Renal function after solid organ transplantation

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Chapter 4

Long-term renal outcome after lung transplantation is predicted by the 1 month post-operative renal function loss

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Abstract

Progressive renal function loss is common after lung transplantation. To design renoprotective strategies, identification of early predictors for long-term renal function loss would be useful.

We prospectively analysed renal function (glomerular filtration rate(GFR); ^{125}I-iothalamate clearance) in a closely monitored cohort of 57 lung transplant recipients with at least 24 months of follow up transplanted between November 1990 and September 1996 in our centre. Analysed end points were the slope of GFR from 6 months post-transplant onwards and the GFR at 24 months after transplantation.

Before transplantation GFR was 100 ml/min (median, range 59 to 163). It decreased to 67 ml/min (29 to 123) at six months, 53 ml/min (17 to 116) at 24 months and 51 ml/min (20 to 87) at 36 months after transplantation. The magnitude of the loss of GFR 1 month post transplantation was the only factor significantly correlated with absolute GFR at 24 months after transplantation. Pulmonary diagnosis was significantly associated with long-term rate of renal function loss. Median loss of GFR was greatest in patients with cystic fibrosis (-10 ml/min/yr, range –14 to –6 ml/min/yr), preserved in pulmonary hypertension (-1 ml/min/yr, range –6 to +7 ml/min/yr) and in between in emphysema (-6 ml/min/yr, range –27 to +12 ml/min/yr). No other factors could be identified.

In lung transplant recipients the 1 month post-operative loss of GFR is an early marker for long-term renal prognosis. Pulmonary diagnosis appears to be a relevant predictor as well. These factors may guide further research and the development of preventive strategies.

Introduction

Progressive renal function loss is an important complication of solid organ transplantation. The severity of long-term renal function loss is particularly prominent in heart and heartlung transplant recipients, with end stage renal failure in up to 10 percent of the patients that survive for five years or more after transplantation[1]. In liver transplant recipients renal function loss appears to be less prominent[2]. We previously reported considerable long-term renal function loss in lung transplant recipients[3]. The interindividual difference in renal function loss was large, ranging from a slightly impaired but stable renal function in a minority of patients to severe and rapid renal function loss in others.

For the design of strategies for the prevention of long-term renal function loss it would be important to identify patients at high risk for long-term renal function loss at an early stage. We previously found that interindividual differences in renal function loss were particularly marked early after transplantation[3].

In the present study, therefore, we questioned whether early renal function loss could serve to identify patients at risk for long-term renal function loss. To this purpose we analysed renal function data in a prospectively monitored cohort of lung transplant recipients transplanted between November 1990 and September 1996 in our centre. We previously found that pre-transplant renal function was influenced by pulmonary diagnosis[3]. To account for diagnosis related confounders, therefore, in the present study we analysed the course of renal function for diagnosis groups separately.

Patients and Methods

Patients

Consecutive patients, receiving a bi- or unilateral lungtransplant, between November 1990 and September 1996 with at least 24 months of follow up and at least 4 GFR measurements from 6 months post-transplant onwards were included in this study. The latter criterion was taken to allow an accurate calculation of the GFR slope over time. Of ninety-two patients transplanted in this period, fifty-seven patients fulfilled these criteria. Twenty-nine died within 24 months after transplantation and in six patients serial GFR measurements were not available due to patient refusal, inability to perform the GFR measurement or follow up at another hospital.

Methods

Induction therapy was given the first 7 days after transplantation with rabbit anti-human thymocyte globulin (RIVM, Bilthoven, The Netherlands). Immunosuppression consisted of a

triple-drug protocol of oral cyclosporin A (CyA), azathioprine, and corticosteroids, starting at day 1. During the first three weeks, the target CyA serum level was 400 ug/l; thereafter, 150 ug/l was considered the lowest acceptable level. Initial CyA dosing schedules were based on individual assessment of CyA kinetics that had been performed pre-transplantation. Based on these kinetic data, CyA was administered twice a day, but in all patients with cystic fibrosis three times a day. CyA trough levels were measured by high-performance liquid chromatography daily in the postoperative period and at each outpatient visit during follow up. The corn-oil based soft gel cap formulation (Sandimmune, Novartis Pharma B.V., Arnhem, The Netherlands) was used until September 1995. After September 1995 all patients were started on or switched to the microemulsion formulation (Neoral, Novartis Pharma B.V., Arnhem, The Netherlands). Rejection episodes were treated with intravenous bolus therapy methylprednisolone (500-1000 mg, depending on body weight; Solumedrol, Upjohn, Kalamazoo, MI) daily for 3 days. All patients received antibiotic prophylaxis with ceftazidime. Antibiotics were changed, if necessary, in accordance with sputum or other cultures: aminoglycosides were added when necessary, under close monitoring of serum levels. Prophylaxis for herpes infections consisted of oral aciclovir (4x200 mg) during the first 6 months, and prophylaxis for Pneumocystis carinii consisted of oral co-trimoxazole 800/160 mg every other day (lifelong).

Renal function studies were performed in all patients during the pre-transplant workup. Posttransplant renal function was measured 1 month after surgery if the clinical condition was stable. If not, the measurement was postponed until a stable condition had been reached. Follow up measurements were done every 6 months after transplantation.

Glomerular filtration rate (GFR) was measured as the urinary clearance of constantly infused ^{125}I-iothalamate. Simultaneous measurement of ^{131}I-Hippuran clearance allows to correct for errors induced by incomplete bladder emptying as described previously[4]. GFR measurement performed in this way has a variation coefficient of only 2.2 %, which allows accurate follow up of renal function loss[4].

Data analysis

Data are presented as median with ranges. Not only data for the cohort as a whole are presented, but also data grouped according to diagnostic category; i.e. for pulmonary hypertension, emphysema and cystic fibrosis separately. To identify patients at high risk for long-term renal function loss we analysed for long-term renal function loss in a dual fashion, i.e. the rate of long-term GFR decline over time, and GFR at 24 months after transplantation, respectively. The rate of GFR decline was defined as the individual slope of GFR over time (ml/min/yr) as of 6 months after transplantation and calculated by least squares linear regression. By taking this starting point, the obtained data can be considered to reflect the

process of long-term renal function loss devoid of bias by fluctuations by early, potentially reversible events. Early renal function loss was defined as the difference between the GFR at one month after transplantation and the pre-transplant GFR.
During the follow up of this cohort, CyA treatment was switched from the corn-oil based formulation to the microemulsion formulation. To analyse for possible effects of differences in bioavailability, we analysed trough levels and oral dosage before and after conversion to the microemulsion formulation of CyA in patients converted later than 6 months after transplantation. Furthermore, the rate of long-term GFR decline until conversion in patients on the corn oil based soft gel cap formulation for at least 24 months, was compared with the rate of GFR decline in patients treated with the microemulsion formulation only.

Statistical analysis

Differences between or within groups were analysed by unpaired and paired Wilcoxon rank sum test, respectively. Three group comparisons were tested by non-parametric Kruskal-Wallis ANOVA followed by Dunn's multiple comparison test. Correlations between GFR at 24 months and GFR slope with possible predictive factors were tested by non-parametric Spearman's rank correlation. All reported p-values are two-tailed. A two-tailed p-value < 0.05 was considered to indicate statistical significance.

Results

Patient characteristics are shown in *table 1 (pag. 56)*, grouped according to pulmonary diagnosis. Patients with cystic fibrosis were significantly younger than the others. Most patients received a bilateral transplantation, except for those with pulmonary hypertension in whom all but two patients received a unilateral transplant. Cystic fibrosis patients had a significantly higher pre-transplantation GFR than patients with pulmonary hypertension or emphysema. Prior to transplantation diabetes was present in 3 patients with cystic fibrosis. None of the patients had proteinuria. Median follow up was 48 months (range 24 to 84) and not different between the diagnosis groups.
Before transplantation GFR was 100 ml/min (59 to 163) in the group as a whole decreasing to 67 ml/min (29 to 123) at six months, 53 ml/min (17 to 116) at 24 months and 51 ml/min (20 to 87) at 36 months after transplantation. *Figure 1 (pag. 56)* shows the individual serial GFR measurements grouped according to pulmonary diagnosis. Renal function loss is most rapid in the first six months after transplantation and there is large interindividual variability in the course of renal function.
The absolute early renal function loss (at 1 month after transplantation) as well as the rate of long-term renal function loss (ml/min/yr) from 6 months post-transplant onwards are shown

Table 1 **Patient characteristics according to pulmonary diagnosis in 57 patients (median (range))**

	PH	E	CF
N	8	42	7
Age	41 (29-53)	47 (26-64)	26 (20-31) *
Female	5	15	3
Unilateral transplant	6	4	0
GFR in ml/min #	84 (72-124)	100 (59-143)	124 (96-163) **
MAP in mmHg #	93 (61-100)	96 (77-117)	88 (87-98)
Follow up in months	60 (36-84)	42 (24-84)	54 (36-78)

PH=pulmonary hypertension, E=emphysema, CF=cystic fibrosis
# pre-transplantation * p<0.001 CF vs E and PH ** p<0.01 CF vs E and PH

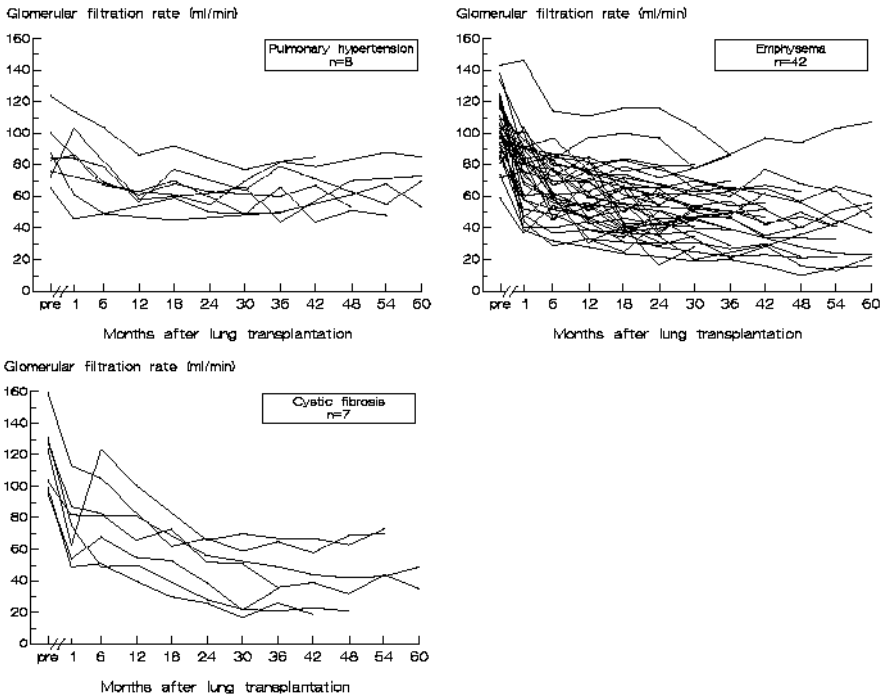

Figure 1 Individual serial glomerular filtration rate (GFR) measurements prior to and after lung transplantation in 57 patients grouped according to pulmonary diagnosis.

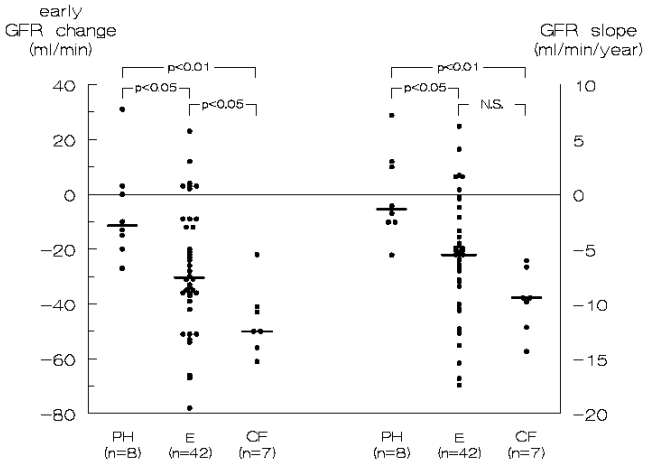

Figure 2 Individual early glomerular filtration rate (GFR) change in ml/min (GFR change at 1 month compared to pre-transplant GFR) (left) and GFR slope in ml/min/year calculated from 6 months post-transplant onwards (right) in 57 patients according to pulmonary diagnosis. (PH=pulmonary hypertension, E=emphysema, CF=cystic fibrosis)

in *figure 2*, grouped according to pulmonary diagnosis. In cystic fibrosis patients, both the early renal function decline and the long-term rate of renal function loss were more pronounced than in patients with emphysema or pulmonary hypertension. In patients with cystic fibrosis the early change was –50 ml/min (range, -22 to –61 ml/min) as compared to –29 ml/min (range, -78 to +23 ml/min) in emphysema and –10 ml/min (range, -27 to +31 ml/min) in pulmonary hypertension. The rate of long-term GFR loss was greatest in patients with cystic fibrosis (-10 ml/min/yr, range –14 to –6 ml/min/yr), and significantly different ($p<0.01$) from patients with pulmonary hypertension (-1 ml/min/yr, range –6 to +7 ml/min/yr). In the emphysema patients the rate of GFR loss was inbetween (-6 ml/min/yr, range –27 to +12 ml/min/yr) and significantly different ($p<0.05$) from patients with pulmonary hypertension. Calculation of the GFR slopes was based on 7 (median, range 4 to 14) serial GFR measurements; there was no difference between the diagnosis groups in the number of GFR measurements. Other than pulmonary diagnosis no factors were found to be significantly associated with the rate of long-term GFR loss.

Mean arterial blood pressure increased from 93 mmHg (range 61 to 100) pre-transplant to 98 mmHg (range 73 tot 130) and 101 mmHg (range 73 to 120) at 6 and 24 months post-transplant, respectively. Blood pressure was not different between the 3 pulmonary diagnosis groups at any of these time points (data not shown).

Trough CyA levels were not different for the three different diagnosis groups at 1, 6 and

Table 2 Oral cyclosporin A dose (mg/kg/day at 1, 6, and 24 months post-transplant) and trough cyclosporin A levels (median and range from the preceeding period in ug/l) according to pulmonary diagnosis at 1, 6, and 24 months after lung transplantation in 57 patients. PH=pulmonary hypertension, E=emphysema, CF=cystic fibrosis

	1 month		6 months		24 months	
	Oral dose (mg/kg/d)	Level (µg/l)	Oral dose (mg/kg/d)	Level (µg/l)#	Oral dose (mg/kg/d)	Level (µg/l)##
PH	4.2 (3.3-6.8)	273 (238-326)	3.3 (2.6-5.8)	181 (147-213)	3.4 (1.4-7.4)	168 (148-205)
E	4.5 (0.9-9.5)	288 (225-344)	4.1 (0.9-7.1)	174 (150-226)	3.7 (0.6-7.0)	160 (125-367)
CF	8.9[a] (4.8-21.8)	314 (230-425)	9.8[a] (5.4-11.1)	191 (151-291)	8.2[a] (4.5-10.9)	179 (168-252)

\# median trough level in the preceding 5 months
\## median trough level in the preceding 6 months
a $p<0.001$ compared to PH and E

24 months post-transplant, although oral CyA dose was higher at all time points of follow up for patients with cystic fibrosis as compared to patients with emphysema and pulmonary hypertension (*table 2*). As the oral CyA formulation was changed during the study period, the possible impact of this change on renal function was analysed. Twenty-six patients were converted after more than 6 months therapy on the corn oil based soft gel cap to the microemulsion formulation. No difference was found between trough CyA levels before (176 ug/l; range 127 to 375) and after (170 ug/l; range 124 to 214) conversion to microemulsion formulation. The oral CyA dose was marginally but significantly lower ($p=0.001$) after conversion to the microemulsion formulation of CyA (4.0 mg/kg/day (2.2 to 10.9) before, and 3.8 mg/kg/day (2.0 to 8.4) after conversion), consistent with a higher bioavailability of the microemulsion formulation. Eighteen patients were on the corn oil based soft gel cap formulation for at least 24 months. The GFR slope over the period of time until conversion was –5.4 ml/min/yr (-17.2 to –2.0). In twenty five patients, treated by the microemulsion form only, the GFR slope was similar, i.e -5.9 ml/min/yr (-26.8 to 11.6). There was no difference in early post-operative renal function loss between the two groups either. Trough CyA levels and oral dose were also similar (data not shown).

At 24 months after transplantation GFR was 52 ml/min (range; 26 to 67) in patients with

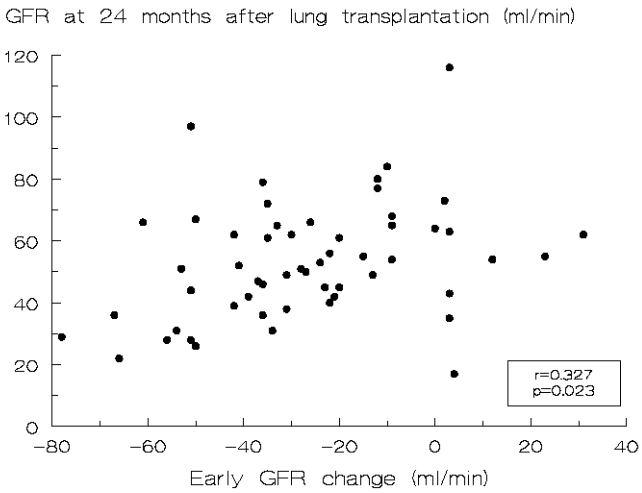

Figure 3 Correlation between the early glomerular filtration rate (GFR) change in ml/min (GFR change at 1 month compared to pretransplant GFR) and the absolute GFR in ml/min at 24 months after transplantation.

cystic fibrosis, 51 ml/min (range; 17 to 116) in those with emphysema and 62 ml/min (range; 50 to 84) in those with pulmonary hypertension and not significantly different between these 3 diagnosis groups. Univariate analysis revealed that the magnitude of the early loss of GFR (from pre-transplant to 1 month after transplantation) was significantly correlated with GFR at 24 months after transplantation. Patients with the largest early post-operative fall in GFR had the lowest absolute GFR at 24 months after transplantation *(figure 3)*. No other factors predictive of the GFR at 24 months were identified. Pre-transplant GFR was weakly associated with the GFR at 6 months post-transplantation (r=0.287, p=0.034), but not with GFR at 24 months post-transplantation (r=0.054, NS).

Discussion

The population of patients receiving a lung transplant is relatively small. Renal function monitoring by frequent ^{125}I-iothalamate clearance measurements affords accurate calculation of the rate of renal function loss in individual patients with a low variation coefficient, thus allowing proper analysis despite the relatively small number of patients[4]. As expected, considerable renal function loss occurred after lung transplantation with a great between-patient variability and a clear biphasic course. Importantly, by univariate analysis long-term renal prognosis could be predicted from the loss of GFR at one month post-transplantation.

In addition, renal prognosis was different for patients with different underlying pulmonary conditions.

In lung transplant recipients, many factors may contribute to renal function loss. Pre-transplantation characteristics (pulmonary diagnosis and pre-transplant GFR) and short-term peri-operative factors (haemodynamic instability, type of surgery, use of nephrotoxic antibiotics, infectious complications and the use of CyA), as well as long-term factors (use of CyA and blood pressure) may be involved. Many factors are related to either the treatment regimen (and thus can be modified if identified as deleterious), to medical complications or a combination of these. For such multifactorial conditions, a multivariate analysis to assess the relative importance of different independent risk factors would be helpful to analyse long-term renal function loss after lung transplantation. The small number of recipients after lung transplantation in our study, however, precluded such an analysis.

By univariate analysis we found that the early GFR loss – but not pre-transplant GFR – is a predictor of renal function 2 years after transplantation. This finding not only allows early identification of patients at high risk for renal function loss, but also suggests that early peri-operative renal damage bears lasting impact on long-term renal prognosis. In the first month after transplantation the trough CyA levels were deliberately higher than afterwards. These high levels could contribute to the early renal function loss and suggest a critical reappraisal of the necessity of these high target levels in the first month after transplantation. It is unknown however, whether an alternative CyA dosing regimen is feasible without losing immunosuppressive potency.

During the follow up of this patient cohort the formulation of CyA was altered. The conversion to the microemulsion formulation of CyA might have impact on renal function by improving gastrointestinal absorption and bioavailability of CyA[5,6], by altering peak and or trough levels. Our data, however, do not allow to support an effect of conversion to the microemulsion formulation on long-term GFR loss.

We previously found that pre-transplant renal function was influenced by pulmonary diagnosis[3]. To account for diagnosis related confounders, therefore, in the present study we analysed the course of renal function for diagnosis groups separately. Interestingly, early as well as long-term renal function loss were related to pulmonary diagnosis. Renal function loss was largest in cystic fibrosis, smallest in pulmonary hypertension and in-between in emphysema, implicating that a global assessment of renal risk can already be made prior to transplantation. Whether these differences in renal prognosis are related to differences in nephrotoxic insults between the groups or to other diagnosis-associated factors, cannot be ascertained from our data. CyA trough levels were similar for the diagnosis groups. However, cystic fibrosis patients used higher oral CyA doses, presumably reflecting reduced bioavailability[5,6]. Moreover, cystic fibrosis patients used 3 in stead of 2 doses daily. The more frequent and higher dosing required to obtain target trough serum levels may therefore

have contributed to the worse renal prognosis in these patients[7]. More frequent exposure to nephrotoxic antibiotics, or specific renal vulnerability in cystic fibrosis may also have been involved[8,9,10,11]. In pulmonary hypertension, on the other hand, renal prognosis appears to be favourable both on long-term and on short-term, as apparent from *figure 1 (pag. 56)*. This is remarkable, considering the presence of considerable renal function impairment with intense renal vasoconstriction prior to transplantation in these patients[3]. The favourable short-term outcome in pulmonary hypertension might be explained by improvement of renal perfusion by the normalisation of cardiac output after transplantation. The reason for the long-term resistance against the combined nephrotoxic insults associated with lung transplantation, however, can not be inferred from our data.

Notwithstanding the impact of diagnosis, in all three diagnosis groups the individual differences in the course of renal function was considerable, emphasizing the importance of non-diagnosis related factors.

What are the implications of our findings? The first rough step to identify patients at risk for renal function loss seems possible. Given the limitations of our study, a study with larger numbers of recipients will be needed to identify more specific predictors of renal function loss after lung transplantation. Still, pending the results of such studies, it would be worthwhile to study renoprotective measures in high risk patients – such as rigourous blood pressure control, avoidance of nephrotoxic antibiotics, more intensive monitoring and, if possible, tapering, of CyA levels – in the population after lung transplant recipients[12,13]. The impact of early renal function loss on long-term renal prognosis implicates that identification and possible modification of peri-operative nephrotoxic insults may have the potential to improve long-term renal function.

In conclusion, in lung transplant recipients the early post-operative GFR loss is an early predictor of a high risk for long-term renal function loss. Diagnosis appears to be related to long-term outcome as well. These factors might guide further research in to mechanisms of renal damage and thus for the development of preventive strategies in high risk patients.

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