Diffusion Capacity in Heart Transplant Recipients

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Preoperative diffusion capacity per liter alveolar volume (Kco) in cardiac transplant recipients with an intrinsic normal lung is within the normal range. In the first postoperative year, Kco showed a significant mean decrease of 12 percent (p<0.004). Lung function (TLC, VC, FEV1) tended to normalize after heart transplantation. Ventilation distribution remained stable before and after heart transplantation. Preoperatively, weak correlations were found between Kco and diastolic pulmonary arterial pressure (dPAP) and mean pulmonary capillary wedge pressure (PCWP). Postoperatively, correlation between Kco and PCWP was weak, and between Kco and dPAP it was not significant at all. These pressures determine the capillary blood volume before and after transplantation. Probably these weak correlations indicate that intrapulmonary factors, not cardiac factors, are of primary importance in the regulation of blood distribution. The percentage of decrease in Kco in the first postoperative year correlated with the change in dPAP and PCWP, but also with the cyclosporine level in the first posttransplant year. No correlation was found between cyclosporine level and pulmonary vascular resistance. It is suggested that higher levels of cyclosporine influence the alveolar capillary membrane, so that Kco decreases. The percentage of decrease in Kco was significantly more outspoken in patients who had rules on auscultation preoperatively. Using multiple regression analysis, we found that the factors most strongly related to the percentage of change in Kco in the first posttransplant year were the preoperative Kco, the cyclosporine level in the first postoperative year, and the change in dPAP in that year.

Diffusion capacity in congestive heart failure (CHF) is determined by a number of mechanisms and the question of whether it is disturbed or even improved in those patients is not yet completely resolved. An important factor is the lung volume, which affects not only the effective diffusion surface but also the diffusion distribution and the capillary blood volume. Stam et al found the resulting diffusion capacity per liter alveolar volume (Kco) to increase slightly with decreasing alveolar volume (VA) in a linear fashion. The capillary blood volume of the lung is increased in the case of slight or moderate left cardiac failure, which will increase the diffusion capacity as well as the Kco. With further deterioration of cardiac pump function, edema of the alveolar capillary membrane will occur, of which the severity also depends on fluid balance. In advanced stages, more fluid fills up the interstitium and when alveoli or respiratory bronchioles are flooded, the diffusion capacity decreases. In chronic CHF, lung fibrosis may develop, also contributing to the decrease in diffusing capacity. Kco is decreased in primary pulmonary hypertension.

Lung function tests in patients with severe CHF are characterized by a restrictive pattern. Therefore, changes in diffusion capacity have to be interpreted cautiously, because of the interaction with the reduction of lung volumes. Total lung capacity and vital capacity are reduced due to an enlarged heart and increased intrathoracic fluids, which decreases the intrathoracic gas volume and lung compliance. Reduced exercise tolerance and impaired respiratory muscle strength are other contributory factors to this restriction in lung function. Patients referred for cardiac transplantation show both ventilatory and diffusion (Dco) abnormalities.

In a small number of cardiac transplant recipients, Casan et al found a decrease of both diffusion capacity (Dco) and Kco after transplantation in contrast to the restoration of lung mechanics to normal. They suggested that the observed postoperative reduction in Dco might be due to cyclosporine (CsA) toxicity acting on the lung. In a larger group of patients referred to the Thorax Centre in Rotterdam for heart transplantation, we studied lung function, Kco, and hemodynamic data before and after transplantation and during a three-year follow-up in part of the group. The aim of our investigation was to elucidate the mechanisms responsible for the changes in Kco, both the short-
and long-term effects.

**Methods**

Between June 1985 and January 1990, 124 cardiac transplant recipients have been performed at the Thorax Centre of the University Hospital of Rotterdam in the Netherlands. Of these transplant recipients, patients were selected who fulfilled the following criteria: (1) ability to perform preoperative and postoperative lung function tests, including single breath diffusion capacity; (2) a preoperative chest roentgenogram with no other abnormalities than signs of lung edema, pulmonary blood redistribution, and cardiomegaly, normal erect chest roentgenograms in the successive postoperative years; and (3) a perfusion scan made with \( ^{133} \text{Tc} \)-labeled albumin, showing no abnormalities other than a diminished lower lobe perfusion and an enlarged heart.

**Patients**

Thirty-four patients could be followed up for at least one year, 27 for two years, and 21 for three years. Thirty-one patients were male, three female. The ages of the recipients was 20 to 59 years (mean, 45 years). The mean weight and length was 77.3 kg (range, 61 to 101 kg) and 1.76 m, (range, 1.60 to 1.96 m), respectively. The mean left ventricular ejection fraction before transplantation was 16 percent (range, 5 to 33 percent) and one year afterwards it was 60 percent (range, 31 to 73 percent). Twenty-four of 34 patients were smokers.

Preoperatively, all patients were treated with digitalis, angiotensin-converting enzyme (ACE) inhibitors, and diuretics. Postoperatively, prednisone, cyclosporine (CsA), and dipyridamole were administered, except in one patient, whose prednisone therapy was changed to azathioprine a few weeks after the operation. Twenty-one of the 26 patients with hypertension were treated with nifedipine; the other patients were treated with verapamil, bumetanide, captopril, enalapril, furosemide, and methyldopa. Retrospectively, we reviewed their yearly evaluations, including cardiac catheterization, lung function tests, hematologic and biochemical tests, but also the duration of dysnea, smoking history, rates on auscultation before heart transplantation, and medication. The time from the first signs of dysnea until the date of transplantation was taken as the duration of cardiac failure.

**Lung Function Measurements**

The diffusion capacity for carbon monoxide (Dco) was measured with the single breath method according to the recommendations by the American Thoracic Society.\(^{12}\) Carbon monoxide was measured with an infrared spectrophotometer (Jaeger, Germany) and helium with a thermal conductivity method. Flow was measured with a pneumotachometer (Jaeger, Germany) and electronically integrated to volume, taking proper calibrations into account. The diffusion values were corrected for hemoglobin level and expressed both per square meter of body surface area (Dco/BSA) and per liter alveolar volume (Kco). Reference values were established in our own labored study in 85 female and 75 male volunteers and expressed as a function of age. Predicted values according to age and gender are calculated from the following:

\[
\text{Dco/BSA} = 0.69 \times \text{age} + 99.10
\]

(female subjects) and

\[
-1.01 \times \text{age} + 124.02
\]

(male subjects) in \( \text{mol} / \text{kPa} \cdot \text{s} \). and

\[
\text{Kco} = -0.16 \times \text{age} + 31.73
\]

(female subjects) and

\[
-0.20 \times \text{age} + 32.52
\]

(male subjects) in \( \text{mol} / \text{kPa} \cdot \text{s} \), respectively.

Obtained variables, except Dco, were expressed as percent reference.\(^{17}\) Dynamic FEV, and static lung volumes (VC) were estimated with a water-sealed spirometer (Lode, NL, DS3R). The lung capacities (TLC, FRC, RV) were estimated with a closed-circuit helium dilution method. The ratio between the effective alveolar volume (VA), estimated with the single breath method and the TLC from spirometry, was considered as a measure for the alveolar inhomogeneity, according to Cotes.\(^{18}\) A value lower than 0.85 was regarded as an indication for the presence of significant ventilation inhomogeneity, as compared with normal.

**Hemodynamic Studies**

Preoperative and postoperatively, right heart catheterization was done in the supine position. A Swan-Ganz balloon-tipped thermocatheter was used to measure filling pressures. Pressures were measured at end-expiration, using the midchest as zero reference level. Cardiac output was determined with the thermodilution method in triplicate.

Pulmonary vascular resistance (PVR) in dynes cm\(^{-5}\) was calculated as \( \left( \frac{\text{PAPmean} - \text{PCWP}}{\text{CO}} \right) \times 80 \), where PAP is pulmonary arterial pressure in mm Hg, PCWP is mean pulmonary capillary wedge pressure in mm Hg, and CO is cardiac output in L/min.

The left ventricular ejection fraction was estimated with a radionuclide (technetium 99m) method.

The weight of the removed heart was measured by the pathologist.

**Cyclosporine**

CsA levels were analyzed in all patients with a polyclonal radioimmunoassay (CychoTrac). The values, measured closest in time to the estimation of Kco, were taken for this analysis. CsA dosage was adjusted to plasma trough levels of 100 ng/ml during the first 12 months and 50 to 80 ng/ml thereafter.

**Statistics**

Differences in lung function test results and hemodynamic data

**Table 1—Preoperative and Postoperative Diffusion (Dco, Dco/BSA, Kco) and Spirometric Variables (TLC, VC, FEV\(_1\), FEV\(_1\)/VC) in Heart Transplant Recipients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretransplant (n = 34)</th>
<th>1 (n = 34)</th>
<th>2 (n = 27)</th>
<th>3 (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dco, ( \text{mol} / \text{kPa} \cdot \text{s} )</td>
<td>109 + 21</td>
<td>111 + 19</td>
<td>119 + 28</td>
<td>118 + 27</td>
</tr>
<tr>
<td>Dco/BSA</td>
<td>74 + 14</td>
<td>75 + 14</td>
<td>80 + 21</td>
<td>80 + 20</td>
</tr>
<tr>
<td>Kco, % pred</td>
<td>98 + 21</td>
<td>86 + 16</td>
<td>89 + 18</td>
<td>88 + 18</td>
</tr>
<tr>
<td>TLC(spir), % pred</td>
<td>84 + 13</td>
<td>97 + 9</td>
<td>97 + 10</td>
<td>99 + 10</td>
</tr>
<tr>
<td>TLC(spir), % pred</td>
<td>73 + 11</td>
<td>85 + 8</td>
<td>87 + 10</td>
<td>86 + 10</td>
</tr>
<tr>
<td>TLC(spir)/TLC(spir)</td>
<td>0.86 ± 0.06</td>
<td>0.88 ± 0.05</td>
<td>0.89 ± 0.04</td>
<td>0.88 ± 0.04</td>
</tr>
<tr>
<td>VC(spir), % pred</td>
<td>80 + 13</td>
<td>96 + 9</td>
<td>97 + 10</td>
<td>99 + 10</td>
</tr>
<tr>
<td>FEV(_1), % pred</td>
<td>78 + 14</td>
<td>90 + 14</td>
<td>94 + 15</td>
<td>95 + 15</td>
</tr>
<tr>
<td>FEV(_1)/VC(spir), % pred</td>
<td>0.98 ± 0.10</td>
<td>0.96 ± 0.09</td>
<td>0.96 ± 0.09</td>
<td>0.95 ± 0.09</td>
</tr>
</tbody>
</table>

*Also, TLC measured with the single breath method and TLC(spir)/TLC(spir) are indicated. Data given are means + SD.

\( t p < 0.004 \) for the change with regard to the pretransplant value.

\( t p < 0.001 \)
before and after transplantation were analyzed by Wilcoxon's test. Correlation coefficients given are Pearson's. Comparison of percentage of change in Kco before and after transplantation between patients with and without rules was done with analysis of variance. Multiple regression analysis on percentage of change in Kco, posttransplantation, was performed with pretransplant Kco, hemodynamic data, and CsA levels. Data analysis was performed with a specific computer package (SPSS/PC+); p<0.05 was considered statistically significant.

RESULTS

Before transplantation, 33 of 34 patients with intractable cardiac failure showed Kco values within the normal range. One patient had an elevated Kco of 141 percent of predicted. Mean Kco was 98 percent of predicted (Table 1). In the first postoperative year, mean Kco decreased with 12 percent (p<0.004). The amount of decrease in Kco correlates with the preoperative Kco (R = 0.68, p<0.001).

The preoperatively decreased TLC, VC, and FEV₁ normalized in the successive postoperative years. The FEV₁/VC was in the normal range, both preoperatively and postoperatively (Table 1). The ventilation distribution was not inhomogeneous, as can be concluded from the ratio TLC(sb)/TLC(spir); the mean values were larger than 0.85 at all measuring moments. If a correction would be applied for the somewhat lower VC from the single breath method, also causing a slightly lower TLC(sb) than the real maximum value, then the normality of ventilation distribution is even more notable.

Considering the pretransplant and first-year posttransplant Kco, weak correlations were present with PCWP preoperatively (r = 0.34, p<0.05) and postoperatively (r = 0.42, p<0.02), respectively. Correlations between Kco and diastolic arterial pulmonary pressure (dPAP) were just significant preoperatively (r = 0.36, p<0.04), but not significant postoperatively (r = 0.32, p = 0.067). The decrease in Kco in the first postoperative year correlates with the decrease in dPAP (R = 0.50, p<0.003), but not with the cardiac output or PVR. Hemodynamic data are given in Table 2.

One year after transplantation, the percentage of decrease in Kco, that is (Kcopre-Kcopost) ×100/

Table 2—Hemodynamic Data of 34 Cardiac Transplant Recipients*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretransplant</th>
<th>Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic PAP, mm Hg</td>
<td>47 ± 14</td>
<td>24 ± 7</td>
</tr>
<tr>
<td>Diastolic PAP, mm Hg</td>
<td>24 ± 9</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>34 ± 10</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>24 ± 9</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.8 ± 1.3</td>
<td>7.3 ± 1.3</td>
</tr>
<tr>
<td>PVR, dyne.s.cm</td>
<td>213 ± 114</td>
<td>107 ± 39</td>
</tr>
</tbody>
</table>

*All posttransplant data are significantly improved (p<0.001). Values are means ± SD. PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.

Table 3—Correlations between Percentage of Change in Kco before and after Heart Transplantation and Hemodynamic Changes, Duration of Cardiac Failure, Weight of the Diseased Heart, and Cyclosporine Level in the First Postoperative Year*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation Coefficients of Relation with (Kcopre-Kcopost)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter</td>
</tr>
<tr>
<td>Delta dPAP, mm Hg</td>
<td>0.54</td>
</tr>
<tr>
<td>Delta PCWP, mm Hg</td>
<td>0.40</td>
</tr>
<tr>
<td>Delta PVR, dyne.s.cm</td>
<td>0.15</td>
</tr>
<tr>
<td>Delta cardiac output, L/min</td>
<td>-0.02</td>
</tr>
<tr>
<td>Duration of CHF, wk</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiac weight, g</td>
<td>0.16 (N = 23)</td>
</tr>
<tr>
<td>Cyclosporine, ng/ml</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are Pearson correlation coefficients. Delta = pretransplant minus posttransplant values; Kcopre and Kcopost = diffusion capacity per liter alveolar volume, preoperatively and one year postoperatively.

Kcopre, showed a correlation with the change in dPAP and PCWP, but not with the duration of cardiac failure or the weight of the diseased heart (Table 3). The percentage of decrease in Kco was also higher in patients with rales compared with those without rales: 19.0 percent (confidence interval [CI] 9.3 to 28.9) vs 6.5 percent (CI –0.3 to 13.2) (p<0.04). Medication like nifedipine had no demonstrable influence on Kco or decrease in Kco in the first year.

For CSA, this was different. In the first postoperative year, a negative correlation was found between Kco and the CSA level (r = -0.53, p = 0.001, Fig 1). Also, the percentage of the decrease in Kco correlated

![Figure 1. Correlation between Kco (percent predicted) and cyclosporine level in the first year after cardiac transplantation. Kco = diffusion capacity per liter alveolar volume.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21652/ on 04/20/2017)
Within the patient group, however, preoperatively a significant linear correlation was found between Kco and PCWP, suggesting capillary blood volume and capillary recruitment as a determinant of Kco.

In the first year after cardiac transplantation, despite the unchanged Dco, Kco decreased significantly with an improvement in the restrictive lung function pattern and consequently increased TLC. The significance of the decrease remained even if we made a correction for the normally occurring decrease of Kco with increasing TLC.6

The significant predictors for the percentage of change in Kco values in the first postoperative year appeared to be the preoperative Kco, the CsA level, and the change in dPAP in the first postoperative year.

In the second and third year of follow-up, Kco slowly increased. No correlations were found with hemodynamic factors or CsA levels in the second year. The CsA level is then almost 40 percent lower.

Only those hemodynamic factors that determine the pulmonary capillary blood volume correlated with the diffusion capacity. However, these correlations were weak. It might indicate that intrapulmonary recruitment factors, not cardiac factors, control the blood distribution in the lung. In an extreme situation, when the alveolar capillaries are completely filled with blood, Kco is unaffected by major changes in cardiac output at a given lung volume.4 Others found no significant correlation between diffusion capacity and the results of cardiac catheterization.20,21 The number of patients in these studies was small, however, and, as in our study, methodologic problems remain, such as the different body positions in which cardiac catheterizations were done without control of the position of the catheter tip.

The presence of rales in the preoperative patient predicted a larger decrease in posttransplant Kco than when these rales were absent. In our case, no discrimination was present between low vs normal diffusion capacity, as in another study.3

In our study, CsA level was not related to the PVR. Its effect on Kco appeared to be independent of factors that determine the pulmonary capillary blood volume. That means that it changes the alveolar capillary membrane diffusion coefficient (Dm). Probably this may happen in a dose-dependent way, because there is no effect on the diffusion capacity in the second year. How this temporary effect on Dm happens is not clear. Cyclosporine increases the number of fibroblasts and production of collagen. Indirectly it stimulates smooth muscle generation. If similar processes occur in the lung they are unknown, but one can think of a fibrotic thickening of the alveolar capillary membrane. The two- and three-year follow-up shows that this process is at least partly reversible. A complete reversibility can be concluded only after a longer
follow-up period.

Previous reports mention fibrotic processes in the lung, due to cardiac failure, that might change lung function. In the first postoperative year, we could not demonstrate a restrictive lung function. So fibrosis by a long-lasting cardiac failure seems unlikely. In that case, an improvement in Kco in the second and third year postoperatively should not be expected. Moreover, the duration of cardiac failure had no influence on the diffusion capacity or any other lung function index, so we did not find any indirect support for the fibrotic hypothesis.

In conclusion, we hypothesize that CsA causes a decrease of alveolar capillary membrane diffusion, partially reversible after decreasing its dose. Hemodynamic factors show a weak correlation with lung diffusion capacity.

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21. Flatly FJ, Constantine H, McCredie RM, Yu PN. Pulmonary diffusing capacity and pulmonary capillary blood volume in normal subjects and in cardiac patients. Am Heart J 1962; 64:159-68