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Acute Kidney Injury after Heart Transplantation: Risk Stratification is Good; Risk Modification is Better—But can we do it?

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Acute kidney injury (AKI) is a frequent and consequential complication after heart transplantation (HTx). When evaluated using current Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria, the incidence of AKI after HTx is 40% to 80%, whereas the need for perioperative renal replacement therapy (RRT) ranges from 5% to 35%.[1,2] Even mild AKI appears to adversely impact both early and long-term outcomes after HTx, while severe AKI or need for RRT is associated with markedly higher mortality and permanent renal impairment.[2] The aetiology of AKI in the HTx setting is clearly complex and multifactorial. Preexisting kidney dysfunction is both driven and exacerbated by end-stage heart failure, cardiorenal interactions, and comorbidities. The kidneys are also particularly sensitive to a range of factors that occur commonly during HTx, including renal hypoperfusion, impaired renal oxygenation, prolonged cardiopulmonary bypass, vasoplegia, and the use of vasopressors, primary graft dysfunction (PGD) and nephrotoxic drugs such as calcineurin inhibitors.[2-4]

In this issue of *Transplantation Direct*, Gale et al[5] from St Vincent's Hospital, Sydney, Australia, examined the incidence, outcomes, and risk factors for severe AKI early after HTx in a single-center analysis of 109 adults. Dialysis-dependent or combined heart-kidney transplant (H-KTx) patients were excluded. The authors found an alarming 76% of patients (83/109) developed AKI as defined by the KDIGO AKI criteria within 7 d of HTx, with 39% (42/109) developing severe AKI and 34% (37/109) requiring new RRT. Early mortality was 17% (7/42) for patients with severe AKI compared with no deaths in patients without severe AKI. For patients who survived to discharge, 20% of patients (7/35) who had severe AKI required ongoing dialysis, compared with only 3% (2/67) in the none or mild AKI group. On multivariable analysis, lower preoperative estimated glomerular filtration rate, greater postoperative noradrenaline dose, and need for postoperative mechanical circulatory support (MCS) were independently associated with severe AKI. These findings suggest that optimization of preoperative renal function and strategies to mitigate perioperative vasoplegia, low cardiac output states, and PGD are critical to reducing the incidence and severity of AKI after HTx. An impressive 33% (36/109) of patients underwent donation after circulatory death (DCD) HTx using direct procurement and normothermic machine perfusion (TransMedics OCS). Rates of severe AKI among DCD heart recipients (44%; 16/36) were similar to donation after brainstem death recipients (36%; 26/73). Severe PGD among DCD heart recipients was considerably lower than earlier experiences from St Vincent's,[6] with only 3 patients (8.3%; 3/36) needing postoperative MCS in this latest study.[5]

Acute kidney injury after HTx is a vexing problem with severe consequences for patient outcomes and resource utilization. Gale et al[5] have conducted an important study, albeit with the limitations of a single-institutional cross-sectional analysis. Building on this, multicenter data with longer-term follow-up and standardization of AKI definitions across existing HTx registries are needed but currently lacking. Regionally speaking, this could potentially

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be an achievable target for the cardiac transplant centers in Australia and New Zealand, where collaboration already exists in terms of research, donor organ distribution, and transplant outcomes reporting.

Although studies that report retrospective outcomes and risk stratification are helpful for benchmarking, resource allocation, and identifying targets for future research, it remains critical that efforts are made to tangibly modify these risks. To date, attempts to mitigate AKI after cardiac surgery and HTx have been largely unsuccessful owing to 3 major challenges. The first is that we have limited ability to accurately predict which patients will develop AKI until it is too late. Second, we lack objective methods to monitor the status of the kidneys dynamically and in real-time both intraoperatively and in the intensive care unit (ICU). Third and most crucially, there remains little to no proven interventions to counter AKI and its associated penalty with regard to morbidity and mortality after HTx.

Thus, several areas could be targeted to improve renal outcomes after HTx.

The detection of AKI, or better still "acute kidney stress," should occur sooner, at a time still possible to intervene. Currently, AKI diagnosis after cardiac surgery and HTx is delayed by at least 12–24 h using creatinine and urine output criteria. In the study by Gale et al,[5] progression to severe AKI occurred within 48 h for 69% (29/42) of affected patients, implying that the onset of injury was considerably earlier. Innovations such as continuous real-time assessment of renal oxygenation[7,8] and early biomarkers of AKI[9] may improve monitoring and management of kidney health in the operating room and ICU, thus allowing for more precise, individualized, and goal-directed ways to intervene. Indeed, we may see increased utilization of these kidney monitoring tools in the near future which will better guide interventions such as goal-directed perfusion as well as postoperative resuscitative management.[3,8,10]

There is evidence to support combined heart-kidney transplantation (H-KTx) for patients with simultaneous end-stage cardiac and renal dysfunction.[11,12] Indeed, there has been a doubling in the proportion of combined H-KTx performed globally in the last decade, from ~2.5% to >6% of total HTx activity. However, debate continues[11-13] in terms of candidate selection, multiorgan allocation, post-transplant management, and under what conditions simultaneous versus subsequent H-KTx is the optimal strategy. Currently, there are no consensus guidelines. In terms of candidate selection, differentiating permanent advanced kidney disease from severe reversible injury is critical but not always straightforward. Recent United Network for Organ Sharing (UNOS) registry studies have also highlighted (1) the trade-off between improved long-term survival after combined H-KTx, relative to HTx alone, at the cost of increased early kidney allograft loss,[12] and (2) possible reduced overall survival with combined H-KTx relative to a subsequent KTx strategy, albeit with the popularity and uptake of combined H-KTx far outnumbering subsequent KTx, which has in fact declined.[13] Evidently, there are persisting knowledge gaps in the management of HTx candidates with simultaneous kidney failure and further research and consensus guidelines are greatly needed.

Avoidance of PGD is critical to improving survival after HTx and preventing multiorgan dysfunction, including AKI. In this regard, advances in donor organ preservation are clearly paramount. In this latest study,[5] moderate or severe PGD occurred in 45% (18/42) of patients in the severe AKI group and only 17% (11/67) in the none or mild AKI group. Mean donor heart ischemic time was also over 30 min longer among patients who developed severe AKI (225 versus 191 min). The deleterious effects of prolonged donor heart ischemic time and cold static storage preservation are well established. Donor heart preservation using machine perfusion is a promising and exciting frontier that may reduce the incidence of PGD and translate into a reduction of AKI. Normothermic machine perfusion using the TransMedics OCS has principally been used for resuscitation and evaluation of DCD donor hearts but has also been used for preservation of extended-criteria donation after brainstem death donors without the penalty of increased PGD.[14] However, any impact of normothermic machine perfusion on the incidence of AKI is yet to be clarified. An alternative form of donor heart machine perfusion is hypothermic oxygenated perfusion (HOPE). The Australia and New Zealand multicenter trial of HOPE achieved a mean preservation time of 6.9 h, and a maximum of 8.8 h, with only a 3% rate of PGD requiring MCS.[15] Renal outcomes in recipients of hearts preserved using HOPE, for a mean duration of over 6 h, were comparable or better than those for patients who received hearts preserved with cold static storage with significantly shorter mean ischemic times of 3 h.[16] Specifically, at 72 h post-HTx, new RRT was 37% for conventional cold storage donor heart recipients versus 22% for recipients of HOPE-preserved hearts, and mean creatinine rise was 60 versus 14 μmol/L, respectively. A major barrier to the broader application of donor heart machine perfusion is the substantial economic cost, staffing resources, and expertise required to run a successful program. However, as the technology of cardiac machine perfusion matures, the benefits will likely become clearer. A case could also be made that the expenditure associated with machine perfusion could potentially be offset by reducing the costs of managing PGD and its complications, including the need for MCS and RRT. Given the clear relationship between PGD and multiorgan dysfunction, future studies targeting ex-vivo perfusion and donor heart preservation must also include AKI outcomes.

Gale et al[5] should be congratulated for their latest work on this important topic. As our understanding of AKI after HTx continues to advance, so too should our efforts to reduce and modify the risks of AKI to further improve outcomes for HTx recipients.

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