Trends in Transplant. 2009;3:144-51

The Importance of Preserving Kidney Function after Heart Transplantation

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Abstract

Heart transplantation has significantly improved survival in recent years. However, it is not without complications, among which renal dysfunction is one of the most significant. The prevalence of renal dysfunction at seven years is 60% (GFR < 60 ml/min/1.73m^2) and the prevalence of severe renal dysfunction at ten years is 10.4% (GFR < 30 ml/min/1.73m^2). The presence of renal dysfunction at one year is associated with increased medium/long-term mortality. Most patients receiving a heart transplant have normal renal function, but suffer a significant deterioration in renal function over the first year posttransplantation, which later stabilizes and progresses slowly toward end-stage renal disease.

There are many preoperative, intraoperative, perioperative, and medium/long-term factors that determine the development of renal dysfunction, but their presence is usually attributed to calcineurin inhibitors. Preoperative factors include advanced age, sex, diabetes mellitus, hypertension, hepatitis C virus, and especially renal dysfunction prior to heart transplantation. Among the most important intraoperative factors are hemorrhage, hypotension, hemolysis, and a need for vasopressor drugs. The most important postoperative factors are septic conditions, cytomegalovirus infection, and early exposure to calcineurin inhibitors. The long-term predisposing factors are dyslipidemia, diabetes, infections, hypertension, and the degree of exposure to calcineurin inhibitors.

Calcineurin inhibitors are the drugs most commonly implicated in renal dysfunction. It as been suggested that tacrolimus may be less often associated with renal dysfunction than cyclosporine. An emerging strategy is to prolong induction with anti-interleukin-2 monoclonal antibodies and delay introduction of the calcineurin inhibitor in patients with reduced glomerular filtration rate at transplantation. If renal function subsequently recovers, the calcineurin inhibitor is introduced and, if any degree of renal dysfunction persists, an mTOR inhibitor or calcineurin inhibitor in lower doses can be administered.

One of the major problems is the method for diagnosing renal dysfunction. Plasma creatinine has numerous limitations. Creatinine clearance requires 24-hour urine collection, while the use of formulas such as the Cockroft-Gault method and the MDRD-4 and measurement of cystatin C

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are alternative methods with some limitations. Inulin clearance remains the gold standard, but its use is limited by its labor intensiveness. There is also the possibility of performing a renal biopsy if the diagnosis is uncertain or to confirm the reversibility of renal damage. To prevent renal dysfunction, it is important to avoid all risk factors and predisposing conditions. Careful selection of recipients and management of cardiovascular risk factors prior to heart transplantation is essential. Patients should receive careful management, avoiding hypotensive episodes in the perioperative period. The emergence of new molecules (fenoldopam and dopexamine) to replace classic vasopressor agents requires further clinical studies. With the development of end-stage renal disease, dialysis and inclusion on the waiting list for kidney transplantation should be considered. There is growing evidence suggesting that if renal dysfunction is established at the time of heart transplantation, the patient should be considered for simultaneous heart-kidney transplantation. **(Trends in Transplant. 2009;3:144-51)**

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Key words

Renal dysfunction. Heart transplantation. Kidney function. End-stage renal disease.

Introduction

Heart transplantation (HT) is the indicated treatment for severe, highly symptomatic heart failure without other medical or surgical options. This therapeutic technique has survival rates at 1, 5, and 10 years of 90, 70, and 50%, respectively[1]. Nevertheless, it is not without problems due to graft rejection and the development of complications. One of the most significant complications is renal dysfunction (RD).

A 30-60% prevalence of RD in HT recipients at seven years has been reported, considering RD as a serum creatinine > 1.5 mg/dl or a glomerular filtration rate (GFR) < 60 ml/min/1.73m^2, respectively[2,3]. The incidence of RD measured by GFR is about 5% in the first year, with a 3-4% annual incidence from the second year onward. If we calculate the incidence of RD based on creatinine values, it is about 20% in the first year, followed by a 5% annual incidence one year after transplantation[4-6]. In any case, the cumulative incidence of severe, chronic RD (GFR < 30 ml/min/1.73m^2) increases progressively over time, and is 4.2, 10.4, and 12.5% at 5, 10, and 15 years of HT[7].

However, studies on the prevalence and incidence of RD in HT have the limitation of the heterogeneity in the definition of the concept itself of RD.

Morbidity and mortality from renal dysfunction

The impact of RD on mortality has been confirmed in multiple studies[4,8-10]. The classic study by Ojo, et al.[4] was one of the first to report the impact of RD at one year on mortality for all types of nonrenal solid organ transplants (heart, lung, heart-lung, intestine, liver). Similarly, Arora, et al.[8] showed that mortality increased as GFR declined at one year of HT. Several studies have shown the increase in mortality associated with the development of end-stage renal disease post-HT. In the multivariate analysis of the Spanish Registry of Heart Transplantation[11], it was observed that RD and the need for dialysis post-HT were associated

with increased mortality, especially in the medium/long term. In a French study, survival post-HT was statistically lower in patients who had to start a dialysis program[12]. In the Canadian Organ Replacement Registry, patients on dialysis following HT had worse survival than those not on dialysis. However, survival was similar between patients with end-stage renal disease who underwent a kidney transplant after HT and those who did not require dialysis[13].

In the different studies, the causes of mortality in patients with established RD were diverse, but one of the most important was sudden death[8]. It is well known that RD is associated with an increased prevalence of ischemic heart disease[14]. However, studies that have analyzed the presence of cardiac allograft vasculopathy (CAV) have not been able to demonstrate a relationship between RD and the development of CAV[8]. Perhaps, increased use of coronary intravascular ultrasound (IVUS) will improve its diagnosis and allow new data to be provided on this issue.

Natural history of renal function after heart transplantation

Most patients receiving a solid organ transplant do so with normal or nearly normal renal function[15]. The course of renal function in the first year post-HT was shown to be crucial in a study where it was shown to follow a biphasic curve, with a 50% decrease in GFR in the first year, followed by stabilization and a subsequent slow but steady decline towards end-stage renal failure[5]. For this reason, progression of RD within the first year is key predictor of subsequent development of end-stage renal disease, the need for dialysis, and mortality, and its assessment at one year is fundamental for the prognosis of the patient[4,8,16].

Pathophysiology and etiopathogenesis of renal dysfunction

Numerous studies have shown the deleterious effect of calcineurin inhibitors on renal function[17-20]. Multiple mechanisms have been described by which calcineurin inhibitors contribute to RD. There is a drop in renal plasma flow, a loss of the filtration capacity by glomerular capillaries, vasoconstriction of afferent arterioles due to increased sympathetic tone, activation of the renin-angiotensin system, an altered balance between thromboxane and prostaglandins, an increased production of endothelin-1, and a decreased production of nitric oxide by endothelial cells[21].

Although RD is usually attributed to the use of calcineurin inhibitors, it should be considered a multifactorial process. Thus, in a study in which a renal biopsy was performed on 24 HT recipients with end-stage renal failure, although 60% of the biopsies showed changes compatible with calcineurin inhibitor toxicity, the damage caused by other conditions such as hypertension, diabetes mellitus, and focal segmental glomerulosclerosis was observed in a considerable percentage of patients[15].

Risk factors and clinical conditions predisposing to the development of renal dysfunction

The risk factors and clinical conditions associated with RD can be grouped into preoperative, intraoperative, postoperative, and medium/long term[22]. In general, the first three are not (or only slightly) modifiable factors and intervention is only possible on medium- and long-term predisposing factors. Among these, the most important is nephrotoxicity induced by immunosuppressant drugs, which we will review separately.

Preoperative factors include advanced age, sex, race, genetic factors, diabetes mellitus[23], arterial hypertension[24], ischemic heart disease, and the presence of hepatitis C virus antibodies[25]. The effect of some cardiovascular risk factors may be minimized due to exclusion from the waiting list of patients with more rebellious arterial hypertension or with established diabetic retinopathy. In any case, it has been shown that one of the most important predictive factors is the presence of RD prior to transplantation[7,22,26].

The most important intraoperative factors are those that can lead to acute renal dysfunction during the surgical procedure. Thus, the presence of surgical hemorrhage, intraoperative hypotension, hemolysis by extracorporeal circulation and the need for vasopressor drug use can promote the development of RD[22,27].

Postoperative factors include acute renal failure after surgery, septic conditions, cytomegalovirus infection, and early exposure to calcineurin inhibitors[22,28]. A study by this group (under review for publication) suggests that cytomegalovirus infection not only predisposes to the development of RD, but that prophylaxis with antivirals has a protective effect in preventing its development.

Medium- and long-term predisposing factors hold a prominent place because they usually involve factors or clinical conditions that are susceptible to some type of intervention. These include dyslipidemia[29], proteinuria, infections (hepatitis B and C virus, cytomegalovirus), posttransplant arterial hypertension[30], nephrotoxic drugs, and the degree of exposure to calcineurin inhibitor drugs[22,28]. As previously indicated, evaluation of renal function at one year post-HT is particularly important because of its prognostic value[4,8,16].

Immunosuppressant drugs and development of renal dysfunction

Patients may or may not receive induction therapy after HT, and usually receive maintenance immunosuppression with triple therapy consisting of a calcineurin inhibitor, an antiproliferative drug, and a corticosteroid. There are few data in the literature regarding the effect of different induction drugs on renal function post-HT. There are publications suggesting that prolonging treatment with anti-CD25 antibodies (daclizumab and basiliximab) and delaying introduction of the calcineurin inhibitor could preserve renal function to a greater extent in patients with reduced GFR at transplantation[31-33]. Regarding the antiproliferative drug, in a large multicenter trial it was shown that dose adjustment of the calcineurin inhibitor combined with intensification of the less nephrotoxic medication (mycophenolate mofetil) was able to preserve renal function to a greater extent[34]. It has been suggested that the choice of mycophenolate mofetil, because it is associated with a lower number of rejections[35], allows the dose of the calcineurin inhibitor to be reduced, therefore showing a protective effect on renal function when compared to azathioprine.

The detrimental effect of calcineurin inhibitors has been verified in numerous studies both in HT and other solid organ transplants, and constitutes one of the main determinants of posttransplant renal failure[17-20]. A recent analysis of the risk factors associated with the development of moderate-to-severe RD in the Spanish CAPRI registry determined that the choice of tacrolimus versus cyclosporine was a protective factor for its development[2]. In renal transplantation, the ELITE-Symphony study showed that a regimen of daclizumab, mycophenolate mofetil, and steroids in combination with low-dose tacrolimus may be beneficial in terms of renal function, graft survival, and rejection rate as compared with low-dose

cyclosporine, low-dose sirolimus, or standard-dose cyclosporine without induction[36]. However, before it can be stated that tacrolimus is associated with significantly decreased development of RD, specific studies designed for this purpose will probably be needed.

A new emerging strategy in the management of immunosuppression is the replacement or minimization of the dose of calcineurin inhibitor by an mTOR inhibitor (everolimus) with the aim of improving renal function[37].

Measurements for estimation of renal function – Diagnosis

One of the most significant problems when determining incidence and prevalence is the definition itself of RD. There are numerous methods of estimating renal function, which have different advantages and disadvantages depending on their precision and difficulty to perform.

Determination of plasma creatinine is probably the most widely used method, but it has numerous limitations. It requires that loss of renal function is 50% in order to reflect significant changes in its values, so its utility for early diagnosis is limited[38].

Creatinine clearance, which uses plasma and urinary concentrations of creatinine, is a more accurate predictor of renal function. However, it requires meticulous 24-hour urine collection, which hampers its use for the follow-up of outpatients[38].

Calculation of glomerular filtration rate by indirect formulas has become one of the most widely used methods in recent years. The most important are the Cockroft-Gault formula[39] and the Modification of Diet in Renal Disease (MDRD-4)[40]. The latter is the one recommended by the National Kidney Foundation in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines[41]. The formulas permit earlier detection of RD, but are still an indirect method, with limitations in the calculation of glomerular filtration rate.

The use of cystatin C as a marker of renal function has been gaining importance in recent years. It is an endogenous molecule that is totally filtered by the glomerulus and is not reabsorbed or secreted. Its hypothetical advantage is that it is not affected by age, gender, or race, but studies are still needed to validate the utility of cystatin C in the setting of HT[42-44].

However, the method considered the gold standard for calculation of glomerular filtration rate is clearance measured by inulin. Its complexity and laboriousness complicate its use[45,46]. In addition, there are other methods that use radiolabeled isotopes and nonradioactive contrast agents to estimate glomerular filtration rate, but again their complexity makes their use as markers impractical in routine clinical practice[47,48]. Although they are not parameters that directly estimate renal function, we should not forget the additional prognostic information offered by proteinuria and microalbuminuria[49].

Lastly, the indication for renal biopsy should be determined by the nephrologist. Percutaneous computed tomography or ultrasound-guided renal biopsy provides diagnostic, prognostic, and therapeutic information. In general, it is indicated if there is a suspicion of underlying disease other than chronic RD in the context of a nonrenal transplant, in the presence of altered urinary sediment, or to confirm the chronicity of the RD prior to switching to an mTOR inhibitor[50].

Strategies to prevent renal dysfunction

Prevention of RD should begin with attempts to avoid all circumstances that may

predispose to deterioration of renal function. Careful selection of recipients, as well as efforts to ensure that the end-stage heart failure patient arrives in the best possible condition to HT, are key measures to prevent long-term RD. As previously mentioned, the presence of prior RD is one of the main predictors of long-term RD, and therefore its correct detection is essential[7,22,26]. The presence of end-renal stage disease at the time of HT should make us consider the possibility of a simultaneous kidney transplant. Recently, a U.S. registry of 263 simultaneous heart-kidney transplants has been published. Most notable among its results was the good outcome of these patients compared to patients with RD requiring dialysis, with a much lower benefit in those with end-stage renal disease not requiring dialysis[51].

Regarding intraoperative and postoperative clinical situations, it is necessary to ensure correct volume management, attempting to avoid any situation that generates hypotension and promotes the development of RD. Recently, publications have appeared that suggest that the use of two new molecules (dopexamine and fenoldopam) may be associated with better tissue perfusion in the critical intra- and postoperative period than the use of classic vasopressor drugs. Fenoldopam is a selective dopamine-1 receptor agonist, which would produce a vascular vasodilatory effect that would improve renal blood flow[52]. Dopexamine is another new dopamine receptor agonist that has been shown to increase blood flow in various organs[53]. However, these molecules require studies evaluating clinical endpoints and demonstrating their efficacy over classic vasopressor drugs.

After the surgical period, efforts should be focused on strict control of all factors that could promote medium/long-term RD, taking to account that the course of RD in the first year is crucial[5]. Therefore, arterial hypertension, dyslipidemia, diabetes, etc. should be controlled[54,55].

Regarding the management of immunosuppression, once signs of RD are detected, the introduction of mTOR inhibitors either to reduce or to replace the calcineurin inhibitor is indicated[37]. One of the lessons learned from kidney transplantation, which has been extrapolated from the rest of solid organs, is that conversion to the mTOR inhibitor should be done as early as possible because, once nephropathy is established, the patient will not benefit from the conversion[56-58]. In fact, some groups recommend performing a renal biopsy prior to conversion to verify the reversibility of RD. It is also recommendable to assess proteinuria before conversion because, if significant, the change may deteriorate renal function even more. It is generally recommended to reduce the dose of the calcineurin inhibitor by half and to start everolimus at a dose of 0.75 mg/12 hours, and then to gradually reduce the calcineurin inhibitor until its complete withdrawal as soon as therapeutic levels of everolimus are reached[59].

As with any non-transplanted patient, a HT patient who develops end-stage renal disease should be prepared for dialysis according to the K/DOQI guidelines[43]. Several studies have shown that mortality of these HT patients after a kidney transplant is similar to that of patients only having a kidney transplant, and with greater survival at five years than those who remain on the waiting list[4,13].

Conclusions

Renal dysfunction following HT is a common complication with great impact on patient survival. Renal function suffers a rapid deterioration in the first year, followed by a slow but steady decline thereafter. There are numerous techniques to detect this RD that have surpassed the use of plasma creatinine. Although the etiology of RD is usually attributed to calcineurin inhibitors, there are a wide range of factors that contribute to its development.

Several of these factors are correctable and should be intervened on, among which the most important are careful perioperative management, prevention of viral infections, and conversion to an mTOR inhibitor in early stages. In advanced stages, kidney transplant should be considered as an alternative to dialysis.

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