High Left Ventricular Filling Pressure on Doppler Echocardiography Is Associated With Graft Failure and Overall Mortality Following Kidney Transplantation

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Objective: **Although E/e´ is prognostic of mortality in patients with end-stage renal disease (ESED), little is known about the prognostic implications of E/e´ following kidney transplant (KT). The objective of this study was to evaluate whether an elevated E/e´ is associated with graft function, postoperative hemodialysis, and overall mortality in end-stage renal disease patients following KT.**

Design: **A retrospective observational study.**

Setting: **Tertiary teaching hospital.**

Participants: **In total, 1,045 patients underwent KT at the authors' hospital between January 2006 and December 2013.**

Intervention: **None.**

Measurements and Main Results: **Patients were divided into groups with an E/e´ <15 or ≥ 15, as assessed by preoperative echocardiography (median time from preoperative assessment of echocardiography to surgery: 37 days [IQR: 16-68 days]). Of 1,045 patients, 821 patients (78.6%) had an E/e´ <15, and 224 patients (21.4%) had an E/e´ ≥ 15. Multivariate analysis indicated that age (odds ratio [OR]: 1.03; 95% confidence interval [CI]: 1.01-1.04, p = 0.001), diabetes mellitus (OR: 2.7; CI: 1.94-3.83, p < 0.001), β-blocker (OR: 1.4; CI: 1.03-1.95, p = 0.034), left atrial dimension (OR: 1.07; CI: 1.04-1.11, p < 0.001), and left ventricular mass index (OR: 1.02; CI: 1.01-1.03, p < 0.001) are predictive of E/e´ ≥15. After adjustment using inverse probability of treatment weighting, E/e´ ≥15 also was associated independently with postoperative hemodialysis (OR: 2.0; 95% CI: 1.5–2.6, p < 0.001), graft failure (OR: 1.7; 95% CI: 1.4-2.2; p < 0.001), and overall mortality (hazard ratio [HR]: 3.2; 95% CI: 2.1-4.8, p < 0.001).**

Conclusions: **Preoperative E/e´ is a prognostic indicator of overall mortality in ESRD patients undergoing KT.**

KEY WORDS: *end-stage renal disease, kidney transplantation, left ventricular filling pressure, Doppler echocardiography*

PATIENTS WITH end-stage renal disease (ESRD) are at increased risk of cardiovascular disease.[1,2] Moreover, ESRD patients not only demonstrate left ventricular (LV) systolic dysfunction[3,4] but also LV diastolic dysfunction and increased LV filling pressure, which might be associated independently with mortality.[5–8]

Previous studies have reported the mitral annular velocity on tissue Doppler imaging, which is relatively load independent, can be used to evaluate diastolic dysfunction.[9,10] Early diastolic transmitral flow velocity (E) in combination with early diastolic mitral annular velocity (e')—known as the E/e´—is well correlated with LV filling pressure.[9,11,12] Recent studies have demonstrated that E/e´ >15 is an independent risk factor for morbidity and a major adverse cardiac event following coronary bypass graft surgery.[13,14] It also has been shown that elevated E/e´ can predict cardiovascular events, morbidity, and mortality in ESRD patients.[5,8]

Of note, ESRD patients with an elevated E/e´ seem to have increased incidences of diabetes, atherosclerotic vascular disease, and inflammation and lower residual kidney function.[5] Moreover, the loss of residual kidney function is associated independently with an elevated E/e´.[5] These findings suggest that elevated E/e´ may have influence on postoperative kidney function following kidney transplant (KT) in ESRD patients. However, little is known about the relationship between E/e´ and prognosis following KT in ESRD patients. Therefore, the aim of this study was to determine whether an elevated E/e´ was associated with graft function and postoperative hemodialysis following KT in ESRD patients. Furthermore, the authors assessed the association between E/e´ and overall mortality following KT.

METHODS

Study Population

This retrospective study evaluated all patients who underwent KT between January 2006 and December 2013 at the authors' institution. In total, 1,348 patients who underwent KT initially were included in the study population. Of these 1,348 patients, 303 patients were excluded, including 9 patients who were <18 years old, 135 patients with missing data on the E/e′, 19 patients with valvular heart disease, and 140 patients who underwent cadaveric KT. The study protocol was approved by the institutional review board of Asan Medical Center (IRB approval number: 2012-0114).

Patients

All patients were prepared according to the authors' institution's standard protocol. No premedications were administered, and cardiovascular and antihypertensive medications were continued until the day of surgery except angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker (ACEI/ARB).[15] Anesthesia was induced using thiopental (4-5 mg/kg), remifentanil (0.5-1 μg/kg), and atracurium (0.6 mg/kg), or esmeron (0.6 mg/kg) followed by inhaling isoflurane (2%-3%) or desflurane (6%-7%) in oxygen through a facemask, and then, endotracheal intubation was performed. Anesthesia was maintained with isoflurane (1%-2%) or desflurane (5%-7%) in

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50% oxygen with nitrous oxide. Anesthesia monitoring included invasive blood pressure, central venous pressure, pulse oximetry, electrocardiography, end-tidal carbon dioxide, and cardiac output and stroke volume variation (EV 1,000 [Edwards Lifesciences, Irvine, CA]) using a multiparameter monitor (Datex-Ohmeda S/5™, S/5 Collect, Datex-Ohmeda, Helsinki, Finland), which were recorded simultaneously throughout the entire procedure. Fluid and volume management were performed using Plasmalyte solution (Plasma Solution A Inj., CJ Pharma, Seoul, Korea) and 20% albumin (0.25-0.5 kg/mL), and 10 mmHg central venous pressure and stroke volume variation <10 were considered targets. To promote diuresis, 0.5 g/kg of mannitol and 40 mg of furosemide were administered during the vascular anastomosis phase. Inotropic or vasopressor drugs were infused when blood pressure fell by more than 20% from baseline.

Clinical and Echocardiographic Data

The computerized patient record system of the authors' institution (Asan Medical Center Information System Electrical Medical Records) was reviewed retrospectively to obtain baseline characteristics and laboratory, surgical, and anesthetic data and postoperative outcomes on all patients. Patient demographic data included patient age, sex, weight, height, body mass index, smoking history, comorbidities (eg, hypertension, diabetes mellitus, coronary artery disease, chronic renal failure duration, dialysis duration, cerebrovascular accident, hypercholesterolemia), and the use of prescription medications (eg, calcium channel blocker, ACEI/ARB, β-blocker, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor). Preoperative transthoracic echocardiography was performed to assess cardiac morphology and function using a Hewlett-Packard Sonos 2500 or 5500 imaging system (Andover, MA). All echocardiograms were performed on an inter-dialytic day when the patient was likely to be euvolemic.

Clinical parameters were measured using comprehensive 2-dimensional and Doppler echocardiography, including Doppler tissue imaging, diameter of the left atrium, end-diastolic volume, end-systolic volume, LV ejection fraction (LVEF), peak systolic right ventricular-to-right atrial pressure gradient (PG sys RV-RA), and LV mass index (LVMI). LVMI was calculated by dividing the LVM by the patient's body surface area. Diastolic function was assessed using the E/A ratio where E is the early maximum ventricular filling velocity, and A is the late diastolic or atrial velocity measured using pulsed-Doppler echocardiography. The Doppler image-derived mitral annular systolic peak S-wave velocity (DTI S′) and early diastolic mitral annular velocity (e′) were determined on the septal side of the mitral annulus on apical 4-chamber view. The right ventricular-to-right atrial peak systolic pressure gradient was estimated from the tricuspid regurgitation velocity. The authors divided patients into 2 groups and used an E/e′ of 15 as the cutoff value because E/e′ >15 generally is considered indicative of an increase in LV filling pressure.[9,16]

Clinical Outcomes

Associations between clinical, laboratory, surgical, and anesthesia data and an E/e′ ≥ 15 were assessed, as were the associations between graft failure, postoperative hemodialysis, and overall mortality.

Statistical Analysis

Continuous variables are reported as the mean ± SD or median and interquartile range. Categorical variables are expressed as frequencies and percentages and were analyzed using the χ^2 test or Fisher exact test as appropriate. Multiple logistic regression analysis was performed to identify independent predictors of E/e′ ≥ 15. All variables with $p < 0.1$ according to the univariate analysis were included in the multivariate analysis. Multivariate Cox proportional hazard regression analysis was used to assess the adjusted hazard ratios (HRs) of the relationship between E/e′ and outcome variables. The adjusted variables included the preoperative variables shown in Table 1 (except DTI S′ [n = 755] and PG sys [RV-RA] [n = 871] due to insufficient data) and all intraoperative variables in Table 2. Weighted logistic regression and Cox proportional hazards regression models were used to reduce the influence of possible confounding variables on the association between E/e′ and mortality, after adjusting for major differences between patients with an E/e′ ≥ 15 or <15 using the inverse probability of treatment weighting (IPTW) method.[17] IPTW uses propensity scoring to manage confounders and estimate the possibility of discrete exposure according to the detected and time-dependent covariates. The weights of patients with E/e′ ≥ 15 were the inverse of 1 propensity score, and the weights for patients without E/e′ ≥ 15 were the inverse of the propensity scores. All propensity scores for IPTW matching were estimated for all the variables shown in Tables 1 and 2 without regard to outcomes, and multiple logistic regression analysis was used to obtain the odds ratio (OR) or hazard ratio (HR) as appropriate. As a result, it was essential to have as many independent variables as possible to correct the authors' results. C-statistics were used to judge the models, and calibration was assessed using Hosmer–Lemeshow statistics. Cumulative survival rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test.

RESULTS

The median follow-up duration for the general patient population was 3.4 years (interquartile range: 1.7-5.5 years). Of 1,045 patients, 821 patients (78.6%) had an E/e´ <15 (10.1 ± 2.3), and 224 patients (21.4%) had an E/e´ ≥ 15 (18.6 ± 4.0). Patients with an E/e′ ≥ 15 were older and had higher BMI and lower albumin and sodium levels. Moreover, patients with E/e′ ≥ 15 demonstrated higher incidences of diabetes, hypertension, coronary artery disease, cerebrovascular accident, and use of β-blockers and calcium channel blockers than patients with an E/e′ <15. The preoperative echocardiographic findings showed that patients with an E/e′ ≥ 15 had a larger left atrium, end-systolic volume, end-diastolic volume, LVMI, and PG sys RV-RA but smaller DTIS′ and LVEF values than patients with an E/e′ <15 (Table 1). The demographic and preoperative data of the kidney donors are presented in Supplementary Table S1. The intraoperative data showed that patients with an E/e′ ≥ 15 required more inotropic