlation between rate of change in PFT and speed of DTPA clearance**

In SSc-ILD, the speed of total DTPA clearance correlated with the rate of FVC change (p=0.03; R=0.17), but not with the rate of DLco change (p=0.33; R=0.08). In IPF, the speed of total DTPA clearance did not correlate with the rate of FVC change (p=0.44; R=-0.09), nor the rate of DLco change (p=0.21; R=-0.14).

**Prognostic value of $^{99m}$Tc-DTPA clearance in mild and extensive disease**

The prognostic value of $^{99m}$Tc-DTPA clearance was re-examined separately in mild (n=115) and
extensive (n=53) disease (see Table E3). A shorter time to FVC decline was linked to increasingly rapid total clearance in both mild disease (p=0.02) and extensive disease (p<0.05). A shorter time to FVC decline was associated with the presence of abnormally rapid clearance in mild disease (p<0.05) but not in extensive disease. Neither clearance variable was predictive of either mortality (Table E4) or time to DLco decline (see Table E3).

*99mTc-DTPA clearance versus time to decline in FVC: influence of therapeutic status*

In 65 patients receiving therapy within three months of measurement of *99mTc*-DTPA clearance (the “intention to treat” patient sub-group), time to FVC decline was not linked to the rapidity of clearance. By contrast, in the remaining 87 patients (the “intention to observe” patient sub-group), a shorter time to FVC decline was associated with both increasingly rapid clearance (HR=1.03; 95% CI 1.01, 1.05; p=0.002) and the presence of abnormally rapid clearance (HR=2.29; 95% CI 1.17, 4.49; p=0.02).

*Prognostic value of clearance curve components*

Outcome was re-examined against clearance curve components in 126 of 168 patients (75%). On univariate analysis, a shorter time to FVC decline was linked to increasingly rapid clearance of the fast component, a higher %FC, but not the rapidity of clearance of the slow component (Table 4). On multivariate analysis, a shorter time to FVC decline was linked to rapid clearance of the fast component and a higher %FC (see on-line depository). Neither mortality (Table 3) nor time to DLco decline (see Table 5) was linked to any clearance curve component.
B) Prognostic value of $^{99m}$Tc-DTPA clearance in IPF

Neither mortality (Table 3) nor progression of disease (Table 4 and Table 5) was linked to the rapidity of total clearance or the presence of abnormally rapid clearance. A shorter time to FVC decline (Table 4) was associated with delayed clearance of the slow component ($p<0.01$), but was not linked to the fast component or the %FC. On multivariate analysis, the association between time to FVC decline and the clearance of the slow component was independent of the extent of disease on HRCT and the CPI in separate models. Neither mortality nor time to DLco decline was linked to any clearance curve component.
DISCUSSION

Our findings indicate that in SSc-ILD, increased epithelial permeability is linked to disease severity and is predictive of disease progression, in both mild and extensive disease and in the subset of patients not receiving immediate treatment. By contrast, increased epithelial permeability was not linked to disease severity in IPF and disease progression was associated only with a $^{99m}$Tc-DTPA clearance profile indicative of abnormally slow clearance in some lung regions. These relationships persisted after adjustment for disease severity.

Although these observations might appear to suggest a clinical role for the measurement of $^{99m}$Tc-DTPA clearance in SSc-ILD, the procedure is not without limitations, including confounding by current or recent smoking and radiation constraints, which also preclude quantification of the intra-patient variability of the test. Although routinely performed at our institution, measurement of $^{99m}$Tc-DTPA is not available in many centres. Thus, we have not explored the precision of prognostic evaluation, using ROC analysis, but have instead focussed on pathogenetic implications of our findings.

The findings in the present study provide support for a direct relationship between epithelial events and progression of fibrosis in SSc-ILD. Until now, the pathogenetic focus has been on vascular, immunologic and fibrotic processes, with endothelial cell injury viewed by some as central to the pathogenesis of SSc vasculopathy (21). However, indirect support for the pathogenetic importance of epithelial injury has been suggested in several studies. In SSc-ILD, early histological changes include both endothelial and epithelial injury, together with interstitial oedema and excess collagen deposition (22). Epithelial cells may also contribute to the fibrotic
process through epithelial-mesenchymal-transition (23). Rapid clearance of $^{99m}$Tc-DTPA has been linked to functional decline in a small cohort which included patients with SSc-ILD (1). However, in that study, patients with idiopathic interstitial pneumonia were also included and, crucially, disease severity was not taken into account. In the current study, all relationships between disease progression and increased epithelial permeability were independent of disease severity, as judged by functional and morphologic quantification in separate models, and, thus, it seems unlikely that epithelial injury is linked to outcome in SSc-ILD only as an epiphenomenon. Furthermore, epithelial cells are a rich source of a number of profibrotic cytokines, including transforming growth factor β1 (24;25), platelet derived growth factor (26) and tumour necrosis factor-α (24;27). More compellingly, in a recent transgenic mouse model of scleroderma (28), even minor epithelial injury was shown to induce significant pulmonary fibrosis, mediated by perturbation of TGF beta signalling, supporting an important pathogenetic role for epithelial injury. Taken together, the current and previous observations suggest that epithelial events are likely to be pathogenetically important in SSc-ILD. It should be stressed that statistically significant findings across an entire cohort sometimes result from strong trends within a large patient sub-group. We have not established that epithelial events have pathogenetic significance in all patients with SSc-ILD. However, our findings suggest that attempts to deconstruct core pathogenetic mechanisms in the whole cohort of SSc-ILD patients without incorporating epithelial injury may be fatally flawed.

The fact that increased $^{99m}$Tc-DTPA clearance was less predictive of outcome in patients who were treated from presentation is also compatible with an epithelial pathogenetic pathway. In a recent placebo controlled trial (29), oral cyclophosphamide therapy was associated with a
reduction in disease progression. However, the difficulties in controlling for a treatment effect in a large retrospective cohort (14), even with the use of a prospective clinical protocol, should be emphasised. In many cases, therapy is introduced after a period of observation and the choice, timing and duration of treatment necessarily vary widely during follow-up, due to side effects or disease progression. This problem is partially addressed by separate analyses based on initial management, with the designation of “intention to treat” and “intention to observe” sub-groups (14). In the latter group, it was our policy to introduce treatment only if disease progression was observed and this probably accounts for the stronger linkage between epithelial injury and decline in forced vital capacity in this sub-group. Even in a prospective study, the constraints discussed above are likely to hinder the deconstruction of a treatment effect, except in the setting of large placebo-controlled treatment cohorts.

The findings in the present study suggest that attempts to delineate the mathematical components of $^{99m}$Tc-DTPA clearance do not add to prognostic evaluation in SSc-ILD. Disease progression was linked to increased rapidity of the fast component of clearance, whether evaluated as a discrete variable or as a proportion of overall clearance. However, these relationships were weaker than those between total clearance and outcome. It has been argued that the fast component of clearance might represent clearance in injured lung, with the slow component reflecting clearance in normal lung. The observations of Mogulkoc et al (8) provide some support for this hypothesis, with the fast component of clearance predicting mortality in IPF. However, we were unable to reproduce this finding or to detect any associations between abnormally rapid clearance and disease progression in IPF.
The negative findings in IPF in our study were, at first sight, surprising as the core pathogenetic pathway is now widely viewed as an epithelial-fibrotic process. However, there are at least two possible explanations for this apparent discrepancy. The usual histopathological pattern in SSc-ILD is non-specific interstitial pneumonia, in which disease is diffuse and homogenous. By contrast, usual interstitial pneumonia in IPF is heterogeneous, with honeycomb and fibrotic changes interspersed with normal lung. The profusion of fibroblastic foci, and not the extent of fibrosis, is linked to outcome in histological studies of IPF (6;7), but fibroblastic foci make up only a tiny percentage of abnormal lung, and there is no current method of deconstructing their contribution to overall clearance abnormalities: serum biomarkers that directly reflect focal epithelial events may be more useful in this regard. A second confounding factor is the occurrence of acute exacerbations, which are increasingly recognised in IPF and may profoundly weaken relationships between outcome and measures of epithelial injury at presentation.

However, one intriguing observation emerged from curve deconstruction in IPF: delayed clearance of the slow component was associated with a shorter time to decline in FVC. Thus, in IPF, there are regions of abnormally slow clearance which, when more extensive, denote a poor outcome, a phenomenon that is not seen in SSc-ILD. Although not addressed by our study, this finding may represent the presence of honeycombing in IPF, which is also an adverse prognostic determinant. It is known that honeycomb lung ventilates normally in IPF but is entirely non-perfused, leading to the simulation of pulmonary embolism on ventilation-perfusion scanning (30). Thus, it can be expected that a $^{99m}$Tc-DTPA aerosol should deposit normally in honeycomb lung but would not be cleared, accounting for the prognostic significance of delayed slow clearance in the present study.
Some bias exists due to patient selection, with IPF patients less likely to undergo $^{99m}$Tc-DTPA than SSc-ILD patients as a matter of unit policy, with the existence of a weekly quota of clearance measurements for routine clinical purposes. Another limitation is that the retrospective nature of our analyses, but it should be stressed that all patients underwent a prospective protocol of investigation, except when demand exceeded the routine availability of $^{99m}$Tc-DTPA clearance measurements. No differences were disclosed when baseline characteristics were compared between the study cohort and patients not undergoing $^{99m}$Tc-DTPA measurement, either in IPF or SSc-ILD and, thus, it appears unlikely that these biases had a major confounding effect..

In conclusion, our findings indicate that epithelial injury may have a central pathogenetic role in some or all patients with SSc-ILD, independent of disease severity: pathogenetic models in this disease that include no epithelial component may be fatally flawed. By contrast, although IPF pathogenesis is viewed as an epithelial-fibrotic process, outcome is not linked to the extent of epithelial injury, as judged by clearance of $^{99m}$Tc-DTPA, suggesting that core pathogenetic events may be more spatially focal in IPF than in SSc-ILD, and may be better captured by biomarkers of disease activity.
Acknowledgements: We would like to thank Mr Jim Bailey, from the department of Nuclear Medicine at the Royal Brompton Hospital, for his time and efforts with the collection of DTPA data.
Table legends:

Table 1. A comparison of demographic and clinical data between SSc-ILD and IPF patients.

Table 2. A comparison of $^{99m}$Tc-DTPA clearance between SSc-ILD and IPF patients.

Table 3. A comparison of mortality and “progression-free-survival”, expressed as hazards ratio (HR) with 95% confidence intervals (95% CI), in relation to $^{99m}$Tc-DTPA clearance in SSc-ILD and IPF patients.

Table 4. A comparison of time to FVC decline, expressed as hazards ratio (HR) with 95% confidence intervals (95% CI), in relation to $^{99m}$Tc-DTPA clearance in SSc-ILD and IPF patients.

Table 5. A comparison of time to decline in DLco, expressed as hazards ratio (HR) with 95% confidence intervals (95% CI), in relation to $^{99m}$Tc-DTPA clearance in SSc-ILD and IPF patients.
Table 1.

<table>
<thead>
<tr>
<th></th>
<th>SSc-ILD (n=168)</th>
<th>IPF (n=97)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.5 ± 13.2</td>
<td>63.7 ± 8.8</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>31:137</td>
<td>73:24</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Smoking status</td>
<td>never=108; ex=60</td>
<td>never=17; ex=80</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>60/168 (36%)</td>
<td>84/97 (87%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>- Five-year-survival</td>
<td>76%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>No. of patients with FVC decline</td>
<td>87/152 (57%)</td>
<td>63/89 (71%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>- median time to decline (mths)</td>
<td>57</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>No. of patients with DLco decline</td>
<td>88/152 (58%)</td>
<td>61/89 (69%)</td>
<td>0.10</td>
</tr>
<tr>
<td>- median time to decline (mths)</td>
<td>62</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>No. of patients with pfs</td>
<td>32/152 (21%)</td>
<td>6/89 (7%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>- median time to decline (mths)</td>
<td>36</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>78.2 ± 21.5</td>
<td>67.8 ± 20.6</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>DLco (% predicted)</td>
<td>55.4 ± 17.0</td>
<td>36.9 ± 14.7</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>CPI</td>
<td>39.8 ± 15.4</td>
<td>55.0 ± 13.7</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>HRCT disease extent (%)*</td>
<td>13.3 (1.0 to 84.0)</td>
<td>56.5 (8.5 to 96.0)</td>
<td>&lt;0.00005</td>
</tr>
</tbody>
</table>

pfs = progression free survival; FVC = forced vital capacity; DLco = gas transfer; CPI = composite physiologic index.

*Median values, with ranges in parentheses
Table 2.

<table>
<thead>
<tr>
<th>DTPA clearance variables</th>
<th>SSc-ILD (n=168)</th>
<th>IPF (n=97)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clearance (min)</td>
<td>33.0 (8.8 to 128.5)</td>
<td>22.7 (7.5 to 83.2)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Patients with an abnormal clearance (min)</td>
<td>113/168 (67%)</td>
<td>84/97 (87%)</td>
<td>0.001</td>
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<tr>
<td>Fast clearance (min)</td>
<td>5.1 (0.8 to 28.5) *</td>
<td>5.0 (1.4 to 32.8) †</td>
<td>0.64</td>
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<tr>
<td>%FC</td>
<td>18.3 (1.0 to 67.0) *</td>
<td>27.3 (3 to 100) †</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Slow clearance (min)</td>
<td>49.9 (21.4 to 145.7) *</td>
<td>48.5 (19.2 to 137.0) †</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Results are expressed as medians with ranges in parentheses unless otherwise stated.

%FC = percentage of tracer cleared by the fast component. *n=126 patients. † n=81 patients.
### Table 3.

<table>
<thead>
<tr>
<th>DTPA clearance variables</th>
<th>SSc-ILD Mortality vs IPF</th>
<th>Progressive Free Survival SSc-ILD vs IPF</th>
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<tbody>
<tr>
<td></td>
<td>HR 95% CI p value</td>
<td>HR 95% CI p value</td>
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<tr>
<td>Increasing rapid total</td>
<td></td>
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<tr>
<td>Patients with an abnormal clearance (min)*</td>
<td>1.02 1.00, 1.03 0.02</td>
<td>1.01 0.99, 1.02 0.28</td>
</tr>
<tr>
<td>Increasing %FC†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing delayed Slow</td>
<td>1.02 1.00, 1.04 0.06</td>
<td>1.00 0.99, 1.02 0.66</td>
</tr>
</tbody>
</table>

* n=168 SSc-ILD patients; n=97 IPF patients. †n=126 SSc-ILD patients; n=81 IPF patients
<table>
<thead>
<tr>
<th>DTPA clearance variables</th>
<th>Time to decline in FVC</th>
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<tr>
<td></td>
<td>SSc-ILD vs IPF</td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
<td>HR</td>
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<tr>
<td>Increasing rapid total clearance (min)*</td>
<td></td>
<td>1.02</td>
<td>1.01, 1.03</td>
<td>0.001</td>
<td>0.99</td>
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<td>Patients with an abnormal clearance (min)*</td>
<td></td>
<td>2.10</td>
<td>1.25, 3.53</td>
<td>0.005</td>
<td>0.59</td>
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<tr>
<td>Increasing rapid Fast clearance (min)†</td>
<td></td>
<td>1.15</td>
<td>1.04, 1.28</td>
<td>&lt;0.01</td>
<td>0.98</td>
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<tr>
<td>Increasing %FC†</td>
<td></td>
<td>1.02</td>
<td>1.00, 1.04</td>
<td>0.02</td>
<td>0.99</td>
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<tr>
<td>Increasing delayed Slow clearance (min)†</td>
<td></td>
<td>0.99</td>
<td>0.98, 1.01</td>
<td>0.36</td>
<td>1.01</td>
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</table>

*n=168 SSc-ILD patients; n=97 IPF patients. †n=126 SSc-ILD patients; n=81 IPF patients
Table 5.

<table>
<thead>
<tr>
<th>DTPA clearance variables</th>
<th>Time to decline in DLco</th>
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<tr>
<td></td>
<td>SSc-ILD</td>
<td>vs</td>
<td>IPF</td>
<td></td>
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<tr>
<td></td>
<td>HR 95% CI p value</td>
<td>HR 95% CI p value</td>
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<tr>
<td>Increasing rapid</td>
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<tr>
<td>total clearance (min)*</td>
<td>1.01  1.00, 1.02  0.07</td>
<td>1.00 0.99, 1.02 0.62</td>
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<td>Patients with an</td>
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</tr>
<tr>
<td>abnormal clearance (min)*</td>
<td>1.45  0.90, 2.34  0.12</td>
<td>1.52 0.65, 3.56 0.34</td>
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<tr>
<td>Increasing rapid</td>
<td></td>
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<tr>
<td>Fast clearance (min)†</td>
<td>1.04  0.96, 1.14  0.33</td>
<td>1.00 0.93, 1.06 0.90</td>
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<tr>
<td>Increasing %FC†</td>
<td>1.02  1.00, 1.03  0.09</td>
<td>1.00 0.99, 1.02 0.72</td>
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<tr>
<td>Increasing delayed</td>
<td>1.00  1.00, 1.01  0.32</td>
<td>1.01 1.00, 1.02 0.12</td>
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</tr>
<tr>
<td>Slow clearance (min)†</td>
<td>1.00  1.00, 1.01  0.32</td>
<td>1.01 1.00, 1.02 0.12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n=168 SSc-ILD patients; n=97 IPF patients. †n=126 SSc-ILD patients; n=81 IPF patients
Reference List


(12) Diot E, Giraud Stances B, Maillot F, Diot P. Decrease in DL,CO in systemic sclerosis


(25) Khalil N, Greenberg AH. The role of TGF-beta in pulmonary fibrosis. Ciba Found Symp


