Clinical Investigation

The Impact of Donor and Recipient Renal Dysfunction on Cardiac Allograft Survival: Insights Into Reno-Cardiac Interactions

OLGA LAUR, MD,[1,#] MEREDITH A. BRISCO, MD, MSCE,[2,#] ALEXANDER J. KULA, BS,[1] SUSAN J. CHENG, MD,[1] ABEEL A. MANGI, MD,[1] LAVANYA BELLUMKONDA, MD,[1] DANIEL L. JACOBY, MD,[1] STEVEN COCA, DO, MS,[1] W.H. WILSON TANG, MD,[3] CHIRAG R. PARIKH, MD, PhD,[1] AND JEFFREY M. TESTANI, MD, MTR[1]

New Haven, Connecticut, United States; Charleston, South Carolina, United States; Cleveland, Ohio, United States

ABSTRACT

Background: Renal dysfunction (RD) is a potent risk factor for death in patients with cardiovascular disease. This relationship may be causal; experimentally induced RD produces findings such as myocardial necrosis and apoptosis in animals. Cardiac transplantation provides an opportunity to investigate this hypothesis in humans.

Methods and Results: Cardiac transplantations from the United Network for Organ Sharing registry were studied (n = 23,056). RD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. RD was present in 17.9% of donors and 39.4% of recipients. Unlike multiple donor characteristics, such as older age, hypertension, or diabetes, donor RD was not associated with recipient death or retransplantation (age-adjusted hazard ratio [HR] = 1.00, 95% confidence interval [CI] 0.94–1.07, $P = .92$). Moreover, in recipients with RD the highest risk for death or retransplantation occurred immediately posttransplant (0–30 day HR = 1.8, 95% CI 1.54–2.02, $P < .001$) with subsequent attenuation of the risk over time (30–365 day HR = 0.92, 95% CI 0.77–1.09, $P = .33$).

Conclusions: The risk for adverse recipient outcomes associated with RD does not appear to be transferrable from donor to recipient via the cardiac allograft, and the risk associated with recipient RD is greatest immediately following transplant. These observations suggest that the risk for adverse outcomes associated with RD is likely primarily driven by nonmyocardial factors. (*J Cardiac Fail 2016;22:368–375*)

Key Words: Reno-cardiac syndrome, cardio-renal syndrome, renal dysfunction, cardiac transplantation.

Renal dysfunction (RD) is common in patients with cardiovascular disease and is strongly associated with increased morbidity and mortality.[1–7] Notably, this association persists after extensive adjustment for potential confounders raising the possibility of a causal relationship. One potential mechanism by which RD may directly worsen outcomes is via direct myocardial damage.[8–12] Support for this possibility is derived from animal studies in which experimentally induced RD results in pathology such as necrosis, apoptosis, fibrosis, arteriolar thickening, decreased capillary density, and contractile dysfunction.[13–19] Remarkably, some of these findings have also been reported following only brief exposures to RD in the setting of experimental acute kidney injury.[20]

Whether RD can cause direct myocardial damage in humans with enough severity to influence outcomes is unknown and represents a difficult hypothesis to test. In addition to potential direct myocardial effects, the epidemiologic signal for adverse outcomes associated with RD could also be driven

From the [1]Department of Internal Medicine and the Program of Applied Translational Research, Yale University School of Medicine, New Haven, Connecticut, United States; [2]Department of Medicine, Cardiology Division, Medical University of South Carolina, Charleston, South Carolina, United States and [3]Department of Medicine, Cardiovascular Division, Cleveland Clinic Foundation, Cleveland, Ohio, United States.

Manuscript received May 6, 2015; revised manuscript received August 17, 2015; revised manuscript accepted November 12, 2015.

Reprint requests: Jeffrey M. Testani, MD, MTR, Program of Applied Translational Research, Yale University, 60 Temple Street, Suite 6C, New Haven, CT 06510. Tel.: +203 737 6227; Fax: +203 746 8373. E-mail: jeffrey.testani@yale.edu

Funding Sources: NIH Grants, 1K23HL114868, L30HL115790 (JT) and K24DK090203 (CP): The funding source had no role in study design, data collection, analysis, or interpretation.

[#]First Authors: Note: Authors Laur and Brisco contributed equally to this work.

See page 374 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2015.11.009

by nonmyocardial/peripheral factors intrinsic to the RD milieu, which are difficult to measure. These factors could take the shape of systemic myocardial depressant factors' (ie, "uremic toxins") effects on the vasculature and other organs, in addition to unmeasured confounding factors (ie, underutilization of beneficial therapies because of the RD or unmeasured disease severity).

Cardiac transplantation provides an opportunity to begin to investigate the importance of myocardial vs peripheral effects of RD because the heart is being transplanted into and out of the RD environment. When a heart is removed from a donor with RD, the peripheral RD environment will remain with the donor. However, any RD-induced myocardial damage will travel to the recipient with the graft. This is similar to the concept that the myocardial damage induced by a longer graft ischemic time or from advanced donor age results in worsened posttransplant outcomes (despite the rigorous graft selection process that seeks to avoid these exposures); if significant myocardial damage occurs with RD, we would expect to see worse outcomes in transplants from donors with RD.[21] Similarly, transplanting a healthy heart into a recipient with RD would be expected to result in a progressive increase in risk over time as myocardial damage accumulates from the RD. However, if the risk associated with RD is primarily driven by the host's peripheral RD environment (ie, systemic myocardial depressant factors), we would expect to see limited risk from donor RD, but a significant up-front risk associated with transplant of a healthy donor heart into the environment of recipient RD. As such, the primary purpose of this analysis was to evaluate the risk associated with donor RD on posttransplant outcomes and to determine the temporal pattern of risk associated with recipient RD.

Material and Methods

Patient Population

Cardiac transplant donor and recipient data were obtained for adult cardiac transplants between January 2000 and March 2013 (N = 28,513) from the United Network for Organ Sharing (UNOS) database. Patients receiving either heart-lung or heart-kidney transplants and those with missing data on donor and recipient serum creatinine, donor race, or graft outcomes were excluded. For patients who underwent retransplantation (n = 1620), only data on the first transplant were retained. Overall, 23,056 patients met the inclusion criteria (Supplementary Fig. 1).

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[22] Terminal creatinine was used for donor eGFR calculation; serum creatinine at the time of transplant was used for recipient eGFR calculation. Subsequent recipient renal function was evaluated in a subset of patients with follow-up data available (n = 8802). RD was defined as an eGFR < 60 mL/min/1.73 m^2.[23,24] Both donor and recipient groups were additionally stratified into National Kidney Foundation stages of chronic kidney disease severity (GFR ≥ 90 mL/min/1.73 m^2, GFR 60–89 mL/min/1.73 m^2, GFR 30–59 mL/min/1.73 m^2, and GFR <30 mL/min/1.73 m^2 when National Kidney Foundation stages 4 and 5 were combined).[23]

Primary Outcome Definition

The primary focus of this analysis was (1) the association between donor RD and graft failure and (2) the time-dependent nature of the association between recipient RD and graft failure. A secondary analysis focused on the relationship between donor proteinuria and graft failure. Six months after cardiac transplantation and annually thereafter, transplant centers report graft status as functioning or failed to the UNOS registry. Graft failure occurs when the heart is "removed (ie, retransplantation), the recipient dies, or the recipient is placed on a chronic allograft support system (ie, mechanical circulatory support).[25]" The UNOS registry does not require further specification as to which of the 3 components of the graft failure definition is met by a given recipient. As a result, we will refer to the primary outcome captured by the graft failure variable as recipient death or retransplantation, which serves as the primary endpoint of all analyses.

Statistical Analysis

Values reported are mean ± standard deviation or median (quartiles 1–4) for continuous variables, or percentile for categorical variables. Independent Student's *t* test was used to compare continuous variables. The Pearson chi-square test was used to evaluate associations between categorical variables. Correlation coefficients reported are Spearman's rho. Cox proportional hazards models were used to evaluate time-to-event associations between both donor RD and recipient RD with recipient death or retransplantation. Patients were censored if lost to follow-up or alive at the conclusion of the data collection period (March 2013). Given the strong influence of donor age on graft survival and the strong influence of age on calculated eGFR, all models evaluating the association between eGFR and recipient death or retransplantation were adjusted for age unless otherwise specified.[21,26] Covariates for multivariable models included all donor, recipient, and graft-related factors with a univariate association with recipient death or retransplantation at $P < .2$ or a theoretical basis for confounding (donor and graft covariates = gender, diabetes, hypertension, cigarette use, cause of death, cytomegalovirus status, infection, inotrope use, ischemic time, and donor ejection fraction; recipient covariates = eGFR, age, gender, race, body mass index, diabetes, hypertension, cerebrovascular disease, ischemic cardiomyopathy, cigarette use, UNOS status at listing, mechanical ventilation, inotrope, intra-aortic balloon pump, mechanical circulatory support use, recipient cytomegalovirus status, and donor-recipient mismatch in gender). Variables included in the adjusted models with greater than 10% missingness were recipient hypertension (49.7%) and recipient cigarette use (35.8%). To ensure that the multivariable models captured as much risk as possible, these variables were coded using 3 levels (ie, cigarette use yes, no, missing). Kaplan-Meier survival curves were plotted for 4 groups of donor and recipient eGFR (eGFR ≥ 90, eGFR 60–89, eGFR 30–59, and eGFR < 30 mL/min/1.73 m^2). The x-axis was terminated when the number at risk was < 10% and statistical significance was determined using the log-rank test. When evaluating the association between recipient eGFR and recipient death or retransplantation, the magnitude of the effect of RD on recipient death or retransplantation clearly changed over time. As such, we performed a subsequent additional extended adjusted Cox model using 2 Heaviside functions to examine the magnitude of the effect of RD on recipient death or retransplantation at inflection points of changing risk that occurred in the first 30 days and from 30 days to 1 year. For all analyses, a P value of < .05 was considered statistically significant. Statistical analyses were performed using SPSS, version 19 (IBM SPSS