Chronic kidney disease in prevalent orthotopic heart transplant recipients using a new CKD-EPI formula

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Summary

Background: Heart transplantation is an established treatment for advanced heart failure. However, chronic kidney disease (CKD) is an important long-term complication of all forms of organ transplantation other than renal. It has been shown that a GFR <60ml/min is predictive of premature cardiovascular death.

Material/Methods: The aim of this study was to assess the prevalence of kidney dysfunction in heart transplant recipients using a new CKD-EPI formula in a cohort of 169 prevalent patients (mean age 53.30±13.80 years).

Results: Mean serum creatinine in this population was 1.71±1.10 mg/dl, Serum creatinine was normal (<1.4 mg/dL in males and <1.2 mg/dL in females) in 45.4% of the patients. According to the Cockcroft-Gault formula, stage 2 CKD (i.e. GFR 60–89 ml/min) was demonstrated in 79 patients (46.75%), stage 3 CKD (i.e. GFR 30–59 ml/min) in 49 patients (29.00%) and stage 4 CKD (i.e. GFR 15–29 ml/min) in 15 patients (8.88%). According to MDRD formula stage 2 CKD was found in 36 patients (21.30%), stage 3 CKD was found in 79 patients (46.75%) and stage 4 in 27 patients (15.98%). According to new CKD-EPI formula, stage 2 CKD was found in 35 patients (20.71%), stage 3 CKD in 79 patients (46.75%) and stage 4 in 28 patients (16.57%). According to the creatinine clearance stage 2 CKD was found in 61 patients (36.09%), stage 3 CKD in 63 patients (37.28%) and stage 4 in 19 (11.24%) patients. Clinically significant CKD (GFR <60 ml/min) was found in 37.88–63.91% depending on the formula used to estimate the GFR. Normal kidney function was found in 27 patients (15.98%) according to MDRD formula, in 27 patients (15.98%) according to new CKD-EPI formula, in 26 patients (15.38%) according to Cockcroft-Gault formula and 26 patients (15.38%) on the basis of 24-hours creatinine clearance.

Conclusions: We conclude that the prevalence of CKD is high in heart transplant recipients. Evaluation of renal function is important in order to select the appropriate strategy to reduce the cardiovascular risk. New CKD-EPI formula seems to more accurate in assessment kidney function that previously used, however, it merits further studied and validation against gold standard of isotope GFR measurement.

Key words: chronic kidney disease • orthotopic heart transplant recipients • CKD-EPI formula

Heart transplantation has become an established treatment for advanced heart failure. Although pitfalls to long-term survival remain, the outcome among transplant recipients has improved over the past 30 years as a result of careful recipient and donor selection, progress in immunosuppression, and the prevention and treatment of infection [1]. Chronic kidney disease (CKD) is an important long-term complication of all forms of non-renal organ transplantation [2,3]. As outcomes following non-renal solid organ transplantation have improved, chronic kidney disease (CKD) has become an increasingly prevalent complication in this population [2–4]. This has been attributed to long-term treatment with calcineurin inhibitors (CNI) [5,6]. However, CKD occurs despite advances in immunosuppression, tailored and CNI-free regimens, better peri-operative management as well as attention given to cardiovascular risk factors and infectious complications [1–3]. Studies have shown that the development of CKD (i.e. a GFR <60 ml/min) is predictive of premature cardiovascular death [7]. Evaluation of renal function is important in order to select the appropriate strategy to reduce the cardiovascular risk and change the immunosuppressive regimen if it is possible. Levey et al. [8] recently (2009) proposed a new equation (CKD-EPI) to estimate the GFR. The aim of our study was to assess the prevalence of CKD using this new formula in orthotopic heart transplant (OHT) recipients.

Material and Methods

The studies were performed on 169 prevalent patients after orthotopic heart transplantation. Indications for OHT were: ischemic cardiomyopathy, n=98, dilated cardiomyopathy, n=64, end-stage valvular disease, n=7. All the patients were transplanted according to the Shumway-Cooley-Brock technique. Mean CIT (cold ischemia time) was 211 minutes (preservation fluid was Celsior). Mean cross-clamping time was 70 minutes. Mean stay in ICU (intensive care unit) was 7 days. Prior to OHT in all the patients serum creatinine was below 162 µmol/L. In 20% of the patients induction therapy with ATG (antithymocyte globulin) at a dose of 1.25 mg/kg. was given for 3 consecutive days. Lymphocyte subpopulations were monitored during this time by flow cytometry. The immunosuppressive regimen of prevalent patients consisted of tacrolimus (n=57), cyclosporine (n=109), in combination with mycophenolate mofetil (n=134), azathioprine (n=4), everolimus (n=28) or sirolimus (n=8). Fifty four patients were given also prednisone

All of them maintained sufficient and stable graft function, showed no clinical signs of rejection, no inflammation. All subjects gave an informed consent, and the protocol was approved by the Medical University Ethics Committee. Blood was drawn in the morning after an overnight fast. The CKD stages were defined according to NKF/DOQI guidelines [7]. GFR was estimated using the new CKD-EPI formula [8], the simplified MDRD formula [9] and the Cockcroft-Gault formula [10]. The creatinine clearance was performed in each patient on a 24-h urine collection.

Complete blood count, urea, serum, fasting glucose, creatinine, were studied by standard laboratory method in the central laboratory of the hospital.

Data were expressed as mean ±SD. The data given were analyzed using a Statistica 7.0. computer software. The examination of the distribution normality of variables was done using W Shapiro-Wilk test. The data were also logarithmically transformed to achieve normal distribution, whenever possible.

Results

Mean age in the population studied was 58.30±13.80 years, mean time after transplantation was 105±51 months (median 104, ranges 10–210 months). Mean serum creatinine in this population was 1.71±1.10 mg/dl, whereas normal serum creatinine (less than 1.4 mg/dL in males and less than 1.2 mg/dL in females) was observed in 45.4%
patients. Mean GFR was 63.41±32.34 ml/min (Cockcroft-Gault formula), 55.63±26.91 ml/min (MDRD), 55.87±27.54 ml/min (CKD-EPI), and 63.01±35.90 ml/min (creatinine clearance). The current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines advocate creatinine-based equations for estimating GFR to identify patients with potential kidney disease and to classify them into different stages on the basis of these values (1). According to the Cockcroft-Gault formula, stage 2 CKD, i.e. GFR 60–89 ml/min was diagnosed in 79 patients (46.75%), and stage 3 CKD i.e. GFR 30–59 ml/min in 49 patients (29.00%) and stage 4 CKD i.e. GFR 15–29 ml/min in 15 patients (8.88%). According to MDRD formula stage 2 CKD was found in 36 patients (21.30%), stage 3 CKD was found in 79 patients (46.75%) and stage 4 in 27 patients (15.98%). According to new CKD-EPI formula stage 2 CKD was found in 35 patients (20.71%), stage 3 CKD in 79 patients (46.75%) and stage 4 in 28 patients (16.57%). According to the creatinine clearance stage 2 CKD was found in 61 patients (36.69%), stage 3 CKD in 63 patients (37.28%) and stage 4 in 19 (11.24%) patients. Clinically significant CKD (GFR <60 ml/min) was found in 37.88–63.91% depending on the formula used to estimate GFR or creatinine clearance. Kidney function was normal in 27 patients (15.98%) according to the MDRD formula, in 27 patients (15.98%) according to the CKD-EPI formula, in 26 patients (15.38%) according to the Cockcroft-Gault formula and 26 patients (15.38%) on the basis of 24-hours creatinine clearance.

**DISCUSSION**

We found that a substantial number of patients ranging from one third to two thirds of the population studied had an abnormal renal function (at least stage 3 CKD) following OHT. Surprisingly, we found a high prevalence of severe CKD (eGFR below 30 ml/min), on the basis of estimated GFR, in up to 17.16% of OHT patients. It is noteworthy that in all the patients serum creatinine prior to transplantation was <1.8 mg/dl. None of the patients were receiving pretransplant renal replacement therapy. There are limited data on kidney function in OHT. The reported incidence of CKD (GFR <60 ml/min) after OHT widely varies among studies, ranging from 54% [11] in the early post-transplant period to 93% 10 years post transplant in a prospective study [11] and 38.3% to 73.3% in cross-sectional studies [12]. The reported incidence of CKD after solid organ transplantation varies according to the organ transplanted. The criteria for assessing CKD also vary among studies (e.g. serum creatinine concentration, calculated eGFR or creatinine clearance by the Cockcroft and Gault formula). These differences in methodology make interstudy comparisons difficult. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend estimating GFR in patients who are at risk for kidney disease using the Modification of Diet in Renal Disease (MDRD) study formula. Within the 5th and 95th percentile for age, both formulas, MDRD and Cockcroft-Gault, provide similar results which are consistent with age-specific historic inulin clearance values [13]. The Cockcroft-Gault equation provides higher estimates at younger ages and lower estimates at older ages (eg. >70 years) than those obtained with the simplified MDRD formula [9]. However, the accuracy of the MDRD formula in patient populations outside of the United States is also unclear [14]. Despite this, the use of the MDRD or the Cockcroft-Gault formulas to estimate GFR may provide a better assessment of kidney function than the serum creatinine concentration alone [10]. A 24-hour collection for determining the creatinine clearance is also likely to overestimate the GFR in patients with renal disease as the contribution of tubular secretion of creatinine to total clearance is increased in this subset of patients. The GFR is estimated according to body size, whereas the MDRD formula provides an estimated eGFR that is corrected for the body surface area. Nevertheless, it seems possible that this finding could be related to the method we used for estimating GFR. Despite this the MDRD equation is currently one of the most reliable means for assessing renal function [13,14]. Moreover, since current equations have limited accuracy and systematically underestimate measured GFR at higher values (over 60 ml/min for MDRD formula), therefore, a new equation for estimating the GFR: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed by Levey et al. [8]. The new equation was derived from research studies and clinical populations (“studies”) with measured GFR (using iothalamate) and NHANES (National Health and Nutrition Examination Survey), 1999 to 2006 on 8254 subjects and validated on 3896 participants (with GFR assessed by iothalamate and other markers). The new formula proved to be more accurate than MDRD, however, a limited number of elderly people and racial and ethnic minorities with measured GFR in the samples is a limitation of CKD-EPI equation It was validated for patients with diabetes and after transplantation [15], therefore we assessed eGFR using this new
formula in the prevalent heart transplant recipients. In our study we found that GFR estimated using CKD-EPI formula was slightly higher than using MDRD. Nevertheless, the incidence of CKD reported here is higher than in some other studies.

In a recent paper, Hamour et al. [11] retrospectively analyzed the renal function for 352 OHT in single center from January 1995 to January 2005 to determine the incidence and risk factors for CKD. In their population the mean GFR (MDRD) was 48 ml/min at year one and 41 ml/min at year 10 after transplantation. They found in multivariable logistic regression model that the risk factors for progressing to KD stage 3 were post-operative renal replacement therapy for acute renal failure; pretransplant diabetes; increasing recipient age; female recipient; female donor, but not CsA regimen (normal versus low dose). However, in the recent paper by Lyster et al. [16], from the same group [11], 39 patients with deteriorating kidney functions after OHT treated by cyclosporine A were switched either to high- or low dose of sirolimus and mycophenolate mofetil. They observed a rapid but partial improvement of kidney function. The concluded that CKD was rapidly but partially reversible following withdrawal of cyclosporine, whereas the same group in the paper published a few months before stated that incidence of CKD was not affected overtime by cyclosporine. However, the mean values of eGFR in our study were higher than in the study of Hamour et al. [11].

**Conclusions**

Concluding, the prevalence of CKD is high in heart transplant recipients. New formula CKD-EPI validated for diabetes and transplantation may be more useful for assessment of eGFR than previously used MDRD or Cockcroft-Gault equations. Evaluation of renal function is important in order to select the appropriate strategy to reduce the cardiovascular risk.

**References:**