conducted adjusting for clinically relevant variables (p value <0.10 on univariate analysis). A C-statistic was used to compute the predictive power of abnormal WM and MP in predicting EFS. Statistical analyses were carried out with SAS Software version 9.3 (SAS Institute, Cary, North Carolina).

Patients were followed for a median of 39 months (range 4 to 112 months). Forty-seven (10%) patients experienced an event (death in 24, myocardial infarction in 8, and heart failure hospitalization in 15). Three-year EFS following a negative RTMCE was 98% (95% confidence interval: 96% to 99%). Revascularizations (coronary bypass grafting or percutaneous intervention) were performed in 10 patients with abnormal studies prior to transplantation. There was no difference in the number of abnormal MP or WM segments for those that underwent revascularization versus those that did not undergo revascularization ($p = 0.67$ for MP, $p = 0.26$ for WM).

Patients with abnormal stress MP and grade II/III diastolic dysfunction were at a 5-fold higher risk of an event (hazard ratio: 5.1; 95% confidence interval: 1.8 to 14.6). EFS in patients with inducible MP or WM abnormalities that were not revascularized was significantly worse ($p < 0.005$; C-index 0.93 for both WM and MP). The extent of the MP defect (<2 segments, ≥2 segments) was also predictive of events ($p = 0.02$), while this same cutoff for abnormal WM was not as predictive ($p = 0.06$). In the multivariate backward-selected model, only older age ($p = 0.023$) and diabetes mellitus ($p = 0.0033$) were associated with higher risk of a major adverse cardiovascular event, along with a longer time interval between stress RTMCE and RT (HR: 1.02 for each month increase; $p = 0.046$) (Table 1).

This study demonstrates that MP analysis with RTMCE during demand stress echocardiography is helpful in identifying higher-risk ESRD patients. Patients who are not revascularized after an abnormal study are at significant risk for complications, especially if concomitant grade II/III diastolic dysfunction exists. Because revascularization decision making was based on angiographic obstruction within the abnormal RTMCE territory, this would indicate that abnormal RTMCE in the absence of a significant angiographic abnormality identifies high-risk patients with microvascular disease. Although this study was a single-center study and RTMCE requires expertise, the current study emphasizes the importance of microvascular and WM abnormalities during demand stress in predicting cardiovascular outcomes following RT.

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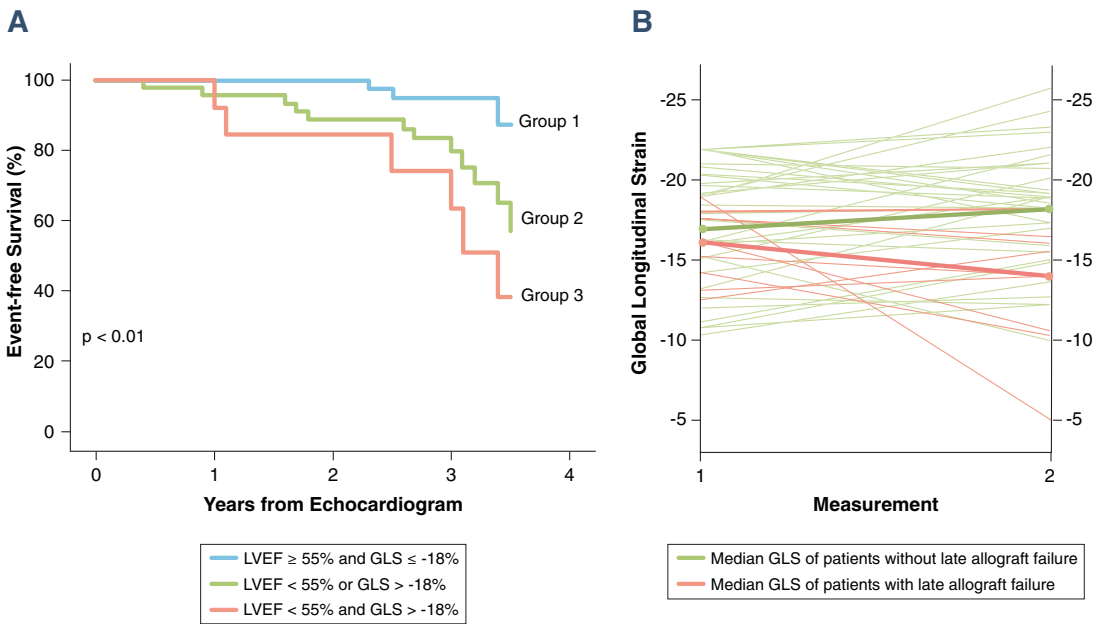
Diminished Global Longitudinal Strain Predicts Late Allograft Failure in Pediatric Heart Transplant Recipients

Noninvasive measures to assess allograft status and prognosis in children post-heart transplantation (HT) have long been an area of investigation (1), yet robust markers of allograft dysfunction remain elusive. Recent adult guidelines recommend the serial evaluation of global longitudinal strain (GLS) in HT recipients to detect subclinical left allograft dysfunction (2). We hypothesized that abnormal GLS obtained by speckle-tracking echocardiography would predict late allograft failure in pediatric HT recipients.

We prospectively-recruited 104 pediatric HT patients to undergo speckle-tracking echocardiography prior to surveillance cardiac catheterization and endomyocardial biopsy. Standard 2-dimensional echocardiograms were performed using a GE Vivid

FIGURE 1 Prognostic Value of GLS in Pediatric Heart Transplantation Patients



(A) Kaplan-Meier curve for outcome of late allograft failure. **(B)** Deterioration in global longitudinal strain (GLS) during follow-up was associated with allograft failure. LVEF = left ventricular ejection fraction.

E9 or E7 ultrasound system (GE Healthcare, Waukesha, Wisconsin). Longitudinal strain of the left ventricle was assessed using apical 4-, 3-, and 2-chamber images, and offline analysis of digitally stored images was performed using EchoPAC software version 110.0.2 (GE Healthcare). The primary study endpoint was allograft failure, defined as cardiac death, hospice enrollment, or listing for repeat HT. Patients with evidence of rejection (greater than or equal to grade 2R) on histologic review of the enrollment biopsy specimen were excluded, as GLS can be reduced during episodes of acute rejection (3), and due to the potential of acute rejection to introduce error as both a cause of death and as a mediator of allograft failure. Cox multivariable regression models were created using: 1) continuous echocardiographic measures; and 2) data-driven threshold values to potentially provide improved clinical utility to the measures. Interobserver variability of GLS was excellent (intraclass correlation coefficient 0.94, n = 20 studies).

Median age at enrollment was 10.5 years (interquartile range [IQR]: 6.0 to 16.2 years) and median duration of follow-up was 3 years (IQR: 2.5 to 3.4 years). Median age at transplant was 3.2 years (IQR: 0.8 to 11.1 years), and median allograft age at the time of the echocardiogram was 3.3 years (IQR: 0.9 to 7.1 years). Twenty-one (20%) patients developed allograft failure at a median follow-up of 2.6 years (IQR: 1.7 to 3.2 years) post-echocardiogram. Factors associated with allograft failure by univariable analysis included older age at transplant, higher mean pulmonary capillary wedge pressure, cardiac allograft vasculopathy, lower left ventricular ejection fraction (LVEF), higher mitral early diastolic velocity (E)/late diastolic velocity (A) ratio, larger left atrial volume, and reduced GLS and GLS rate. By multivariable analysis using continuous echocardiographic measures, reduced GLS (hazard ratio [HR]: 1.2 per 1% increase; 95% confidence interval [CI]: 1.02 to 1.40; p = 0.02), larger left atrial volume (HR: 1.6 per 10 ml/m^2 increase; 95% CI: 1.1 to 2.3; p = 0.02), and cardiac allograft vasculopathy (HR: 3.6; 95% CI: 1.4 to 9.4; p < 0.01) remained independent predictors of allograft failure.

Using accepted normal values, LVEF was transformed into a categorical variable. To identify a clinically useful threshold value for GLS, analysis by quartiles supplemented by a receiver operating curve analysis were performed. A GLS of -18% or higher (less negative) had a sensitivity of 91% and specificity of 55% for allograft failure, with an area under the curve of 0.710 (p < 0.01). The categorical variables

LVEF and GLS were then combined to create an additional nested variable, consisting of 3 subgroups: group 1 (reference group) had normal LVEF and better strain, group 2 had either lower LVEF or worse strain, and group 3 had both lower LVEF and worse strain (**Figure 1**). Factors independently associated with allograft failure were EF <55% or GLS >-18% (HR: 4.0; 95% CI: 1.1 to 14.4; p = 0.03), or presence of both EF <55% and GLS >-18% (HR: 6.7; 95% CI: 1.6 to 27.3; p < 0.01). Among 44 patients with at least 2 echocardiograms (median elapsed time between studies 249 days [IQR: 165 to 347 days]), 10 of whom developed allograft failure at a median of 1.9 years (IQR: 1.6 to 2.6 years), worsening GLS between examinations predicted allograft failure (HR: 1.1 per 1% increase; 95% CI: 1.02 to 1.30; p = 0.03, secondary univariable analysis (**Figure 1**).

This study shows that reduced baseline GLS and worsening GLS at follow-up provides important prognostic information in pediatric HT patients and may enhance the identification of high-risk HT patients, independent of and incremental to LVEF. The small number of outcomes limits the strength of the analysis, but our results support the integration of GLS into surveillance protocols following pediatric HT.

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Female Athlete's Heart: Appropriate Scaling to Body Size May Resolve Diagnostic Conundrums

I read with great interest the study by Finocchiaro et al. (1), which evaluated left ventricular (LV) geometry in a considerable number of athletes with a particular focus on adaptations to different types of exercise (static, mixed, dynamic) in female athletes versus male athletes. The investigators observed a normal LV geometry in most of the athletes, but particularly among subgroups that performed dynamic exercise, a significantly higher proportion of female athletes exhibited eccentric hypertrophy, whereas male athletes predominantly developed concentric adaptations. The investigators concluded that a pattern of concentric hypertrophy in female athletes who perform dynamic sports represents a rare finding that may raise the suspicion of underlying pathologies in single cases.

In recent years, both scientific and clinical interest in imaging of athlete hearts has increasingly shifted toward the implementation of modern techniques, such as cardiac magnetic resonance or novel echocardiography techniques, into the diagnostic pathways of pre-participation screening (2). In light of this ongoing development, the study by Finocchiaro et al. (1) virtually represents a step backward to a more traditional approach. However, it should be emphasized that we have already accumulated a wealth of data on classic echocardiographic parameters in female athletes. For example, as acknowledged in the discussion, Pelliccia et al. (3) evaluated 600 female athletes in a single study compared with only 439 female athletes in the current study. Considering this, the most important novel aspect of the current study is the calculation of LV geometry by using the combination of relative wall thickness (WT) and left ventricular mass (LVM).

Interestingly, female athletes demonstrated lower LV end-diastolic diameters (LVEDDs) in absolute terms, but when correcting for body surface area (BSA), dimensions turned out to be higher compared with their male counterparts. Recognizing this, the