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Long-term prognostic value of invasive and non-invasive measures early after heart transplantation

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ABSTRACT

Background: Invasively assessed coronary microvascular resistance early after heart transplantation predicts worse long-term outcome; however, little is known about the relationship between microvascular resistance, left ventricular function and outcomes in this setting.

Methods: A total of 100 cardiac transplant recipients had fractional flow reserve (FFR) and the index of microcirculatory resistance (IMR) measured in the left anterior descending artery and echocardiographic assessment of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) at 1 year after heart transplantation. The primary endpoint was the composite of death and retransplantation occurring beyond the first post-operative year.

Results: The mean FFR, IMR, LVEF, and GLS values at 1 year were 0.87 ± 0.06, 21.3 ± 17.3, 60.4 ± 5.4%, and 14.2 ± 2.4%, respectively. FFR and IMR had no significant correlation with LVEF and GLS. During a mean follow-up of 6.7 ± 4.2 years, the primary endpoint occurred in 24 patients (24.0%). By ROC curve analysis, IMR = 19.3 and GLS = 13.3% were the best cutoff values for predicting death or retransplantation. Cumulative event-free survival was significantly lower in patients with higher IMR (log-rank $p = 0.02$) and lower GLS (log-rank $p < 0.001$). Cumulative event-free survival can be further stratified by the combination of IMR and GLS (long-rank $p < 0.001$). By multivariable Cox proportional hazards model, higher IMR and lower GLS were independently associated with long-term death or retransplantation (elevated IMR, hazard ratio = 2.50, $p = 0.04$ and reduced GLS, hazard ratio = 3.79, $p = 0.003$, respectively).

Conclusion: Invasively assessed IMR does not correlate with GLS at 1 year after heart transplantation. IMR and GLS determined at 1 year may be used as independent predictors of late death or retransplantation.

Heart transplantation (HT) continues to be an important treatment option in patients with end stage heart failure. With careful recipient/donor selection, advances in immunosuppression, and prevention/treatment of opportunistic infections, early survival after HT is improving [1,2]. Still, the major gains in survival have been largely limited to the first 6 to 12 months after HT [2], and long-term (>1 year) management of patients after HT remains challenging, given the difficulty in identifying patients at high risk of long-term complications.

The index of microcirculatory resistance (IMR) is a coronary wire-based, quantitative measure of coronary microvascular resistance [3] that is obtained in the cardiac catheterization laboratory at the time of routine coronary angiography after HT. In a recent study by Yang et al., higher IMR measured at 1 year after HT was shown to predict worse long-term outcomes, suggesting it might serve as a useful stratification tool [4]. At the same time, echocardiography is routinely performed to monitor left ventricular function after HT. An especially sensitive measure of left ventricular function, global longitudinal strain (GLS), is recommended for diagnosing subclinical allograft dysfunction [5] and has been shown to predict short-term outcomes (during the first year) when assessed at 1–3 weeks after HT [6].

To date, the relationship between coronary microvascular resistance and GLS after HT has not been well investigated; moreover, whether IMR and GLS have incremental long-term prognostic value is not known. Accordingly, the primary objective of this study was to investigate the relationship between incremental prognostic value of invasive coronary microvascular function as assessed by IMR, and the non-invasive echocardiographic measure, GLS, at 1 year after HT.

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1. Methods

1.1. Study design and patient population

This study is a retrospective post-hoc analysis of patients who underwent successful HT at Stanford University Medical Center between 2000 and 2014, and who had invasive coronary physiologic assessment and echocardiographic assessment at 1 year after HT. Patients were originally enrolled in two consecutive prospective studies. The aim of the first study was to evaluate the role of cytomegalovirus in the development of cardiac allograft vasculopathy (PO1-AI50153) [7]. The second study evaluated the role of the angiotensin-converting enzyme inhibitor ramipril in the development of cardiac allograft vasculopathy (5R01HL093475-05; ClinicalTrials.gov number NCT01078363) [8]. In patients who underwent HT and survived at least 1 year, coronary angiography and coronary physiologic assessment of the left anterior descending coronary artery were performed. Echocardiographic assessment was performed in a similar time frame.

Patients were excluded if they had a concomitant solid organ transplant at the time of HT or if invasive coronary physiologic data or echocardiographic images were not available. Both prospective studies were approved by the Stanford University Institutional Review Board and informed consent was obtained from each participant.

A total of 100 patients who had both invasive coronary physiologic assessment and echocardiographic assessment at 1 year after HT were identified and enrolled in this study. Of these, 64 patients were recruited from a previous study [4] and 36 patients were added for the present study. Ten patients originally included in the previous study were excluded due to the unavailability of 1 year echocardiographic data at our institution.

1.2. Immunosuppressive regimen

All patients received standard immunosuppressive therapy, including induction therapy with daclizumab, an anti-interluekin-2 monoclonal antibody, OKT3, or antithymocyte globulin. Corticosteroid therapy was initiated postoperatively and tapered progressively over the first 8 months after transplantation in the absence of rejection. A calcineurin inhibitor (tacrolimus or cyclosporine) and cell-cycle inhibitor (mycophenolate mofetil or azathioprine) were used for maintenance therapy, and a proliferation signal inhibitor (everolimus or sirolimus) was used according to the clinical status. Cytomegalovirus prophylaxis was used in those with seropositive donor or recipient status with ganciclovir or valganciclovir [4]. Patients were monitored for acute cellular rejection using right ventricular endomyocardial biopsies at scheduled intervals post-transplant: weekly during the first month, biweekly until the third month, monthly until the sixth month, and then at 9 and 12 months. Biopsy results were graded according to the International Society for Heart and Lung Transplantation (ISHLT) revised grading scale [9] and significant acute cellular rejection was defined as one or more episode(s) of a grade ≥2R during the first year post-transplant [10].

1.3. Coronary physiologic assessment

FFR, coronary flow reserve (CFR), and IMR were measured in the left anterior descending artery by methods previously described [3,11]. Prior to wire advancement, intracoronary nitroglycerin (200 mcg) was administered. Following calibration, a 0.014 inch pressure-temperature sensor guidewire (PressureWire™ Certus™, St. Jude Medical, St. Paul, Minnesota) was equalized to the guide catheter pressure with the sensor positioned at the ostium of the left coronary artery. The PressureWire was then advanced to the distal two-thirds of the left anterior descending artery. With commercially available software (Radi Analyzer®; St. Jude Medical, St. Paul, Minnesota), the shaft of the PressureWire can act as a proximal thermistor by detecting changes in temperature-dependent electrical resistance. The sensor near the tip of the wire simultaneously measures pressure and temperature, and can thereby act as a distal thermistor. The transit time of room-temperature saline injected down a coronary artery is then determined with a thermodilution technique. The inverse value of the mean transit time (T_{mn}) correlates with coronary blood flow. During intravenous infusion of adenosine (140 μg/kg/min) administered to induce a steady state of maximal hyperemia, 3 intracoronary injections of 3 mL of room-temperature saline were performed and the hyperemic T_{mn} was calculated. Simultaneous measurement of mean proximal coronary pressure (P_a, by guide catheter) and mean distal coronary pressure (P_d, by PressureWire) were also acquired during maximal hyperemia. FFR was calculated as the ratio of P_d/P_a at hyperemia. CFR was calculated as resting T_{mn} divided by hyperemic T_{mn}. IMR was calculated as P_d at hyperemia multiplied by hyperemic T_{mn}.

1.4. Echocardiographic assessment

All echocardiographic studies were performed using commercially available ultrasound systems (Sonos 7500, iE33, and EPIQ 7C; Philips Medical Imaging, Eindhoven, the Netherlands). Standard measurements of ventricular wall thickness and dimensions as well as ejection fraction were performed according to the guidelines of the ASE recommendations [12]. Left ventricular ejection fraction (LVEF) was obtained using the biplane Simpson method. GLS was measured with the previously validated software-independent methodology, which uses Lagrangian strain of the average values of longitudinal strain obtained from the apical 4-, 3-, and 2-chamber views. We measured myocardial length in end-diastole (L_0) and in end-systole (L_1) and calculated strain values as $100 \times (L_1 - L_0) / L_0$ [13]. GLS is usually expressed using negative numbers, as longitudinal shortening leads to a smaller segment length in systole compared with baseline; however, to avoid any confusion induced by the 'minus' sign and the cut-off values, we presented GLS as an absolute value. All echocardiographic analyses were done blinded to patient characteristics, outcomes, and invasive coronary physiologic data. To assess intra- and interobserver variability, LVEF and GLS from 20 randomly selected patients were re-analyzed by the same investigator and the second investigator at least 2 weeks later who was blinded to the initial measurements.

1.5. Primary endpoint and objectives

The primary endpoint of this study was the composite of all-cause death and retransplantation occurring beyond the first post-operative year.

The primary objective of this study was to compare the primary endpoint according to high or low IMR or GLS according to the cutoff values from receiver operating characteristics (ROC) curve analysis. The primary endpoint was further compared to the combination of the IMR and GLS groups. The above analyses were repeated using the previously published cutoff values of IMR = 20.0 and GLS = 14.0% [4,14]. Secondary objectives included: 1) correlation model between physiologic and echocardiographic parameters; 2) comparisons of physiologic and echocardiographic parameters between patients with and without the primary endpoint; and 3) univariable and multivariable Cox proportional hazards model to explore predictors of the primary endpoint.

1.6. Statistical analysis

Continuous variables are presented as means with standard deviations and categorical variables are presented as counts and percentages. Normality of the continuous variables was confirmed with Shapiro-Wilk test. Depending on the result of Levene test for homoscedasticity, variables with normal distribution were compared with Student *t*-test or Welch *t*-test. If the normality test failed, variables were compared with Mann-Whitney *U* test. Pearson's χ^2 test or Fisher's exact test was used for comparisons of categorical variables, as appropriate. The reproducibility of LVEF and GLS were evaluated using intraclass correlation. Correlations between parameters were tested with Spearman's correlation coefficient (Spearman's rho). Kaplan-Meier curves are shown for the time-to-event distributions of endpoints (a composite of death or retransplantation) in each group. Patients were censored when lost to follow-up. Univariable Cox proportional hazards models were run to identify univariable predictors of death or retransplantation, including donor/recipient characteristics, coronary physiology, and echocardiographic parameters. Variables with $p < 0.10$ in the univariable Cox proportional hazards model were entered into the multivariable Cox proportional hazards model with forward selection to determine independent predictors of death or retransplantation. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS® version 21.

2. Results

A total of 100 patients who had both invasive coronary physiologic assessment and echocardiographic assessment at 1 year after HT were enrolled in this study. Overall, the recipient mean age was 51 ± 11 years with 74% male sex. The donor mean age was 34 ± 13 years with 67% male sex. Recipient-donor sex mismatch, blood type mismatch, and cytomegalovirus immunoglobulin G mismatch were found in 31%, 16%, and 27% of patients, respectively (Table 1). During a mean follow-up of 6.7 ± 4.2 years (median 5.6 years (interquartile range: 3.5–10.8)) after the first year coronary physiologic and echocardiographic assessment (mean 7.7 years after HT), a composite endpoint of death or retransplantation occurred in 24 patients (23 deaths and 1 retransplantation).

Mean FFR, CFR, and IMR values obtained at 1 year after HT were 0.87 ± 0.06, 3.8 ± 1.8 and 21.3 ± 17.3 (median IMR 16.2 (interquartile range: 12.7–23.5)), respectively. Mean LVEF and GLS values obtained at 1 year after HT were 60.4 ± 5.4% and 14.2 ± 2.4%, respectively (Table 2). Distributions of FFR, IMR, LVEF, and GLS are shown in Supplemental Fig. 1. The intraobserver variability of LVEF using the intraclass correlation analysis was 0.88 (95% confidence interval: 0.73 to 0.95, $p < 0.001$). The intraobserver variability of GLS using the intraclass correlation analysis was 0.97 (0.93 to 0.99, $p < 0.001$). The interobserver variability of LVEF using the intraclass correlation analysis was 0.88 (0.73 to 0.95, $p < 0.001$). The interobserver variability of GLS using the intraclass correlation analysis was 0.88 (0.60 to 0.96, $p < 0.001$). GLS value was not correlated with the date of 1 year follow-up when the date was used as a continuous variable (Spearman's rho = −0.06, $p = 0.53$).

FFR and IMR had no significant correlation (Spearman's rho = 0.12, $p = 0.21$), whereas LVEF and GLS had a significant positive correlation (Spearman's rho = 0.57, $p < 0.001$). As shown in Fig. 1, 79% of patients had normal LVEF (>55%) but reduced GLS (<18%), when cutoff values