Scintigraphy at 3 months after single lung transplantation and observations of primary graft dysfunction and lung function

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Abstract

Scintigraphy has been used as a tool to detect dysfunction of the lung before and after transplantation. The aims of this study were to evaluate the development of the ventilation-perfusion relationships in single lung transplant recipients in the first year, at 3 months after transplantation, and to investigate whether scintigraphic findings at 3 months were predictive for the outcome at 12 months in relation to primary graft dysfunction (PGD) and lung function. A retrospective study was carried out on all patients who prospectively and consecutively were referred for a routine lung scintigraphy procedure 3 months after single lung transplantation (SLTX). A total of 41 patients were included in the study: 20 women and 21 men with the age span of patients at transplantation being 38–66 years (mean ± SD: 54.2 ± 6.0). Patient records also included lung function tests and chest X-ray images. We found no significant correlation between lung function distribution at 3 months and PGD at 72 h. There was also no significant correlation between PGD scores at 72 h and lung function at 6 and 12 months. The same applied to scintigraphic scores for heterogeneity at 3 months compared with lung function at 6 and 12 months. Fifty-five percent of all patients had decreased ventilation function measured in the period from 6 to 12 months. Forty-nine percent of the patients had normal perfusion evaluations, and 51% had abnormal perfusion evaluations at 3 months. For ventilation evaluations, 72% were normal and 28% were abnormal. There was a significant difference in the normal versus abnormal perfusion and ventilation scintigraphic images evaluated from the same patients. Ventilation was distributed more homogeneously in the transplanted lung than perfusion in the same lung. The relative distribution of perfusion and ventilation to the transplanted lung of patients with and without a primary diagnosis of fibrosis did not differ significantly from each other. We conclude that PGD defined at 72 h does not lead to recognizable changes in ventilation-perfusion scintigraphy at 3 months, and scintigraphic findings do not correlate with development in lung function in the first 12 months.

Keywords: Education • Lung • Lung transplantation

INTRODUCTION

Single lung transplantation (SLTX) has become a treatment option for patients with terminal obstructive or restrictive lung disease since the first successful single-lung transplant in 1983 [1], and of the close to 2000 lung transplantations performed annually ~28% are SLTX [2].

Some patients develop an impairment of the graft function in the early phase after lung transplantation, and have diffuse infiltrates visible on chest radiograph, which may represent primary graft dysfunction (PGD). PGD occurs in ~11–63% of lung transplant patients [3, 4]. Development of PGD in the early postoperative period negatively affects long-term survival of lung-transplanted patients and level of lung function obtained, even in those patients who do not develop bronchiolitis obliterans syndrome (BOS) [3, 5] and mortality rates between 17 and 50% have been reported [3, 6].

Ventilation and perfusion scintigraphy have been used as tools to detect dysfunction of the lung before and after transplantation [7]. The aim of this study was to evaluate the development of ventilation-perfusion relationships in single lung transplant recipients in the first year after the transplantation to investigate whether scintigraphic findings at 3 months were predictive for the outcome at 12 months in relation to PGD and lung function.

METHODS

A retrospective study was carried out on all patients who prospectively and consecutively were referred for a routine lung scintigraphy procedure at 3 months postoperatively for SLTX. The study was a retrospective study spanning from February 2004 to December 2008, and during this period, 70 single lung transplants were carried out. To make our results comparable, we included only patients who had a complete set of 3-month scintigraphy examinations of good quality (both ventilation and perfusion scintigraphy). One patient died before the start of the examination and 12 patients were not examined due to logistical...
reasons. In 11 patients scintigraphy examination records were only subjectively described. The computed records for these patients were not available and, due to technical reasons, it was not possible to compute new scintigraphic values from the stored images. Therefore, only 46 patients had complete sets of routine 3-month scintigraphy performed. However, the scintigraphic images from five patients were poor in quality and were thus also excluded from the study. We therefore had 41 patients, who had appropriate and available scintigraphic examination results for analysis.

As such, a total of 41 patients only were included in the study: 20 women and 21 men with the age span at transplantation of 38–66 years (mean ± SD: 54.2 ± 6.0). From the patients’ records, we derived scintigraphic images, chest X-rays and the following lung function tests: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), residual volume (RV), total lung capacity (TLC) and single breath diffusion capacity for carbon monoxide CO (DLCO) and the DLCO per unit of alveolar volume (DLCO/VA).

PGD—imaging with chest X-ray within 72 h
To determine the presence or absence of PGD, X-ray images taken routinely within the first 72 h after transplantation were evaluated by two observers (M.I. and E.O.B.) and consensus was obtained. The chest X-ray images were graded according to the recommendations of the International Society of Heart and Lung Transplantation (ISHLT) for grading PGD, where scores are based on the presence or absence of infiltrates and the PaO2: FiO2 (ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen, also termed P/F ratio). X-ray images with no infiltrates received a score of 0, images with infiltrates were given a score from 1 to 3, with 1 = P/F ratio of >300, 2 = P/F ratio 200 to 300, 3 = P/F ratio <200. We recorded 2–3 PGD values within the first 72 h, based on the data available and chose the highest PGD value recorded within this period as the valid PGD value.

In the evaluation of infiltrates on chest X-ray images for PGD, the ISHLT recommendations differentiated between the absence and presence of infiltrates only. Based on a study by Burton et al. [4], we have taken further steps to grade the infiltrates seen on chest X-ray images into four grades, ranging from 0 to 3 based on the visual severity. Table 1 is modified from this series.

Lung scintigraphy—imaging at 3 months
To evaluate the perfusion distribution in the lung, 150 (75–175) MBq 99mTc macro-aggregated albumin was injected intravenously and was caught in the lungs pre-capillary vessels. A gamma camera recorded scintigraphic images of the lungs regional perfusion.

When evaluating lung ventilation, 600 MBq 81m Krypton (from a 81m Rubidium generator, Rigshospitalet, Denmark) was inhaled. The scintigraphic images showed regional ventilation distribution in the lungs.

Perfusion and ventilation scintigraphy were obtained simultaneously in anterior and posterior projections of the patients (Figs 1–4). We used a one-headed GE Maxi camera (GE, USA) or

<table>
<thead>
<tr>
<th>Table 1: Infiltrate grading on X-ray images</th>
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<tbody>
<tr>
<td>Grade 0 No infiltrates with consolidation seen, a little diffuse bladdering can be seen</td>
</tr>
<tr>
<td>Grade 1 Diffuse blurring or infiltrates with consolidation in &lt;50% of the lung</td>
</tr>
<tr>
<td>Grade 2 Consolidation between 50 and 90% of the lung</td>
</tr>
<tr>
<td>Grade 3 Consolidation of over 90%</td>
</tr>
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</table>

Figure 1: Anterior and posterior views of scintigraphic images of perfusion of the lungs. Grade 1: Homogenous distribution.

Figure 2: Anterior and posterior views of scintigraphic images of perfusion of the lungs. Grade 2: Slightly uneven—no defects.

Figure 3: Anterior and posterior views of scintigraphic images of perfusion of the lungs. Grade 3: Slight changes on the anterior and posterior side or one normal side and one side with defects.

Figure 4: Anterior and posterior views of scintigraphic images of perfusion of the lungs. Grade 4: Abnormal on both sides (anterior and posterior) and defects on both sides.
Scintigraphic scoring—imaging at 3 months

To evaluate and score both our perfusion and ventilation scintigraphic images, we used the criteria outlined in Table 2, which were modified from Stavngaard and Mortensen [8]. Two observers (J.M. and E.O.B.) scored all images individually twice at least 1 month apart and in consensus twice at least 3 months apart. These scores were further dichotomized into two groups, wherein group 1 was categorized as normal and included patients with a score of 1–2 for homogeneity and group 2 was categorized as abnormal and included patients with a score of 3–4 for heterogeneity based on the results of our second consensus.

Lung function tests—at 6 and 12 months

Patients were monitored pre- and postoperatively with lung function tests. We collected the FEV1, FVC, RV, TLC and single breath diffusion capacity for carbon monoxide CO (DLCO) and the DLCO per unit of alveolar volume (DLCO/VA). We calculated the relative change from 6 to 12 months in FEV1, FVC, TLC, RV, DLCO, DLCO/VA (for example, FEV1 at 6 months—FEV1 at 12 months/FEV1 at 6 months) and the absolute level of lung function at 12 months in percentage of the predicted value (for two normal lungs). These values were correlated to PGD, the relative perfusion and ventilation distribution to the transplanted lung, and the perfusion and ventilation heterogeneity score.

Table 2: Scintigraphic score criteria for anterior and posterior images of perfusion and ventilation

<table>
<thead>
<tr>
<th>Score</th>
<th>Caption</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Homogenous distribution</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Slightly uneven—no defects</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Slight changes on the anterior and posterior image or one normal side and one side with defects</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Abnormal with defects on both the anterior and posterior image</td>
</tr>
</tbody>
</table>

RESULTS

PGD—imaging with chest X-ray within 72 h

The PGD scores at 72 h correlated strongly with the infiltrate grades obtained from chest X-rays at 72 h. The correlation coefficient for the two parameters was 0.78.

PGD seems to be heterogeneous in its appearance on computed tomography and PGD scores at 72 h were compared with visual qualitative scintigraphic distribution at 3 months to see whether there was any persistence in the heterogeneous pattern at this stage. We found no significant correlation with the Spearman correlation for perfusion and ventilation score category against PGD being: 0.15, confidence limits (CL): −0.58 to 0.88 and 0.29, CL: 0.5–1.0, respectively.

Lung scintigraphy—imaging at 3 months

We found that out of 41 patients, 20 (49%) had normal qualitative perfusion evaluations (grade 1 in 10% and grade 2 in 90%) and 21 (51%) had abnormal perfusion evaluations (grade 3 in 57% and grade 4 in 43%). For ventilation evaluations, 29 (72%) were normal (grade 1 in 45% and grade 2 in 55%) and 11 (28%) were abnormal (grade 3 in 73% and grade 4 in 27%). Ventilation results from one patient were unavailable.

There was a significant difference in the normal versus abnormal perfusion and ventilation scintigraphic images evaluated from the same patients (Fisher’s exact test, P = 0.0172). Ventilation images were often normal or close to normal in patients with abnormal perfusion. Five patients out of 41 had a primary diagnosis of fibrosis, while the other patients had chronic obstructive pulmonary disease (COPD).

The quantitative analysis showed that perfusion and ventilation were quite similar in the subgroups of patients with COPD and lung fibrosis (Table 3). In the COPD and fibrosis group, perfusion to the transplanted lung was 75 and 75%, respectively, and ventilation was 73 and 69% respectively.

Lung function tests at 6 and 12 months

There was no significant correlation between PGD scores at 72 h and lung function parameters when analysed with the absolute

Table 3: Quantitative distribution of perfusion to the transplanted lung, measured in percentage at 3 months after the transplantation

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>COPD and other lung disease</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Perfusion</td>
</tr>
<tr>
<td>Mean</td>
<td>75</td>
</tr>
<tr>
<td>Maximum</td>
<td>91</td>
</tr>
<tr>
<td>Minimum</td>
<td>60</td>
</tr>
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</table>

Five of the 41 patients had fibrosis as primary diagnosis; the other patients had COPD.
l lung function value in percent predicted at 12 months, and the changes in lung function between 6 and 12 months. The same applied to the scintigraphic score for heterogeneity at 3 months and the quantitative perfusion/ventilation distribution to the transplanted lung compared with lung function parameters when analysed with the absolute lung function value in per cent predicted at 12 months, and the changes in lung function between 6 and 12 months.

Table 4 shows the Spearman correlation coefficients of the absolute values of lung function tests (FEV₁, FVC, TLC, RV, DLCO, DLCO/VA) at 12 months in percentage of predicted, and the relative differences between 6 and 12 months in the same lung function tests (FEV₁, FVC, TLC, RV, DLCO, DLCO/VA) correlated to PGD, perfusion and ventilation heterogeneity score, and quantitative distribution of perfusion and ventilation to the transplanted lung.

### Scintigraphic scores

Kappa values were calculated for the inter-observer reproducibility for observer one (J.M.) and observer two (E.O.B.) for the first and the second evaluation of both perfusion and ventilation. The results for the first and second perfusion evaluation were 0.77 and 0.80, respectively, while the first and second ventilation evaluation kappa values were 0.71 and 0.76 respectively. This was considered to show good agreement, in accordance with standard statistical values [9].

The first and second evaluations of each observer for both perfusion and ventilation were compared to obtain intra-observer reproducibility. Observer one had kappa values of 0.96 and 0.93 for perfusion and ventilation respectively, while observer two had kappa values of 0.89 and 0.84. Both observers were considered to have very good intra-observer reproducibility.

Consensus was obtained after each evaluation, and consensus 1 versus consensus 2 for perfusion was 0.66, while consensus 1 versus consensus 2 for ventilation was 0.76. Both values showed good agreement.

### DISCUSSION

The purpose of this study was to describe the scintigraphic findings at 3 months in relation to early lung damage in the form of PGD and relate scintigraphic findings to the outcome at 6 and 12 months. Severe PGD is a well-recognized cause of long-term graft dysfunction with lower levels of lung function obtained. A persistent change in lung function was expected to be detectable by ventilation-perfusion scintigraphy at 3 months. At this centre, lung transplant recipients obtain their maximal lung function at 6 months, and some will experience decline at 12 months.

The ISHLT PGD grade correlated strongly with infiltrate grades on a 0–3 point scale from chest X-rays at 72 h and this was expected as PGD starts in the first 72 h after lung transplantation.

No significant correlation was found between ISHLT PGD scores and scintigraphy scores for heterogeneity (at 3 months), relative ventilation-perfusion distribution to the transplanted lung (at 3 months), lung function from 6 to 12 months and the absolute value in percentage of predicted lung function at 12 months. PGD does not seem to leave any significant traces that can be observed in ventilation-perfusion scintigraphy at 3 months. PGD is an acute phase disease and an earlier examination than scintigraphy at 3 months might have shown identifiable signs of PGD. Fifty-five percent of all patients had a decrease in lung function measured in the period from 6 to 12 months, which is in line with previous studies [10].

The scoring system for visual evaluation of heterogeneity of ventilation-perfusion scintigraphy was demonstrated to have a good to very good intra- and inter-observer reproducibility, and this is, to our knowledge, the largest study of this type.

Scintigraphy after SLTX has been used in other centres to improve BOS diagnosis [7]. It is also used to diagnose other clinical problems or as a baseline for comparison with later examinations. A limiting factor of the study is the low number of participants, which has low power for statistical analysis or has led to a selection of atypical patients by chance. Since it was a retrospective study, exclusion was due only to the incompleteness of patient data and not due to morbidity. Only one patient was excluded due to mortality. This does not, therefore, constitute a bias, as all

### Table 4: Correlation of lung function tests to scintigraphic evaluations at 3 months and PGD scores within 72 h after lung transplantation (Spearman correlation).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculations</th>
<th>FEV₁</th>
<th>FVC</th>
<th>TLC</th>
<th>RV</th>
<th>DLCO</th>
<th>DLCO/VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGD (within 72 h)</td>
<td>Relative difference</td>
<td>-0.24</td>
<td>-0.06</td>
<td>-0.14</td>
<td>0.00</td>
<td>-0.06</td>
<td>-0.10</td>
</tr>
<tr>
<td></td>
<td>Absolute value</td>
<td>0.04</td>
<td>-0.04</td>
<td>-0.16</td>
<td>-0.15</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>Perfusion distribution to transplanted lung (3 months)</td>
<td>Relative difference</td>
<td>0.02</td>
<td>-0.24</td>
<td>0.03</td>
<td>0.19</td>
<td>-0.17</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Absolute difference</td>
<td>0.13</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.08</td>
<td>-0.11</td>
<td></td>
</tr>
<tr>
<td>Ventilation distribution to transplanted lung (3 months)</td>
<td>Relative difference</td>
<td>0.08</td>
<td>-0.16</td>
<td>-0.18</td>
<td>0.07</td>
<td>-0.02</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Absolute value</td>
<td>-0.03</td>
<td>0.01</td>
<td>0.26</td>
<td>0.20</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>Perfusion score (3 months)</td>
<td>Relative difference</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
<td>-0.01</td>
<td>0.23</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Absolute value</td>
<td>-0.23</td>
<td>-0.20</td>
<td>-0.12</td>
<td>-0.01</td>
<td>-0.08</td>
<td></td>
</tr>
<tr>
<td>Ventilation score (3 months)</td>
<td>Relative difference</td>
<td>-0.24</td>
<td>0.11</td>
<td>0.08</td>
<td>0.11</td>
<td>0.10</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Absolute value</td>
<td>-0.11</td>
<td>-0.19</td>
<td>-0.12</td>
<td>-0.01</td>
<td>-0.17</td>
<td></td>
</tr>
</tbody>
</table>

Relative difference = (for example, FEV₁ from 6 to 12 months/6 months ×100).

Absolute value at 12 month in % of predicted = (for example, FEV₁ at 12 months/predicted value of FEV₁ × 100). The predicted values for DLCO/VA were unavailable for calculating the absolute values. No correlations were statistically significant.
patients with routine 3-month scintigraphy of good quality were included; however, the few numbers of patients included constitutes a potential bias but we have examined several parameters in each patient, which therefore generated a lot of data.

**CONCLUSION**

PGD defined at 72 h does not lead to recognizable changes in ventilation–perfusion scintigraphy at 3 months, and scintigraphic findings do not correlate with development in lung function in the first 12 months. The routine use of ventilation–perfusion scintigraphy in lung transplant recipients at 3 months, is valuable as a baseline examination for comparison with later examinations. However, changes after PGD were not identifiable at 3 months and this examination is thus not warranted for examining changes caused by PGD.

**Conflict of interest:** none declared.

**REFERENCES**


