Renal function after solid organ transplantation
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APPENDIX

Broekroeloef J, Navis G, Stegeman CA, Van der Bij W, De Jong PE
Lancet 1998; 351: 1064
Lung transplantation

Sir,

Jeffrey Hosenpud and co-workers (Jan 3, p 24) note the importance of pulmonary diagnosis for survival benefit after lung transplantation. In the accompanying commentary, John Dark describes the lack of survival benefit in emphysema patients and argues that diagnosis is a factor to consider in allocation schemes. We wish to draw attention to pulmonary diagnosis as a determinant of post-transplantation loss of renal function.

In our centre, glomerular filtration rate (GFR; clearance of iothalamate) is measured before lung transplantation and every 6 months after transplantation, which allows accurate evaluation of renal function. Long-term loss of renal function occurs in most patients. We analysed renal function loss according to diagnosis in 39 patients who underwent transplantation between January, 1992, and December, 1995, with at least 24 months of follow up. Seven patients with cystic fibrosis had a pretransplantation GFR of 124 (range 96 to 163) ml per min per 1·73 m² with a decrease of 60% (46 to 79) at 24 months. In 28 patients with emphysema, pretransplantation GFR was 95 (83 to 124) with a decrease of 44% (17 to 70). In four patients with pulmonary hypertension, pretransplantation GFR was 95 (83 to 124) with a decrease of 36% (24 to 46). Overall, loss of renal function differed between the three groups (p<0·05). This difference was not explained by perioperative differences, since the rate of long-term renal function loss (6-24 months after transplantation) also differed between the groups (p<0·05). Loss of renal function was most rapid in patients with cystic fibrosis (~15 [-20 to -10] ml per min every year) attenuated in pulmonary hypertension (~1 [-3 to 2] ml per min every year), and in-between in patients with emphysema (~6 [-17 to 7] ml per min every year).

Thus, diagnosis is relevant to renal morbidity after lung transplantation. Although our population is small, the accurate renal measurements revealed differences in loss of renal function between the groups within a short observation time. The main concern about renal function is the development of end-stage renal failure, which depends not only on the rate of renal function loss but also on survival time. We found that survival was better in patients with emphysema (85% at 24 months) and pulmonary hypertension (89%) than in those with cystic fibrosis (58%). After 24 months, there were too few patients for a valid comparison of renal outcome. Data thus far suggest that diagnosis is relevant to renal function beyond 2 years. In all four pulmonary hypertension patients, renal function was stable up to 4 years, whereas two patients with emphysema entered dialysis about 5 years after transplantation.

Our findings underline the importance of a pulmonary diagnosis when assessing the benefit of transplantation for lung transplantation candidates, in terms of survival as well as quality
of life. In rapidly progressive pulmonary disorders, such as cystic fibrosis, survival benefit may outweigh a poor renal prognosis. When the pulmonary condition is only slowly progressive, as in many patients with primary emphysema, survival benefit is less likely. For these patients, the negative effect of long-term renal morbidity on initially gained quality of life could be an important factor to consider.

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Renal failure after lung transplantation

Sir,

Jan Broekroelofs and colleagues (April 4, p 1064) comment that pretransplant pulmonary diagnosis influenced the risk of subsequent renal toxicity in their lung-transplant population. Their report did not include any data relating to doses or blood concentrations of immunosuppressives used, but I presume that they used either cyclosporin or tacrolimus, which have very similar renal toxicity.

The faster rate of renal decline they describe in patients transplanted for cystic fibrosis is probably largely a reflection of higher pretransplant glomerular filtration rate in this group; a similar occurrence has been shown in liver-transplant recipients and is probably a feature of cyclosporin nephrotoxicity rather than preoperative diagnosis. Further differences in long-term renal function loss were probably a reflection of variation in metabolism of cyclosporin or tacrolimus in the different patient groups; since these drugs are metabolised in the liver and excreted almost exclusively in bile, any impairment of liver function (which
commonly occurs in cystic fibrosis and -1-antitrypsin deficiency) may reduce their excretion and thus predispose to renal toxicity. The use of trough blood concentrations of cyclosporin or tacrolimus to guide dosage may to some extent reduce the risk of renal toxicity. However, we and others have found that outpatient monitoring of cyclosporin concentrations is a poor guide to risk of renal failure; this is partly because of variation in individual susceptibility to nephrotoxicity, but also perhaps difficulty in obtaining valid trough concentrations in the outpatient setting. In fact, in the long-term we found the dosage (adjusted for weight), rather than cyclosporin concentration was a more reliable guide to risk of nephrotoxicity.

The development of end-stage renal failure in solid organ (other than kidney) transplant recipients carries a high mortality even with renal replacement therapy. Avoidance of this devastating complication in patients who develop renal impairment in the presence of satisfactory graft function requires early and judicious reduction in dose of cyclosporin or tacrolimus, or in some cases complete substitution with non-nephrotoxic immunosuppressives if renal impairment has become irreversible.

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References


Authors’ reply

Sir,

We agree with Neil Fisher that cyclosporin is presumably a main factor in renal function loss in transplant recipients. We emphasise, however, that the severity of cyclosporin nephrotoxicity varies widely between different populations of recipients, suggesting interaction with other renal risk factors. This variation is not only apparent within the population of lung-transplant recipients, but also between recipients of different organ transplants. In cardiac and heart-lung, as well as lung transplant recipients renal morbidity is reported to be higher than that in liver-transplant recipients. Many factors might contribute to differences in renal damage among the various recipients, such as differences in cyclosporin dosing regimen or handling, comorbidity and cotreatment, such as antibiotics. To prevent renal function loss, identification of the specific renal risk factors in the different populations is essential.

To identify determinants of renal function loss in solid-organ recipients, it is important to distinguish between perioperative changes and long-term loss of renal function. Perioperative renal function changes can be hard to interpret in terms of nephrotoxicity, because a successful heart, lung, or liver transplant can improve renal perfusion by normalising cardiac output in patients with heart failure or cor pulmonale, and by curing hepatorenal syndrome, respectively. We have seen postoperative renal function improvement - despite cyclosporin - in patients with intense renal vasoconstriction before lung transplantation. Thus, early changes in net renal function result from the opposed effects of improved renal perfusion and cyclosporin nephrotoxicity. Such haemodynamic factors may explain why patients with a compromised renal function pretransplantation seem to do better after transplantation than those with normal pretransplantation function, as suggested by Fisher. Thus, their net change in renal function may not be a good indication of renal parenchymal damage. Considering that we avoided such bias by analysing short-term and long-term renal function loss separately, the difference in the long-term rate of renal function loss between the diagnosis groups is all the more striking.

Cyclosporin is presumably involved in renal function loss in our patients. All patients were on cyclosporin (three of whom were converted to tacrolimus after 6, 24, and 36 months). To account for differences in cyclosporin handling, our dosing regimen is based on pretransplantation assessment of individual cyclosporin kinetics. Trough cyclosporin concentrations were similar for the diagnosis groups throughout follow up. Remarkably, cystic fibrosis patients require higher cyclosporin doses to obtain similar blood concentrations. This dosage regimen may well have an impact on renal function. Whether cyclosporin dose can be safely reduced, however, is still unknown.

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Introduction of less nephrotoxic immunosuppressives such as mycophenolate may reduce renal morbidity in the future. For the moment, however, cyclosporin is still indispensable. Whereas close monitoring of dosage regimen is important to reduce renal morbidity, it is also crucial to recognise that the severity of cyclosporin nephrotoxicity is apparently modified by other factors that may be specific for a particular patient population. Identification of such factors may provide targets for renoprotective strategies for patients at high risk.

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