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Reduced global longitudinal strain is associated with increased risk of cardiovascular events or death after kidney transplant☆

Kana Fujikura [a,c,*], Bradley Peltzer [a], Nidhish Tiwari [a,b], Hye Gi Shim [a], Ally B. Dinhofer [a], Sanyog G. Shitole [a], Jorge R. Kizer [a,d], Mario J. Garcia [a]

[a] Division of Cardiology, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210 Street, Bronx, NY 10467, USA
[b] Division of Cardiology, Department of Medicine, Jacobi Medical Center, 1400 Pelham Pkwy S, Bronx, NY 10461, USA
[c] Noninvasive Cardiovascular Imaging Section, Department of Radiology and Cardiovascular Division of the Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
[d] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461, USA

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A B S T R A C T

Background: Patients with chronic kidney disease are at increased risk of cardiovascular disease (CVD). Even after kidney transplant, the rate of CVD events and death remain elevated. Early detection of patients at risk would be helpful for guiding aggressive preventive therapy. The purpose of this study was to evaluate global longitudinal strain (GLS) as a predictor of CVD events and death after kidney transplant.

Method: Among patients with successful kidney transplant between 3/2009 and 12/2012 at our institution, 111 individuals had an echocardiogram within 6 months of the transplant. Medical records were evaluated for demographics and patient characteristics. Echocardiograms were analyzed for conventional measurements, and GLS was assessed using speckle-tracking analysis.

Results: The median age of the study sample was 54 years. Overall, 60% were men; 35% were non-Hispanic black, and 50% Hispanic. After a mean follow-up of 3.8 ± 0.5 years, there were 21 cardiovascular events or deaths. Patients who experienced an event were older, more frequently had a history of coronary artery disease, and had higher LV filling/longitudinal diastolic annular velocity (E/e') than those who did not. GLS was significantly associated with event-free survival even after adjusting for age, sex, race-ethnicity, hypertension, diabetes, history of coronary artery disease or heart failure, and E/e'.

Conclusion: Reduced GLS peri-transplant is significantly associated with increased CVD events or death after kidney transplant. Larger studies are required to determine the incremental predictive value of GLS over clinical and other echocardiographic parameters for adverse CVD events following renal transplantation.

1. Background

Cardiovascular disease (CVD) remains the leading cause of mortality in the United States, accounting for 611,105 deaths in 2013 [1]. Chronic kidney disease (CKD) is a common condition with a prevalence of 15.2% among American adults, and has long been identified as a risk factor for CVD [2]. The prevalence of CVD is 69.6% among patients aged 66 and older who have CKD, compared to 34.7% among without CKD [3]. Moreover, CVD is a significant comorbidity for patients along the entire spectrum of CKD and end-stage renal disease (ESRD) [4].

Successful kidney transplant is associated with improved long-term outcomes in patients with CKD. Over 17,000 kidney transplants were performed in the United States in 2013 [2]. However, even after transplant, CVD remains a leading cause of death [5]. Improved detection of individuals at higher risk for CVD at the time of kidney transplant could allow identification of those who might benefit from closer cardiovascular follow-up and more aggressive preventive therapies.

Left ventricular (LV) strain analysis by speckle-tracking echocardiography (STE) is an increasingly adopted modality for assessment of myocardial function [3],[6],[7],[8]. STE has shown utility in identifying LV dysfunction even in the context of normal LV ejection fraction in such disorders as ischemic heart disease, cardiomyopathies, and cardiotoxicity following chemotherapy, along with various other pathophysiological processes of the heart [9],[10]. STE has also been related to long-term outcomes in patients with amyloidosis, type 2 diabetes mellitus, and heart failure with preserved ejection fraction, as well as in the general population [11],[12],[13, 14]. Recently, STE was

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* Corresponding author at: 75 Francis Street, Boston, MA 02115, USA.
E-mail addresses: kfujikura@bwh.harvard.edu (K. Fujikura), bpeltzer@montefiore.org (B. Peltzer), sanyog.shitole@einstein.yu.edu (S.G. Shitole), jorge.kizer@einstein.yu.edu (J.R. Kizer), mariogar@montefiore.org (M.J. Garcia).

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also linked to cardiovascular mortality in patients with end-stage renal disease [15].

The aim of this study was to examine whether STE global longitudinal strain (GLS), used as a measure of subclinical LV dysfunction, is associated with CVD events or death in patients undergoing kidney transplantation at a large urban health system serving a population predominantly composed of race-ethnic minority groups.

2. Methods

2.1. Study population

After receiving institutional review board approval, we conducted a retrospective cohort study involving adult patients (age 18 or older) undergoing successful kidney transplant between March 2009 and December 2012 at Montefiore Medical Center. The onset of the study period was timed to the installation of an updated clinical echocardiographic data storing system at our institution, which was the beginning of 2009. Patients who completed a clinically indicated echocardiogram within 6 months before or after kidney transplant were evaluated for STE. Demographic and clinical variables were extracted using the hospital's proprietary electronic patient information database (Looking Glass™ Clinical Analytics, Streamline Health, Atlanta, GA) [16]. This database integrates clinical data from all inpatient and outpatient encounters, home care, and community service programs within the Montefiore system. Extractions using Looking Glass™ Clinical Analytics were further verified with manual crosschecking of the data by chart review. Clinical information during the follow-up, including admissions for acute coronary syndromes (ACS) and heart failure (HF), were obtained by query of diagnostic discharge codes (Looking Glass™ Clinical Analytics), supplemented by manual chart review. ACS was defined as unstable angina requiring hospitalization, non-ST elevated myocardial infarction, and ST elevated myocardial infarction. CVD events were defined as a combination of ACS and HF admissions. The primary endpoint was the occurrence of CVD requiring hospitalization or death, ascertained by reviewing all medical charts. Follow-up was extended through December 2015.

2.2. Echocardiographic studies

Echocardiograms performed for clinical indications at MMC were acquired using either Philips iE33 xMATRIX or CX50 xMATRIX (both from Philips Healthcare, Andover, MA). Performance of scans at MMC follow a standardized clinical protocol involving 2D imaging, as well as pulsed wave, continuous wave and color Doppler, in accordance with recommendations of the American Society of Echocardiography [17][18][19]. LV volumes and ejection fraction (EF) were calculated by the biplane Simpson's method. Doppler indices of LV diastolic function, including pulsed-wave Doppler of mitral inflow (E), Doppler tissue imaging (TDI) of the lateral mitral annulus (e'), and E/e' were also obtained from the clinical echocardiogram reports. Echocardiographic cine loops comprising 2 cardiac cycles and stored in Xcelera (Philips Healthcare, Andover, MA) were retrospectively processed to analyze STE using TomTec software (TomTec Imaging Systems Corporation, Unterschleissheim, Germany). STE analysis was performed by an experienced echocardiographer (K.F.) The speckle-tracking analysis was performed using two apical views (apical four-chamber (4ch) and two-chamber (2ch) views), with GLS calculated as their average (Fig. 1) [13]. The endocardial border was traced manually, and the region of interest was adjusted to include the entire myocardium and exclude the pericardium by aligning the epicardial border [20]. The integrity of tracking was visually confirmed as well as ascertained from the credibility of the strain curves. If necessary, the region of interest was readjusted. Patients with echocardiograms of poor quality not allowing satisfactory tracking were excluded from the study. The frame rate of image acquisition was 42.1 ± 6.7 for apical 4-chamber images and 43.5 ± 9.3 for apical 2-chamber images. Intra-observer variability for GLS showed an intraclass correlation coefficient of 0.87, consistent with high reproducibility.

2.3. Definition of covariates

Race-ethnicity was defined by self-report. Hypertension was defined by a blood pressure ≥140/90 mmHg, use of antihypertensive medication, or by documented history. Diabetes was defined by fasting blood glucose of ≥126 mg/dl, HbA1c ≥6.5%, use of anti-hyperglycemic medication, or by documented history. Smoking was defined by current or ever smoking as recorded in the medical history. Family history of premature CAD was defined by first-degree relative with CAD before age 55 years in male and age 65 years in female as reported in the medical history. History of CAD and heart failure was based on documentation in the medical record. Dependence on peritoneal dialysis or hemodialysis was defined by medical history prior to renal transplant. Use of specific medications was based on documentation in the medical record.

2.4. Statistical analysis

Comparison of demographic, clinical and echocardiographic characteristics in those who did and did not experience CVD or death was performed with the chi-square or Fisher's exact test, or with the Wilcoxon rank-sum test, as appropriate. The unadjusted association of GLS with time to CVD event or death was examined by the Kaplan-Meier method. For this analysis, GLS was dichotomized at the previously reported mean value of −20% [21] and differences assessed by the log-rank test. Cox proportional hazards models were used to evaluate the association of GLS with incident CVD or death after adjustment for covariates. An initial model adjusted for demographic factors (age, sex, and race/ethnicity), while a subsequent model adjusted for all covariates related to outcome at $p < 0.20$. Sensitivity analyses evaluated the association of GLS with incident CVD or death in two subgroups: patients who underwent echocardiography pre-transplant, and those in whom echocardiography was obtained within 100 days pre- or post-transplant. A two-tailed $p < 0.05$ was used to define statistical significance. All statistical analyses were performed using SAS version 9.4 (Cary, North Carolina).

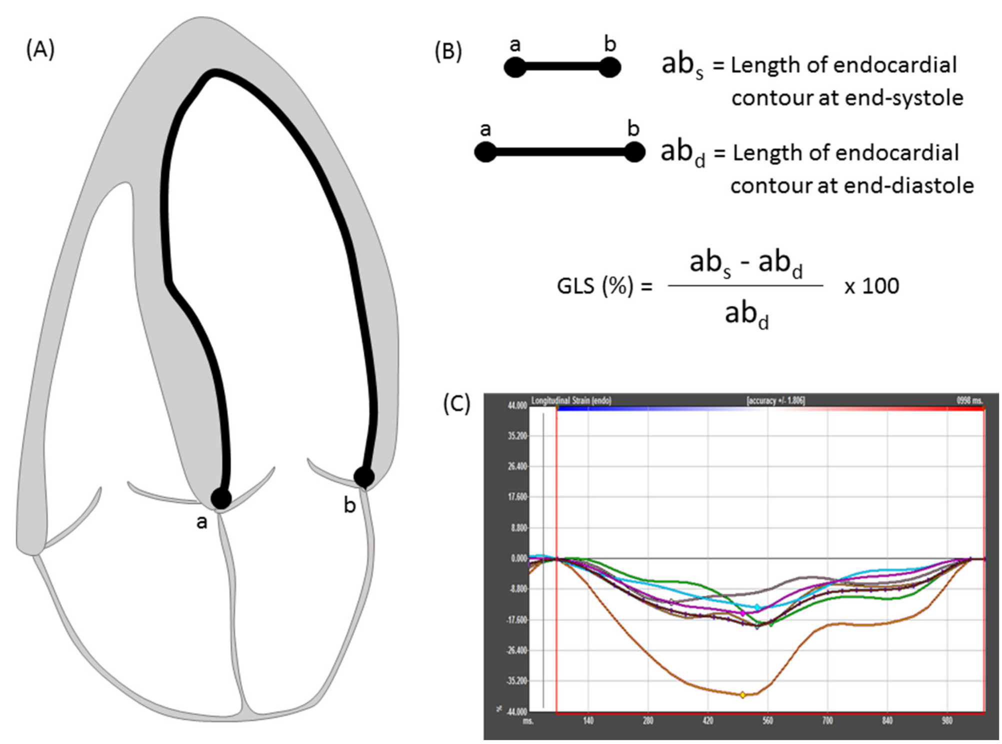

Fig. 1. Strain analysis. (A) Tracing of endocardium for analysis, (B) strain calculation, (C) an example of segmental and average longitudinal strain curve.

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