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INVITED COMMENTARY

Kidney dysfunction after cardiac transplantation: does early acute kidney injury translate into inferior long-term patient and renal outcomes?

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Both cardiac and kidney diseases are extremely common in the population and are intimately interconnected. First, both conditions share several etiological factors (e.g., hypertension, diabetes mellitus). Second, a steady stream of studies has highlighted the negative heart–kidney interaction in such a way that any acute or chronic dysfunction of the former may affect the latter, and reciprocally, as part of the cardiorenal syndromes [1].

Heart failure emerged as the cardiovascular condition that most closely associated with kidney disease [2]. Therefore, the noxious interactions between the heart and kidney systems have become a matter of great concern in cardiac transplantation where kidney disease is an increasingly recognized complication [3]. Kidney failure, both in the acute and chronic settings, increases the complexity of patient management and significantly contributes to both early and late post-transplant morbidity and mortality [4].

Due to underlying comorbidities, including pre-existing chronic kidney disease (CKD), complications of surgery (e.g., acute tubular necrosis secondary to sepsis, shock, and radiographic contrast), and the use of calcineurin inhibitors (CNIs), cardiac transplant recipients are at risk for developing acute kidney injury (AKI) in the early postoperative period [5]. Although AKI is a frequent complication and established risk factor for CKD and mortality after nontransplantation cardiac surgery [6], little has been known about the short- and long-term prognosis of kidney dysfunction after cardiac transplantation. In two retrospective studies of the same

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cardiac transplant recipient cohort, Fortrie and colleagues report on the impact of early AKI on the short- and long-term patient and renal survival [7,8].

In the short follow-up study, published recently in *Transplantation* [7], Fortrie and colleagues evaluated the incidence, risk factors, and 1-year impact of AKI stratified by the consensus criteria for AKI published by the Kidney Disease: Improving Global Outcome (KDIGO) group [9]. With an incidence of 76%, AKI is a frequent complication of cardiac transplantation. The results underline the complexity of AKI as a clinical syndrome, which is affected by preliminary comorbid conditions and by using CNIs, which may potentially amplify the impact of AKI. Moreover, this seems to be even more complex in the cardiac transplantation setting where recipients are prone to suffer from prerenal kidney impairment due to cardiac failure. Regarding mortality, AKI constituted a crude predictor proportional to stage of severity for both hospital and 1-year mortality. After multivariable adjustment, only AKI requiring renal replacement therapy (RRT) was associated with an increased risk for mortality. Although only AKI in its most severe form was associated with increased mortality, the results demonstrated that AKI, even in its mildest form, had its repercussions on kidney function during the first year. Higher AKI stages were associated with lower 1-year kidney function even after adjustment for potential confounders, including baseline kidney function.

In this issue of *Transplant International*, Fortrie and colleagues address the long-term consequences of AKI following cardiac transplantation [8]. Authors had to be congratulated to provide a continuation of a former study and extensive follow-up on 471 adult cardiac transplant recipients over a period up to 26 years after transplant. In contrast to what we would expected, the main results of this study showed that AKI defined and staged by the KDIGO AKI criteria was not associated with an impaired long-term patient and renal survival. The exception was 17 patients (3.6%) with the most severe AKI requiring temporary RRT who had an increased risk for long-term mortality and ESRD. This finding is different to nontransplant settings where patients who developed AKI after general cardiac surgery had a higher risk for long-term mortality, which proportionally increased with AKI stage of severity [10]. While a mild to modest degree of early AKI did not play a significant role in predicting inferior long-term outcomes, kidney dysfunction at 1 year was strongly associated with increased mortality, progressive deterioration in kidney function, and ESRD.

What are the possible explanations for the seemingly discordant results on the impact of early AKI and kidney dysfunction 1 year after cardiac transplantation on long-term outcomes?

First, it should be emphasized that all results of the current study are conditional to 1-year survival. Previous studies demonstrated that the greatest difference in patient survival and greatest decrease in kidney function occur within the first year following cardiac surgery [5,10]. Therefore, the paradox that 1-year kidney dysfunction but not AKI early after transplantation was associated with inferior long-term outcomes can partially be explained by the so-called competing risks where early patient death or ESRD before reaching 1 year represents competing risks.

Second, patients in the current study were relatively young and less likely to suffer from comorbid conditions such as diabetes mellitus and hypertension. Therefore, acute cardiorenal syndrome where recipients suffered from prerenal kidney impairment due to severe cardiac failure could be a predominant clinical cause of AKI in the surviving population and may have a positive effect on the long-term outcomes. As demonstrated in the former study, a large proportion of recipients (27%) showed a significant improvement (≥20%) in kidney function compared to baseline early after transplantation [7].

Third, in the current study, the higher AKI stages were proportionally associated with a significant decrease in eGFR during 10 years of follow-up, potentially connecting AKI and development of CKD in the long term. However, incidences of kidney dysfunction according to eGFR 1 year after transplantation and during follow-up among patients with different AKI stages are not presented. Besides AKI requiring RRT, the differences in 1-year eGFR between the groups with a less severe AKI were probably too small to translate into different long-term outcomes.

Finally, other factors may contribute to an increased AKI and CKD risk in cardiac transplant recipients, including pre-existing CKD, and postoperative exposure to CNIs. In the additional subgroup analyses stratified by the transplantation period and by the type of immunosuppression, the effect of 1-year kidney function on patient and renal survival was lost in recipients transplanted after the year 2000 or treated with tacrolimus, respectively. Despite improvement in surgical techniques and perioperative care over the last decades [11] and protective effects of tacrolimus over cyclosporine [12], low number of events and limited follow-up in these subgroup analyses do not offer the possibility to draw any firm conclusions and warrant further research.

In conclusion, we should rather ask ourselves whether AKI early after cardiac transplantation conveys greater

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risk for the development of CKD. The answer is probably yes. However, final outcomes for the recipients are highly dependent on the preliminary comorbid conditions as well as the etiology of AKI. The presented study data advocate that we should keep our eye on conserving kidney function during the early postoperative period and the years thereafter.

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Conflict of interest

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