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INVITED COMMENTARY

Novel, More Accurate Assessments of Renal Function in Heart Transplant Patients: Commentary on 'Chronic kidney disease after heart transplantation: a single-centre retrospective study at Skåne University Hospital in Lund 1988–2010'

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Emerging improvements in heart transplantation have led to increased survival and a greater need to better understand the long-term complications of heart transplant. An emerging postsurgical issue of nonrenal solid-organ transplantation is development of chronic kidney disease (CKD), which has been related to significant morbidity and mortality in heart transplant patients that is related to factors that exist before, during and after surgeries. A better understanding of these factors is imperative to predicting and diagnosing CKD in patients with heart transplants.

In this issue of *Transplant International*, Soderlund *et al.* [1]. describe a retrospective single-centre study of 134 heart transplantation (HT) patients from 1988 to 2010 with annual follow-ups to monitor renal function. Instead of using traditional creatinine-based calculations such as the CKD-EPI, Schwartz or MDRD formulae to estimate glomerular filtration rate (GFR) and incidence of CKD, the authors of this study instead use iohexol clearance measurements. Iohexol clearance has been shown to be a simple, exact and reliable method for such calculations [2].

A series of interesting observations were made from their analysis. Particularly, a trend towards steepest GFR declines and CKD progression was observed during the first year post-transplant. Specifically, median GFR decreased from 67.0 during transplant assessment to 56.0 at year 1, 53.0 at year 5 and 44.5 at year 10. On average, GFR declined by 2.2 $\pm$ 14.6 ml/min/1.73 m [2] per year post-transplant; however, during the first year, the rate of decline was 11.9 $\pm$ 25.8 ml/min/1.73 m [2], much higher. Following in this trend, observations were made that increases in serum creatinine, serum urea, systolic blood pressure and diastolic blood pressure increased over the first year while only slightly increasing if at all after the first year. Taken together, this study suggests that although renal function declines slowly, the majority of the decline occurs early in the first year post-transplant, suggesting this time period is the most critical for monitoring. This time period encompasses the time when the highest doses of calcineurin inhibitors (CNIs) are used, as this is the period of time when rejection is most likely to occur. For this reason, more comprehensive monitoring is required and the use of iohexol to assess GFR provides a more accurate approach for monitoring renal function and preventing deterioration of renal function.

In a regression model, proteinuria was the only predictor of steeper GFR decline (>30% in year 1) after

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HT, with a hazard ratio of 2.45 (95% CI: 1.04–5.82) in the univariate analysis. GFR after transplant was also related to mortality. Patients with GFR > 60 had a lower risk of death compared to patients with GFR < 60 with a hazard ratio of 0.30 (95% CI: 0.12–0.76). Moreover, slower GFR declines (<30%) over the first year were associated with decreased mortality compared with steeper GFR declines (>30%) with a hazard ratio of 0.35 (95% CI: 0.13–0.90). Early kidney function is important in predicting and determining mortality outcomes, which has been shown in previous studies [3–5].

The observed cumulative incidences of CKD > stage 4 in this study (41% at 10 years) were much higher than other long-term studies after HT [3,6]. Of note, Söderlund *et al.* use iohexol clearance and postulate that other studies underestimate the true incidence of CKD because GFR formulae overestimates true GFR. The authors also observe steeper GFR yearly decline post-HT in their patient population compared with previously published data. They attribute this difference to higher CNI levels received. This difference may also result from iohexol clearance compared with other formulae used in previous studies.

Using iohexol measurements, the authors were able to directly compare its accuracy compared with traditional GFR estimation approaches. They showed that the CKD-EPI and Schwartz formula overestimated GFR by approximately 28 ± 29% and 26 ± 33%, respectively, which directly impacted CKD classifications and potentially underestimated cumulative CKD incidence.

The study was limited by a small cohort of patients and retrospective rather than prospective nature. It would benefit from increased patients for statistical power, which the authors mention. Moreover, most (90%) but not all patients had iohexol measurements. Nevertheless, this is an important study because it elucidates the extent to which the kidney is impacted after HT. Specifically, trends are observed towards steeper declines after the first year, warranting better monitoring during this time period. Moreover, early proteinuria, absolute GFR and rates in GFR decline are important predictive factors for determining CKD outcomes and mortality. Although previously shown, the use of iohexol measurements to elucidate these same conclusions provides even stronger support for these conclusions. Historically, CKD-EPI and Schwartz formulae are used to diagnose CKD, as recommended by KDIGO (Kidney Disease: Improving Global Outcomes) [7]. However, the validity of these and other creatinine-based calculations in HT has yet to be demonstrated – the authors therefore demonstrate that these measurements may be overestimating GFR rates and cumulative CKD incidence. This suggests that future monitoring post-HT may benefit from iohexol measurements rather than traditional calculations based on creatinine. At the very least, these formulae need to be better validated and studied in the context of this patient population, who will benefit strongly from better GFR measurements. The authors correctly identify important questions that are not addressed by this registry. Were changes implemented in the CNI regimens that mitigated renal dysfunction and were these carried out in response to declines in GFR from iohexol assessments? Did strategies that are used in diabetics with proteinuria to mitigate progression of renal disease such as angiotensin receptor blockers or angiotensin converting enzyme inhibitors have similar effects in heart transplant patients? The authors provide important evidence that proteinuria identifies heart transplant patients at risk of developing worsening renal function. These are clearly the patients who need most intensive follow-up and early interventions such as reductions in CNI doses.

Conflicts of interest

The authors have nothing to disclose.

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