Abnormalities of Pulmonary Diffusion Capacity in Long-term Survivors After Kidney Transplantation*

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Study objectives: Alterations in pulmonary function and interstitial changes in the lungs of renal transplant recipients have been described, but prospective longitudinal data are lacking.

Design: A prospective analysis of pulmonary function tests and pulmonary CT in renal transplant recipients in stable condition at two different time points following kidney transplantation (KT).

Patients: Seventy-nine renal transplant recipients in stable condition were included. The first studies were performed 83 months (median) following KT. In 36 of these patients, it was possible to obtain a second set of studies after an additional follow-up period of 22 months.

Results: Approximately 11% of all patients showed significant restrictive and obstructive abnormalities in pulmonary function tests. In the majority of transplant recipients, considerable defects in pulmonary diffusion capacity were documented: lung transfer factor for carbon monoxide, or transfer coefficient for carbon monoxide were < 80% of the predicted value in 57% and 76%, respectively. In 24% of the CT studies, substantial interstitial alterations were found. However, no significant correlations could be established between CT morphology and the presence of diffusion abnormalities. At the time of the second follow-up investigation, we found a further decrease in diffusion capacity in approximately 30% of patients despite an unchanged CT morphology in most of these patients.

Conclusion: We conclude that an impairment of pulmonary diffusion capacity exists in the majority of long-term survivors after KT. In our opinion, CT-detectable interstitial findings do not represent a causative factor for these abnormalities. A plausible hypothesis is a “low-grade pulmonary microvascular injury” in combination with a long-term decrease in pulmonary perfusion. The impact of these diffusion defects on symptomatology and prognosis in kidney transplant recipients is largely unclear, and further studies are needed.

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Key words: CT; diffusion capacity; kidney transplantation; long-term follow-up; pulmonary function test; pulmonary interstitial changes

Abbreviations: hCMV = human cytomegalovirus; Kco = transfer coefficient for carbon monoxide; Kcoec = transfer coefficient for carbon monoxide corrected for hemoglobin; KT = kidney transplantation; RV = residual volume; TLC = total lung capacity; TLCO = lung transfer factor for carbon monoxide; Tlco = lung transfer for carbon monoxide corrected for hemoglobin; VC = vital capacity

So far, longitudinal studies of pulmonary function tests following kidney transplantation (KT) have been rare.1–4 However, the available data indicate that in contrast to improved parameters of obstruc-

tive and restrictive ventilation abnormalities, a considerable reduction of pulmonary diffusion capacity persists following transplantation.

It has been assumed that these diffusion abnormalities develop during the pretransplant period either in association with the disease itself or dialysis mediated.5 Interstitial changes manifesting as thickening of the alveolocapillary membrane in autopsy6 and radiology studies7 may play a causal role. Most important for the diffusion abnormalities appears to be the thickened membrane, which has been documented in detailed studies8,9 of membrane capacity.

Until now, most data have been obtained during the first year following transplantation. Only a few
investigators have reported findings in long-term renal transplant recipients, and longitudinal data over several years are lacking. For these reasons, the impact of transplant-associated effects on parameters of ventilatory function or pulmonary diffusion capacity during long-term observation is largely unknown. Therefore, it was our aim to describe the frequency and severity of ventilatory function abnormalities, including parameters of diffusion capacity, during the long-term follow-up period in renal transplant recipients and to relate these findings to indicators of interstitial abnormalities assessed by serial CT studies.

**Materials and Methods**

**Patients**

We enrolled 79 consecutive patients following KT (22 women [27.8%], 57 men [72.2%], 13 smokers [16.5%], and 66 nonsmokers [83.5%]; Table 1). The mean ± SD age at the time of KT was 38 ± 12 years (range, 12 to 62 years). The most frequent underlying diseases leading to KT were various forms of glomerulonephritis in 55.7% and pyelonephritis in 21.5%. The period of long-term dialysis preceding transplantation was 25 months (mean, 21 ± 20 months; range, 0 to 99 months). During this time, 23 patients (29.1%) had chronic hepatitis develop.

Initially, hepatitis B surface antigen was found in 18 patients (22.8%). Antibodies to hepatitis B core antigen were detected in 30 patients (42.3%), to hepatitis B envelope antigen in 4 patients (6.1%), and to hepatitis D surface antigen in 21 patients (28%). The hepatitis B envelope antigen was found in 14 patients (21.2%), and the hepatitis C virus was found in 19 patients (22.8%). At the time of this study, IgG and IgM antibodies to the human cytomegalovirus (hCMV) were detectable in 46 patients (52.2%) and 8 patients (10.1%), respectively. During the 12 months preceding this study, 32 patients (42.3%) were treated with cyclosporine, azathioprine, or corticosteroid for immunosuppression, and 47 patients (59.5%) received a combination of cyclosporine and corticosteroid or of azathioprine and corticosteroid. In seven patients (8.9%), repeated transplantsations were necessary due to transplant failure.

Following transplantation, a cell-mediated rejection occurred in 49 patients (62%) and hCMV infection developed in 43 patients (54.4%). Of these 43 patients with hCMV infection, only 4 patients had pneumonitis develop with interstitial radiologic findings; however, all of them were free of any significant interstitial changes at the time of the follow-up study.

On entry into the study, all patients were ambulatory and in stable condition without pulmonary diseases, radiologic abnormalities, infection, rejection, or relevant drug toxicity. Prior to inclusion into the study, all patients underwent echocardiography to exclude significant pathologic findings. In addition, the physical examination and the review of medical records had to be without any indication of other diseases that potentially could lead to an altered pulmonary function. All patients gave their informed consent to participate in this study, which was planned and conducted in accordance with the guidelines of the 1975 Declaration of Helsinki.

**Pulmonary Function Tests**

Spirometry and body plethysmography were performed using a constant volume body plethysmograph (Master Lab; Jäger; Würzburg, Germany). For final analysis, the following parameters were selected: vital capacity (VC), FVC, FEV1, the ratio of FEV1 to VC, total lung capacity (TLC), and the ratio of residual volume (RV) to TLC. For the measurement of diffusion capacity, the single-breath technique using carbon monoxide was employed. For final analysis, the lung transfer factor for carbon monoxide (TLCO) and the carbon monoxide transfer coefficient (Kco), as transfer factor for carbon monoxide relative to alveolar volume, in millimeters per minute per kilopascal (1 kPa = 7.502 mm Hg) were selected. Because TLCO is dependent on hemoglobin concentration, we chose to use corrected values as previously described. Using this approach, hemoglobin values of 13.5 g/dL (female) and 14.6 g/dL (male) were utilized as reference values, and the following formulas were used: 0.0646 × hemoglobin (in grams per deciliter) + 0.0568 (male); and 0.0646 × hemoglobin (in grams per deciliter) + 0.1279 (female). TLCO and Kco, when corrected for hemoglobin, are identified as TLCOc and Kco.c.

Diffusion parameters are expressed as a percentage of predicted, and, depending on the extent of impairment, classified as mild (60 to 79%), moderate (40 to 59%), or severe (<40%). The parameters VC, FVC, and TLC were classified as pathologic for values <80% predicted. The FEV1/VC ratio was considered abnormal when <75%, and for RV and the RV/TLC ratio values ≥120% predicted were pathologic. All measurements were performed according to the guidelines of the European Community for Steel and Coal, and for each individual values were also expressed in percentage of predicted values derived from age-matched and sex-matched healthy control subjects.

**CT**

Lung structure was assessed by CT in high-resolution technique (Somatom Plus; Siemens; Erlangen, Germany). The scan time was 2 × 1 s, and 2-mm slices were selected by the use of a 520 × 526 image matrix and a window frame between 450 Hounsfield units and 1,400 Hounsfield units. Whenever there was diminished transparency, a second series of scans was obtained with the patient in the prone position in order to differentiate the true structural lesions from the readily reversible changes that are due to hypostatic or ventilatory effects. Images were evaluated independently by two separate investigators using a simple rating system, which was comparable to those used by other investigators. Lesions were categorized according to their presence or absence, their location (ventralbasal or dorso-basal, apical, subpleural), their morphologic appearance (reticular, nodular, linear, band-type, ground-glass), and to their classification on a 4-grade scale (1 to 4). In addition, the evaluation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>57 (72.2)</td>
</tr>
<tr>
<td>Female gender</td>
<td>22 (27.8)</td>
</tr>
<tr>
<td>Smokers</td>
<td>13 (16.5)</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>66 (83.5)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>44 (55.7)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>17 (21.5)</td>
</tr>
<tr>
<td>Age at transplantation, yr</td>
<td>36 (12–62)</td>
</tr>
<tr>
<td>Time since transplantation, mo</td>
<td>83 (17–290)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) or mean (range).
Follow-up Investigation

As planned prospectively, it was possible to perform a second follow-up study in 45.6% of all patients (36 of 79 patients) after a median period of 22 months (mean ± SD, 21 ± 4 months; range, 10 to 30 months). The reasons for missing studies were follow-up at another hospital (16 of 79 patients), dialysis due to transplant failure (15 of 79 patients), patient refusal (4 of 79 patients), and death (8 of 79 patients). One patient had recurrent pericardial effusions develop without myocardial constriction, while another patient had recurrent pleural effusions during the follow-up period. Three patients had an acute myocardial infarct within the study period with a decline in left ventricular function (ejection fraction < 40%), and one patient underwent percutaneous interventional recanalization due to symptomatic ischemic heart disease. All of these patients had to be excluded from the final analysis because they entered a long-term dialysis program prior to the second time point of study investigation (dropout criteria).

Pulmonary function tests were performed in an identical manner to the first study. Changes of > 15%, relative to the first study, were considered relevant.

CT follow-up studies were done using the identical technique 23 months (mean, 23 ± 4 months; range, 15 to 38 months) following the first study. Two independent investigators assigned a general outcome with respect to the interstitial alterations observed, categorized as regression, constant, or progression. Using this classification, the spatial extent as well as qualitative aspects were considered.

Statistical Analysis

All analyses were performed using SPSS software (version 7.5; SPSS; Chicago, IL). To test for significance between different groups, a t test or the nonparametric Mann-Whitney test were used. Multivariate analyses were performed with analysis of variance. For evaluation of nominally structured data, the χ² test was applied. Changes over time within the group of patients having both follow-up investigations were assessed by paired t test.

The level of significance was p < 0.05. Unless indicated otherwise, data are expressed as median values, and the mean ± SD and range are also given.

RESULTS

The initial follow-up study was performed 83 months (mean, 71 ± 60 months; range, 17 to 290 months) after transplantation (Table 2). In four cases, a reliable diffusion analysis could not be performed for technical reasons.

When using the parameters VC and FVC, 10% and 19% of patients had restrictive physiology, respectively. According to body plethysmographic parameters, 11% of all patients showed restriction.

An abnormal FEV₁ value as an indicator of obstruction was found in 14% of all patients. Using the FEV₁/FVC ratio, this percentage was 10%. RV was increased in 18%, and the relation of RV to TLC was abnormal in 22% of all patients.

An impaired diffusion, according to TLCO, was found in 43% of all patients. After correcting for hemoglobin concentrations, the TLCoC finding was abnormal in 57%. These alterations were mild in 20 of 43 patients, moderate in 18 of 43 patients, and severe in only 5 of 43 patients. When KCo was used, 67% of all patients had diffusion impairment; after correction for hemoglobin (KCoC), this value increased to 76%. These abnormalities were mild in 26 of 57 patients, moderate in 27 of 57 patients, and severe in 4 of 57 patients.

With respect to the selected parameters indicating restriction, obstruction, or diffusion impairment, the following comparisons showed no significant differences between the following groups: underlying glomerulonephritis vs pyelonephritis, smokers vs nonsmokers, presence vs absence of anti-hCMV antibodies, occurrence vs absence of rejection, and occurrence vs absence of hCMV infection.

With respect to the diffusion parameter KCo, patients who used to be smokers were found to have significantly lower values when compared to nonsmokers. However, the duration of the pretransplant dialysis period or the interval between screening and KT had no influence on the results of pulmonary function testing in our patients.

Interstitial abnormalities, which always occurred bilaterally, could be documented in 19 patients (24.1%) after a median follow-up period of 81 months (mean, 63 ± 57; range, 13 to 290 months). Except in one patient (grade 2), these interstitial changes were classified as grade 1 and located in the thoracic cavity. The level of significance was p < 0.05. Unless indicated otherwise, data are expressed as median values, and the mean ± SD and range are also given.

Table 2—Spirometric and Body Plethysmographic Findings

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
<th>% Predicted</th>
<th>Patients With Pathologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, L</td>
<td>4.33 ± 1.0</td>
<td>97.7 ± 14.2</td>
<td>10.1</td>
</tr>
<tr>
<td>FVC, L</td>
<td>4.19 ± 1.0</td>
<td>94.3 ± 15.0</td>
<td>19.0</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.17 ± 1.4</td>
<td>99.3 ± 16.4</td>
<td>11.4</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>3.46 ± 0.9</td>
<td>97.1 ± 15.3</td>
<td>13.9</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>83.95 ± 7.7</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Rtot, kPa/L</td>
<td>108.7 ± 55.3</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>RV, L</td>
<td>1.88 ± 0.7</td>
<td>96.6 ± 29.5</td>
<td>17.7</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>31.1 ± 9.2</td>
<td>99.2 ± 23.1</td>
<td>21.5</td>
</tr>
<tr>
<td>TLCo, mmol/min/kPa</td>
<td>8.57 ± 2.3</td>
<td>85.3 ± 19.1</td>
<td>43.0</td>
</tr>
<tr>
<td>TLCoC, mmol/min/kPa</td>
<td>7.89 ± 2.0</td>
<td>78.3 ± 25.7</td>
<td>57.0</td>
</tr>
<tr>
<td>KCo, mmol/min/kPa/L</td>
<td>1.46 ± 0.30</td>
<td>73.50 ± 14.49</td>
<td>67.0</td>
</tr>
<tr>
<td>KCoC, mmol/min/kPa/L</td>
<td>1.33 ± 0.40</td>
<td>67.10 ± 19.83</td>
<td>76.0</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or %. Rtot = total flow resistance.
dorsobasal region, mostly subpleural. In a few patients, apical and ventrobasal lesions were seen. They mainly appeared as reticular and linear lesions; in two patients, band-type and nodular structures were seen. In four patients, ground-glass alterations were seen.

In addition, CT signs of emphysema, located mainly apically, were seen in five patients, of whom two were smokers. Bronchiectasis was found in one patient. Local thickening of the pleura was seen in 18 patients (22.8%), whereas enlarged mediastinal or hilar lymph nodes were found in only 1 patient (1.3%).

Again, patients showing these CT signs of interstitial lung changes were not different from patients without these alterations with respect to the following: sex; underlying glomerulonephritis vs pyelonephritis, smokers vs nonsmokers, presence vs absence of anti-hCMV antibodies, occurrence vs absence of rejection, and occurrence vs absence of hCMV infection. With respect to lung function studies in patients with interstitial changes, only TLC was significantly lower \( (p = 0.036) \) than in patients with normal CT findings. The duration of the pretransplantation dialysis period and the interval between screening and KT had no influence on the results obtained by CT.

**Follow-up Investigation**

Over time, significant changes in pulmonary function were observed only with respect to diffusion parameters (Table 3). During the follow-up study, significant decreases of TLCO \( (p < 0.05) \) and KCO \( (p < 0.001) \) were found when considering the entire group of 36 patients. Individually, the following parameters \( (p \leq H11021) \) were significantly lower than in patients with normal CT findings. The duration of the pretransplantation dialysis period and the interval between screening and KT had no influence on the results obtained by CT.

**Discussion**

This prospective study included a group of 79 consecutive patients several years following their successful KT, so-called long-term survivors. So far, most of the previous studies\(^\text{1–4,10}\) in this field had relevant limitations with respect to their study design, the number of patients included, or missing data (gender, preexisting disease, or the period of pretransplantation dialysis). Only two studies\(^\text{10,11}\) with a group of 20 patients, included long-term survivors following KT.

In our patient population, restrictive abnormalities were found in 11% (TLC) and 19% (FVC). This appears to be comparable to previously published data.\(^\text{10,11}\) However, Morales et al\(^\text{3}\) found no restriction in 21 patients 12 months following KT. As in our data, no correlation was found between these parameters of restriction and the duration of the pretransplantation dialysis period.

Obstructive ventilatory abnormalities were found in 10% of our patients for the FEV\(_1\)/FVC ratio. These numbers are considerably higher than the

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**Table 3—Spirometric and Body Plethysmographic Findings (Follow-up in 36 Patients)***

<table>
<thead>
<tr>
<th>Variables</th>
<th>First Study</th>
<th>Patients With Pathologic Findings</th>
<th>Values</th>
<th>% Predicted</th>
<th>Values</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, L</td>
<td>4.49 ± 1.0</td>
<td>99.5 ± 13.3</td>
<td>5.1</td>
<td>96.5 ± 12.2</td>
<td>4.33 ± 0.9</td>
<td>96.5 ± 12.2</td>
</tr>
<tr>
<td>FVC n, L</td>
<td>4.36 ± 1.2</td>
<td>97.5 ± 13.1</td>
<td>7.7</td>
<td>100.3 ± 13.5</td>
<td>4.36 ± 1.0</td>
<td>100.3 ± 13.5</td>
</tr>
<tr>
<td>TLC n, L</td>
<td>6.20 ± 1.5</td>
<td>99.5 ± 17.5</td>
<td>12.8</td>
<td>99.8 ± 12.7</td>
<td>6.39 ± 1.4</td>
<td>99.8 ± 12.7</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>3.63 ± 0.8</td>
<td>99.7 ± 13.2</td>
<td>5.1</td>
<td>101.1 ± 14.1</td>
<td>3.61 ± 0.8</td>
<td>101.1 ± 14.1</td>
</tr>
</tbody>
</table>
| FEV\(_1\)/FVC, % | 83.69 ± 7.2 | 10.2               | 83.50 ± 5.9 | 10.2
| Rtot, kPa/L |            | 103.7 ± 50.1               | 23.1   | 89.1 ± 26.7| 89.1 ± 26.7 |
| RV, L     | 1.80 ± 0.8  | 92.6 ± 20.9                    | 12.8   | 103.1 ± 26.8| 1.98 ± 0.7 | 103.1 ± 26.8 |
| RV/TLC, % | 25.9 ± 8.9  | 94.3 ± 20.9                    | 7.7    | 100.2 ± 19.7| 31.3 ± 8.5 | 100.2 ± 19.7 |
| TLCO, mmol/min/kPa | 5.82 ± 2.5 | 58.0 ± 21.1                  | 33.0   | 79.8 ± 18.1| 8.10 ± 2.3 | 79.8 ± 18.1 |
| KCO, mmol/min/kPa/L | 1.47 ± 0.3 | 73.2 ± 15.8               | 61.5   | 64.4 ± 14.0| 1.28 ± 0.3 | 64.4 ± 14.0 |

* Values are presented as mean ± SD or %. See Table 2 for expansion of abbreviation not in text.

\( \dagger \) \( p < 0.05 \).

\( \ddagger \) \( p < 0.001 \).
previously reported incidence of 1% in long-term survivors. In our group, the RV was abnormal in 18%, whereas in the study reported by Bush and Gabriel, this parameter was elevated in 25% of their patients. Approximately 50% of our patients with obstruction were smokers, although there was no significant correlation to smoking status when the entire group was considered.

Impaired diffusion was found in 57% (TLCO) and 76% (Kco) following KT. This is a well-known finding in patients with renal transplantation. In our patient population, smokers had significantly lower values for Kco, a finding not reported by other studies.

According to our CT criteria, 24% of all patients had interstitial lung abnormalities. These changes were located mostly dorso-basal and subpleural, including the entire spectrum from ground-glass appearence to reticular patterns. Frequently, additional pleural thickening could be documented. To our knowledge, these are the first high-resolution CT data in such a group of patients. The previously reported calcifications of lung tissue could not be confirmed in our study.

These data confirm the observation that obstructive or restrictive ventilation abnormalities occur relatively infrequently following KT, whereas a significant proportion of long-term survivors suffers from impaired diffusion. Furthermore, these diffusion abnormalities significantly deteriorate in approximately one third of the affected patients. Age-related mechanisms could be ruled out as a causal factor by calculating age-adjusted data.

To our knowledge, these are the first data supporting the concept that interstitial lung changes, as assessed by CT, are not causally related to the well-known diffusion abnormalities occurring following KT. Currently, CT is the most powerful non-invasive technique for the evaluation of the presence of pulmonary interstitial changes. The interstitial alterations described here were relatively mild, and we found no difference with respect to lung diffusion capacity between patients with and those without these morphologic changes. In addition, the progressive deterioration of diffusion capacity in about one third of the primarily affected patients could not be correlated to new or worsening morphologic changes. These data are in accordance with earlier studies in patients following liver transplantation.

Theoretically, as in patients following heart transplantation, subclinical forms of hCMV infections without radiologic abnormalities or a reduced capillary blood volume could be discussed as causal mechanisms for these reductions in diffusion capacity. Furthermore, a link between the use of cyclosporin and impaired diffusion capacity has been discussed. However, when comparing patients with and without cyclosporin treatment in our group (data not shown), no differences could be found. Moreover, no correlation could be found between the measured cyclosporin drug level and the pulmonary diffusion capacity. Although subclinical infections or the vasopressor effect with intimal proliferation following cyclosporin administration cannot be completely ruled out as causal mechanisms, we propose that a "low-grade pulmonary microvascular injury" is the most likely explanation for these pulmonary diffusion abnormalities despite the absence of CT-detectable interstitial findings in these long-term survivors following KT.

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