Renal Impairment an Impediment to Heart Transplantation?

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Chronic kidney disease and chronic heart failure are now recognized as closely intertwined entities. The noxious interactions between the heart and kidney systems as part of the so-called *cardiorenal syndrome* is a matter of great concern for heart transplant candidates. Not only is chronic kidney disease a commonly associated comorbidity, but its detrimental effect on the outcome of heart transplantation is now well established. In the more advanced stages of kidney disease, it may even deter physicians from carrying out heart transplantation in potential candidates. This review offers insights on epidemiological issues regarding chronic kidney disease among patients awaiting heart transplantation as well as its impact on the outcomes related with heart transplantations. Finally, emerging therapeutic opportunities which may benefit heart transplant candidates with the most severe renal impairment will be reviewed with a special emphasis on combined heart-kidney transplantation.

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INTRODUCTION

Chronic kidney disease (CKD), especially when severe, is widely held as a contraindication to heart transplantation by many medical institutions. Given the widespread prevalence of CKD among heart transplant candidates, a nephrological assessment and management in potential heart transplant recipients is a key issue as renal impairment may potentially jeopardize the access of these patients to a life-saving procedure. Chronic heart and kidney diseases are intimately interconnected. First, both conditions share a great number of etiological factors. 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*.

EPIDEMIOLOGY

Prevalence of Chronic Kidney Disease Among Candidates for Heart Transplantation

In the 2009 annual report of the United States Renal Data System, a near two-third of the patients with CKD also presented with cardiovascular disease. This stands in stark contrast with the population of patients unaffected by kidney dysfunction among whom a cardiovascular condition was present only in a mere 5.8% of the cases. Furthermore, heart failure emerged as the cardiovascular condition the most closely associated with CKD.[1] Reciprocally, a recent meta-analysis designed to determine the prevalence of CKD among patients suffering from heart failure found that 29% among the latter fulfilled the criteria for moderate or severe CKD (estimated glomerular filtration rate [GFR], < 60 mL/min).[2] Of note, the prevalence of CKD remains high regardless of the nature and severity of heart failure, including in patients who exhibit a normal ejection fraction.[3-5] The ominous significance of CKD in this setting is now well recognized and has been shown to be associated with an increased mortality rate.[6] In France, data stemming from the Agence de la biomédecine indicate that one-third of the patients awaiting heart transplantation have concurrent CKD. Elsewhere, figures ranging from 15% to 25% have been reported.[7,8]

The Impact of Post-Heart-Transplantation Chronic Kidney Disease

Heart transplant patients should be regarded as particularly vulnerable to the occurrence of CKD and this includes end-stage renal disease (ESRD). In this respect, cohort studies have established that between 2% to 18% of heart transplant patients develop ESRD requiring permanent hemodialysis. Reported time lapses between heart transplantation and the onset of ESRD range between 72 and 120 months (Table).[7,9-28] Patients usually display maximum loss of kidney function during the first year following transplantation. Ten years after heart transplantation, less than 10% of the patients exhibit a normal kidney function (estimated GFR, > 90 mL/min), doubling of serum creatinine is observed in more than half of them and an approximate 40% demonstrate severely altered kidney function (estimated GFR, < 20 mL/min).[12,14,18,22] The occurrence of ESRD in heart transplant patients also represents a major turning point in the course of heart transplantation as it is associated with a significantly enhanced risk of mortality. Furthermore, the impact of post-heart-transplantation CKD stretches beyond its effect on patients' survival rate as it has been shown to significantly alter heart transplant recipients' cardiopulmonary performance during exercise as well as their quality of life.[29]

Preoperative Chronic Kidney Disease and Its Associated Risks

In the setting of cardiac surgery, the unfavorable impact of preoperative kidney failure on the outcome of surgical patients is a well-known fact. More specifically, CKD has been linked to an increased intra- and extra-hospital mortality and predicted the occurrence of postoperative acute kidney injury (AKI).[30-35] Moreover, CKD also impedes cardiac rehabilitation following surgery. Similar findings have been established in heart transplant patients, preexistent CKD portends an ominous prognosis with a heightened risk of mortality.[20,27] In this regard, Ostermann and colleagues evidenced that the postoperative 30-day mortality doubled in the subgroup of patients whose glomerular filtration rate was lower than 50 mL/min.[20] Likewise, preoperative CKD is also an independent risk factor for postoperative AKI both a frequent and dreaded complication. In a retrospective monocentric study based on 307 heart transplant recipients, AKI occurred in 40% of the patients in the early stages after surgery and extrarenal epuration (ERE) was required in 6% of the patients.[21,24,36] Even higher figures have been reported in other studies (Table). The more severe the AKI, the more likely patients are to die, yet another indication of the intimate connection between kidney failure and the adverse outcome of heart transplantation.[36,37] Furthermore, the occurrence of severe AKI (as defined as AKI requiring ERE) compromises the patient's long-term kidney function with an increased likelihood of CKD.[21] This phenomenon should be interpreted in a broader reappraisal of AKI in general. Long seen as benign event in the sense that full kidney function recovery of AKI was almost universally expected, AKI has now been proven to predispose to CKD.[38,39]

Finally, the kidney function threshold below which heart transplantation should not be performed remains elusive. Nevertheless, some studies have stated that a GFR below 30 mL/min or 40 mL/min may be a reasonable set point.[40] One word should also be said about the "waiting list phenomenon," which lends further confusion when addressing the issue of kidney function of heart transplant candidates. Given the previously mentioned negative heart-kidney interplay, on the one hand, and the significant delay between when patients are cleared for heart transplantation and the transplantation itself, on the other hand, kidney function may deteriorate in the meanwhile. Hence, patients may have a suitable kidney function at initial screening but may fail to achieve the minimum requirements on transplantation day. In fact, Ostermann and colleagues reported that more than half of the patients displayed significant worsening of their kidney function between enrolment for transplantation and surgery.[20]

Chronic Kidney Disease Risk Factors After Heart Transplantation

A retrospective analysis encompassing more than 24 000 heart and combined heart-and-lung transplantations has shed light on risk factors associated with the occurrence of CKD, namely advanced age, arterial hypertension and diabetes (prior to transplantation), and hepatitis C virus infection.[8,41] Calcineurin inhibitors (tacrolimus and

Epidemiology and Impact of Preoperative Chronic Kidney Disease in the Heart Transplant Recipients*

Author	Publication Year	Study Design	Median Posttransplant Follow-up, mo	Number of Patients	ESRD as Outcome				AKI as Outcome		
					% Patients	Time to Onset, mo	Preoperative CKD as a Risk Factor	Other Risk Factors	% Patients	Preoperative CKD as a Risk Factor	Preoperative CKD as a Risk Factor for Mortality
van Gelder et al[11]	1998	CC	79	304	8	79	No	None	...	...	...
Hornberger et al[16]	1998	RS	...	2088	2	...	...	…	...	...	...
Hamour et al[12]	1999	RS	60	352	3	...	No	AKI, Female, DM2	23.6	...	...
Lindelöw et al[14]	2000	RS	120	151	4	...	No	...	10.8	...	...
Satchithananda et al[17]	2002	RS	63	697	5.8	87	No	None	...	...	...
Vossler et al[15]	2002	RS	50	160	3.8	...	Yes	Age, ICM	...	...	...
Sénéchal et al[18]	2004	CC	160	1211	3	120	Yes	…	...	...	...
Rubel et al[19]	2004	RS	...	370	6	75.6	Yes	Cyclosporine, DM2	19	...	...
Ostermann et al[20]	2004	RS	1	1180	...	...	...	...	13.4	...	Yes
Odim et al[7]	2005	RS	...	622	...	...	...	Age, ICM	12.9	No	No
Boyle et al[21]	2006	RS	...	756	...	...	...	...	5.8	Yes	...
Canales et al[22]	2006	RS	79	219	7.3	...	No	Age, Cyclosporine	...	...	...
Lubitz et al[13]	2007	RS	60	218	4.5	92.4	Yes	DM2	...	...	...
Molina et al[23]	2010	CC	81	100	18	64.3	No	Cyclosporine	...	...	No
Jokinen et al[24]	2010	RS	...	93	4	...	...	...	25	Yes	...
Delgado et al[25]	2010	RS	81	1062	...	...	Yes	Age, Male	...	...	...
Thomas et al[26]	2012	RS	60	1495	3	72	Yes	Age, DM2, CHC, IRA	16.2	...	...
Samsky et al[27]	2013	RS	60	454	5	...	...	...	...	...	Yes
Karamlou et al[28]	2014	RS	...	26183	...	...	No	Age, DM2, AA, CIT	9	Yes	Yes

*ESRD indicates end-stage renal disease; AKI, acute kidney injury; CKD, chronic kidney disease; CC, case-control; RS, retrospective; DM2, type 2 diabetes mellitus; ICM, ischemic cardiomyopathy; CHC, chronic hepatitis C; AA, African or African-American; and CIT, Cold ischemia time. Ellipses indicate not reported.

cyclosporine), which represent the cornerstone of immunosuppressive therapy in the setting of transplantation, have been recurrently incriminated as potent inductors of CKD in kidney and other solid organ transplantation including heart transplantation.[19,23] However, irrefutable evidence of its nephrotoxicity is still lacking. In a study including 18 kidney biopsy in heart transplant recipients prompted by severe CKD (estimated GFR, < 30 mL/min), the predominating histological pattern was nephroangiosclerosis, present in all cases. Features evocative of glomerulosclerosis and focal segmental glomeruleosclerosis were also found, albeit less consistently. Calcineurin inhibitor toxicity was suspected in only 2 cases.[42]

MANAGEMENT OF HEART TRANSPLANT CANDIDATES

Nephrological Assessment Prior to Heart Transplantation

Nephrological assessment may represent an essential step for heart transplantation candidates with an altered kidney function.[40] However, current guidelines are rather laconic, to say the least, stating proteinuria and renal artery ultrasonography as the only warranted investigations in this setting.[43] Nevertheless, kidney biopsy should be contemplated as it may provide crucial insights on the underlying mechanisms behind the kidney disease, and most of all, important cues on its prognosis. In a study by Labban and coworkers performed on 30 patients with renal impairment precluding heart transplantation by local standards (estimated GFR, < 40 mL/min), details from kidney biopsy histological analysis were found to be reassuring in 14 cases thus clearing these patients for heart transplantation.[44] As left ventricular dysfunction is directly involved in the pathogenesis of CKD in patients with heart failure, its reversal, through the means of heart transplantation, may also benefit the patient's kidney function. Following this line of thought, a course of intravenous inotropic therapy (phosphodiesterase III inhibitor) was performed on patients awaiting heart transplantation in a bid to simulate the effect of heart transplantation and its potential benefit on kidney function. This strategy may enable caregivers to identify patients whose kidney function is the most likely to profit from heart transplantation.[14]

When heart transplantation is not carried out, the prospects for survival of patients with concurrent advanced left ventricular dysfunction and CKD are dim. For example, in a subgroup of patients undergoing hemodialysis, Schaffer and colleagues reported a 31% mortality within the 3 months following inclusion on a heart transplantation program.[45] A correlative finding was provided by Samsky and associates who reported an acceptable post-heart-transplantation rate (65% at 5 years) when extending criteria for transplantation, including lower GFR.[27]

Combined Heart-Kidney Transplantation

Combined heart-kidney transplantation offers another option when confronted with patients with advanced heart failure together with renal impairment precluding heart transplantation alone. This strategy has been fast expanding even though it is still a marginal procedure with only 50 or so transplantations carried out annually in the United States.[40] Provided candidates for combined heart-kidney transplantation are carefully selected, this approach has yielded survival rates close to that of single heart transplantation.[28,46,47] If the limits of combined heart-kidney transplantation remain elusive and even though guidelines on patient selection have yet to be issued, recent studies have unveiled several risk factors for poor outcome including advanced recipient age (> 65 years), peripheral vascular disease, nonischemic cardiomyopathy, ESRD, and left ventricular assistance.[48]

Protecting Kidney Function Following Heart Transplantation

Early posttransplantation stages. Management in the early postoperative stages is of utmost importance. Special care should be taken at maintaining adequate renal perfusion and avoiding nephrotoxic agents.[40] In the setting of heart transplantation, this equates with restricting contrast agent injections and calcineurin inhibitor concentration monitoring. Calcineurin inhibitors display a well-established acute nephrotoxic profile mediated through renal arteriolar vascoconstriction in a dose-dependent fashion.[49]

Reducing the risk of immunosuppressor-related nephrotoxicity. Numerous strategies have been devised in order to mitigate the nephrotoxicity associated with calcineurin inhibitors. These

include[41,50]: (1) delaying their introduction thanks to immunusuppressive induction therapy,[50] with either basiliximab[51] or thymoglobulin[52,53]; and (2) substituting anticalcineurin inhibitors for other immunosuppressors devoid of nephrotoxic effects; a pilot study involving 8 patients all of which manifested gradual renal impairment under calcineurin inhibitors showed stabilization or improvement of the kidney function in 7 cases once azathioprine and cyclosporine were switched to mycophenolate mofetil. In the same setting, everolimus and sirolimus, both mTOR inhibitors, once again used in as substitute immunusupressors for calcineurin inhibitors, have been the focus of several small-scale studies yielding encouraging results.[54-56] Of note, mTOR inhibitors can only been contemplated after a protracted delay following transplantation as they may otherwise exert negative effects on wound healing.[57] Moreover, at least 1 study demonstrated an increased risk of acute rejection associated with the use of sirolimus.[54] Finally, recent experimental works indicate that sirolimus may induce glomerular proteinuria by interfering with the podocyte's cytoskeleton signalization and function, especially in the case of nephron reduction.[58]

CONCLUSIONS

Chronic kidney disease represents a common issue and a major challenge among heart transplant recipients. If CKD portends a negative vital and renal outcome, it should not be regarded as an unsurmountable obstacle to heart transplantation. A multidisciplinary approach including a nephrological workup may help to better detect patients most likely to benefit from heart transplantation. In addition, several strategies allow extended access to heart transplantation, even in cases where patients display severely compromised kidney function. Among existing options, combined heart-kidney transplantation represents a promising approach.

CONFLCIT OF INTEREST

None declared.

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