Published in final edited form as:

J Magn Reson Imaging. 2019 March ; 49(3): 678–687. doi:10.1002/jmri.26275.

Cardiac Structure-Function MRI in Patients After Heart Transplantation

Ryan S. Dolan, MD¹, Amir A. Rahsepar, MD¹, Julie Blaisdell, MS¹, Kai Lin, MD¹, Kenichiro Suwa, MD¹, Kambiz Ghafourian, MD, MPH², Jane E. Wilcox, MD, MSc², Sadiya S. Khan, MD, MSc², Esther E. Vorovich, MD², Jonathan D. Rich, MD², Allen S. Anderson, MD², Clyde W. Yancy, MD², Jeremy D. Collins, MD¹, Michael Markl, PhD^{1,3,*}, James C. Carr, MD¹

¹Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA;

²Department of Cardiology, Northwestern University, Chicago, Illinois, USA;

³Department of Biomedical Engineering, McCormick School of Engineering, Northwestern University, Evanston, Illinois, USA

Abstract

Background: Following heart transplantation (Tx), recipients are closely monitored using endomyocardial biopsy, which is limited by cost and invasiveness, and echocardiography, which is limited regarding detailed structural and functional evaluation.

Purpose: To test the feasibility of comprehensive structure-function cardiac MRI as a noninvasive modality to assess changes in myocardial structure and function.

Study Type: Prospective.

Subjects: MR was performed in 61 heart transplant recipients (age 47.9 ± 16.3 years, 39% female) and 14 age-matched healthy controls (age 47.7 ± 16.7 years, 36% female).

Field Strength/Sequence: 1.5T; 2D CINE steady state free precession (SSFP) imaging, T₂-mapping, pre- and postgadolinium contrast T₁-mapping, and tissue-phase mapping (TPM).

Assessment: Quantification of myocardial T₂ (as a measure of edema), pre- and post-Gd T₁ (allowing calculation of extracellular volume (ECV) to estimate interstitial expansion), and TPM-based assessment of peak regional left ventricular (LV) velocities, dyssynchrony, and twist.

Statistical Tests: Comparisons between transplant recipients and controls were performed using independent samples *t*-tests. Relationships between structural (T₂, T₁, ECV) and functional measures (myocardial velocities, dyssynchrony, twist) were assessed using Pearson correlation analysis.

Results: T₂ and T₁ were significantly elevated in transplant recipients compared to controls (global T₂: 50.5 ± 3.4 msec vs. 45.2 ± 2.3 msec, $P < 0.01$; global T₁: 1037.8 ± 48.0 msec vs. 993.8 ± 34.1 msec, $P < 0.01$). Systolic longitudinal function was impaired in transplant recipients

*Address reprint requests to: M.M., Department of Radiology, Northwestern University, 737 N. Michigan Ave., Ste. 1600, Chicago, IL 60611. mmarkl@northwestern.edu.

compared to controls (reduced peak systolic longitudinal velocities, 2.9 ± 1.1 cm/s vs. 5.1 ± 1.2 cm/s, $P < 0.01$; elevated systolic longitudinal dyssynchrony, 60.2 ± 30.2 msec vs. 32.1 ± 25.1 msec, $P < 0.01$). Correlation analysis revealed a significant positive relationship between T_2 and ECV ($r = 0.45, P < 0.01$). In addition, peak systolic longitudinal velocities demonstrated a significant inverse relationship with T_2 (global $r = -0.29, P = 0.02$), and systolic radial dyssynchrony was positively associated with peak T_2 and peak T_1 ($r = 0.26, P = 0.04$; $r = 0.27, P = 0.03$).

Data Conclusion: MR techniques are sensitive to structural and functional differences in transplant recipients compared to controls. Structural (T_2, T_1) and functional (peak myocardial velocities, dyssynchrony) measures were significantly associated, suggesting a structure-function relationship of cardiac abnormalities following heart transplant.

Following heart transplantation (Tx), recipients are closely monitored with endomyocardial biopsy,¹ which is limited by cost and invasiveness,²⁻⁴ and echocardiography, which has shown mixed results in the detection of subtle structural and functional changes.^{5,6} Magnetic resonance imaging (MRI) has promise as an alternative noninvasive imaging modality due to its capability to quantify regional changes in left ventricular (LV) structure and function. In addition to standard LV functional measures, such as ejection fraction (EF), by 2D CINE steady state free precession (SSFP) imaging,⁷ MR can assess regional LV changes. Edema, fibrosis, and interstitial expansion can be evaluated using T_2 -mapping and pre- and postgadolinium (Gd) contrast T_1 -mapping (to quantify extracellular volume [ECV] fraction).⁸⁻¹⁰ Regional LV functional changes, such as myocardial velocities, dyssynchrony, and twist, can be evaluated using tissue phase mapping (TPM).^{11,12}

In heart transplant recipients, the majority of research has focused on detection of acute cardiac allograft rejection (ACAR) and cardiac allograft vasculopathy (CAV). Studies have demonstrated increased T_2 during episodes of ACAR¹³⁻¹⁶ and increased ECV and decreased diastolic strain rate^{17,18} in patients with CAV, but few studies have evaluated transplanted hearts in general to determine how they differ from healthy controls.^{11,13} Two studies have incorporated both structural and functional measures from multiparametric MR to examine the relationship between change in myocardial structural and function. A previous study found significant inverse relationships between elevated T_2 and longitudinal peak velocities,¹³ suggestive of a structure-function relationship. Similarly, Miller et al found associations between T_1 and circumferential strain, T_2 and circumferential strain, and T_2 and peak systolic circumferential strain rate.¹⁴

The goal of this study was to apply four complementary MR techniques (T_2 -mapping, pre- and post-Gd T_1 -mapping, TPM) 1) to assess structural and functional characteristics of transplanted hearts in comparison to controls, and 2) to evaluate relationships between altered myocardial structure and function.

Materials and Methods

Study Cohort

This prospective study included 61 heart transplant recipients (age 47.9 ± 16.3 years, 39% female) and 14 age-matched healthy controls (age 47.7 ± 16.7 years, 36% female) who

underwent comprehensive cardiac MR from August 2014 through March 2017. All transplant recipients receiving follow-up care at a tertiary medical center during this period were approached, including both recent recipients (1 month to 12 months posttransplant) and recipients several years following transplant. Exclusion criteria included inability to obtain written consent (diminished decision-making capacity, language barrier, declined participation), age less than 18, and contraindications to MR (pregnancy, implanted metallic device, nonretracted lead or array, foreign body, claustrophobia, etc.). History of ACAR was defined as moderate to severe ACAR (grade 2R) in the past or any histologic evidence of ACAR within 3 months of MR, according to the revised ISHLT endomyocardial biopsy grading system.³ History of CAV was defined as diagnosis of CAV prior to MR based on coronary angiogram or intravascular ultrasound (IVUS). The study was approved by the Institutional Review Board and written informed consent was obtained from all study participants.

MR ACQUISITION.—MR was performed with a 1.5T MR system (Magnetom Aera or Avanto, Siemens, Erlangen, Germany). As shown in Fig. 1, all subjects underwent comprehensive cardiac MR, including ECG-gated 2D CINE SSFP imaging, T₂-mapping, pre- and post-Gd-contrast T₁-mapping, and TPM. T₂-mapping, T₁-mapping, and TPM were acquired during breath-holding at identical short-axis locations at the base, mid, and apex of the LV. Plane locations were determined by the MR technologist and all planes were evaluated in relation to long-axis views and cardiac characteristics at these locations to ensure that they were in the proper location.

CINE SSFP sequences were acquired with the following imaging parameters: repetition time / echo time (TR/TE) = 2.8/1.1 msec; flip angle = 65°, in-plane resolution = 2.1 × 2.1 mm², bandwidth = 930 Hz/pixel, parallel imaging (GRAPPA technique) with reduction factor $R = 2$. Each myocardial slice was acquired within a breath-hold at end-expiration using retrospective ECG gating (with 25 retrospectively reconstructed cardiac phases). 2D CINE SSFP imaging was performed in short-axis orientation with 8 mm slice thickness and a 50% slice gap to cover the entire LV in 8–10 slices from the apex to base.

T₂-mapping was based on the successive acquisition of three T₂-prepared SSFP images with varying T₂-prep times (0, 24, 55 msec).⁸ Further imaging parameters were as follows: TE/TR = 1.1–1.4/2.2–2.6 msec, spatial resolution = 1.5–2.1 × 2.0–2.5 mm, slice thickness = 8 mm, diastolic acquisition window = 270 msec, flip angle = 70°. To correct for motion between images, a fast variational non-rigid registration algorithm was employed, which aligned all T₂-prep frames to the center frame; subsequently, T₂-maps were computed by fitting intensities of corrected images to the monoexponential decay curve: $\text{Signal} = M_0 \times \exp(-T_{2\text{prep}}/T_2)$. The resulting T₂-maps were reconstructed directly on the MR system.

T₁-mapping consisted of single-shot modified Look-Locker inversion recovery (MOLLI) images before and 15 minutes following gadolinium (Gd) contrast administration (Magnevist or Gadavist, Bayer, Leverkusen, Germany, 0.1 mmol/kg).¹⁹ Patients with glomerular filtration rate (GFR) less than 30 or a recent decline in GFR did not receive gadolinium contrast. Pre- and post-Gd MOLLI sequences occurred in a 5(3)3 pattern over 11 heartbeats (measurements obtained at different inversion times over five heartbeats, followed

by a three-beat recovery period, then three additional measurements at inversion times in between the first set of inversion times). Imaging parameters were as follows: TE/TR = 1.0–1.3/2.5–4.2 msec, spatial resolution = 1.0–2.1 × 1.5–2.5 mm, slice thickness = 8 mm, flip angle = 35°. Imaging reconstruction included motion correction of the MOLLI images with different inversion times and calculation of parametric LV T₁-maps.

Tissue phase mapping was used to quantify regional myocardial velocities over the cardiac cycle along all principal motion directions (radial, circumferential, longitudinal) of the heart. TPM data acquisition used a black-blood cine 2D phase-contrast sequence with tridirectional velocity encoding (velocity sensitivity $v_{enc} = 25$ cm/s).^{20,21} Imaging parameters were as follows: temporal resolution = 20.8 msec, spatial resolution = 2.9 × 2.4 mm², slice thickness = 8 mm. Spatiotemporal imaging acceleration (k-t parallel imaging PEAK GRAPPA) with a net acceleration factor of R_{net} = 3.6 was employed, which permitted data acquisition during breath-holding (acquisition time per short axis 2D slice = 25 heartbeats).

MR POSTPROCESSING.—Measures of global LV function were calculated from short- and long-axis cine SSFP images using commercial software (cvi42, v5.3.6, Circle, Calgary, Canada). For all regional analyses, the LV was divided into 16 segments using the American Heart Association (AHA) 16-segment model.²² Global (average of all 16 segments) and peak (maximum out of 16 segments) values were then derived from 16-segment maps. Segmental T₂ and T₁ values were calculated from scanner-generated T₂- and T₁- (pre- and postcontrast) maps using commercial software (cvi42, v5.3.6, Circle). ECV was calculated using pre- and postcontrast T₁-maps and the patient's hematocrit level obtained the day of CMR using the following equation: $ECV = (R1_{myocardium} / R1_{blood}) \times (1 - \text{hematocrit})$, where $R1 = 1/T_1$ and $R1$ are the relaxation rate differences between pre- and postcontrast T₁ images.

TPM data were analyzed using in-house tools programmed in MatLab (MathWorks, Natick, MA). Analysis included manual delineation of endo- and epicardial LV contours and transformation of the acquired tridirectional velocities into radial velocities (representing contraction and expansion), longitudinal velocities (LV lengthening and shortening), and circumferential velocities (LV rotation), as described previously.^{20,23} Velocities were defined as positive for systolic contraction, shortening, or clockwise rotation. Peak and time-to-peak (TTP) velocities during systole and diastole were determined for radial and longitudinal directions. Radial and longitudinal dyssynchrony metrics were calculated during systole and diastole using the standard deviation of TTP velocities, as described previously.^{13,24} LV twist was calculated from the difference between basal and apical circumferential myocardial velocities, allowing for determination of peak systolic twist and peak diastolic untwist.^{11,14,25}

Statistics

Baseline characteristics of study participants, as well as MR measures, were summarized using standard descriptive statistics. MR measures were tested for normality using a Lilliefors test. Comparisons of global and segmental MR measures between transplant recipients and controls were performed using independent samples *t*-tests. Pearson

correlation analysis between global structural measures (T_2 , T_1 , ECV) and global functional measures (myocardial velocities, dyssynchrony, twist, EF, CO) was performed between the transplant recipients. Significant global correlations were examined further with scatterplots and AHA 16-segment plots of the derived Pearson coefficient. A sensitivity analysis to determine if important cardiac comorbidities (ACAR, CAV) influenced MR measures was performed by removing patients with these comorbidities from the sample and running the same analyses to see if any significant differences changed. Additional subgroup analyses comparing structural and functional measures between patients without ACAR or CAV and patients with these comorbidities were performed using independent samples t -tests. All analyses were performed using SPSS (v. 24, IBM, Armonk, NY) or MatLab.

Results

Study Cohort

Of 156 transplant recipients approached for the study, 90 met the inclusion criteria and were enrolled for MR (22 ICD/pacemaker present, 21 declined (six claustrophobic, 15 nonretracted lead, five language barrier, one cochlear implant, one eye shrapnel, one without capacity to consent). Of the 90 enrollees, three had no MR scan (unable to schedule) and 26 had incomplete MRs (three without T_2 , two without precontrast T_1 , 11 without postcontrast T_1 , nine with GFR <30 , two without T_1 sequences, 12 without TPM sequences). As a result, 61 transplant recipients and 14 control patients with complete MRs consisting of 2D CINE SSFP, T_2 -mapping, pre- and postcontrast T_1 -mapping, and TPM were included in the analysis.

Demographic characteristics for controls and transplant recipients are found in Table 1. Controls and transplant recipients were well matched with respect to age and sex. MRs were performed on average 5.5 ± 5.7 years following transplant. Patients <1 year since Tx ($N=16$) and >1 year since Tx ($N=45$) did not differ with respect to any demographic information. Twenty-four (39%) patients presented with a significant history of ACAR or CAV (14 each, four with both). Patients with a history of ACAR were evenly distributed between recipients <1 year since Tx and >1 year since Tx (25% vs. 22%). Patients with a history of CAV were all >1 year since Tx.

Cardiac Structure and Function: Controls vs. Transplant Recipients

Example images from representative patients in each cohort are shown in Fig. 2. TPM-derived LV velocity fields show higher peak diastolic radial velocities in the transplant patient compared to the control. Color-coded T_2 -, T_1 -, and ECV-maps depict elevated values in the transplant recipient compared to the control subject. These representative findings are corroborated by comparisons across the entire study cohort, as summarized in Figs. 3 and 4.

Global and peak T_2 were significantly increased in transplant recipients compared to controls (global: 50.5 ± 3.4 msec vs. 45.2 ± 2.3 msec, $P < 0.01$; peak: 55.7 ± 4.5 msec vs. 49.2 ± 2.4 msec, $P < 0.01$). On a segmental level, T_2 was significantly elevated across all 16 segments (Fig. 3). Global and peak T_1 were also significantly higher in transplant recipients compared to controls (global: 1037.8 ± 48.0 msec vs. 993.8 ± 34.1 msec, $P < 0.01$; peak:

1111.8 $\pm$ 67.9 msec vs. 1064.2 $\pm$ 48.2 msec, $P = 0.02$), and 13/16 segments (all except segments 4, 8, and 11; Fig. 3) demonstrated the same pattern. ECV was significantly elevated in transplant recipients compared to controls in 3/16 segments (Fig. 3).

Systolic longitudinal function was impaired in transplant recipients compared to controls, as shown by reduced peak systolic longitudinal velocities (2.9 $\pm$ 1.1 cm/s vs. 5.1 $\pm$ 1.2 cm/s, $P < 0.01$) and elevated dyssynchrony (60.2 $\pm$ 30.2 msec vs. 32.1 $\pm$ 25.1 msec, $P < 0.01$). Segmentally, peak systolic longitudinal velocities were significantly reduced in 14/16 segments (all except segments 14 and 15; Fig. 4). In contrast, diastolic radial function in transplant recipients was characterized by higher peak diastolic radial velocities (−3.9 $\pm$ 0.9 cm/s vs. −2.9 $\pm$ 0.7 cm/s, $P < 0.01$) and lower dyssynchrony (36.9 $\pm$ 13.5 msec vs. 52.0 $\pm$ 22.0 msec, $P < 0.01$) compared to controls. Segmental differences were found in 10/16 segments (segments 1–4, 6–8, 10, 12, and 15; Fig. 4).

Subgroup Analyses: Influence of ACAR and CAV

A sensitivity analysis revealed that removing patients with a history of ACAR and CAV from the cohort and comparing to controls did not change any of the significant differences in structural or functional measures between patients and controls.

A subgroup analysis comparing transplant recipients with and without a history of significant ACAR demonstrated no significant differences across any structural or functional measures. A subgroup analysis comparing transplant recipients based on a history of CAV demonstrated significantly greater diastolic longitudinal dyssynchrony in patients with a history of CAV (69.9 $\pm$ 28.9 msec vs. 50.4 $\pm$ 24.1 msec, $P = 0.01$).

Relationships Between Myocardial Structure and Function Measures

A moderate to strong significant relationship was found between global T_2 and ECV ($r = 0.45$, $P < 0.01$). In addition, segmental correlation analysis between T_2 and ECV (Fig. 5) revealed significant positive relationships between T_2 and ECV for all 16 segments ($r = 0.17$ – 0.47). A significant positive relationship between T_2 and ECV was demonstrated for both recipients <1 year since Tx ($r = 0.51$, $P = 0.04$) and >1 year since Tx ($r = 0.41$, $P < 0.01$).

Correlation analysis between structural (T_2 , T_1 , and ECV) and functional (peak myocardial velocities, dyssynchrony, twist, EF, CO) measures among all transplant recipients revealed that peak systolic longitudinal velocities are inversely related to global and peak T_2 ($r = -0.29$, $P = 0.02$; $r = -0.26$, $P = 0.04$). Systolic radial dyssynchrony demonstrated a significant positive relationship with peak T_2 and peak T_1 ($r = 0.26$, $P = 0.04$; $r = 0.27$, $P = 0.03$) across all transplant recipients.

Among transplant recipients <1 year since Tx, global and peak T_1 were associated with reduced systolic ($r = -0.63$, $P = 0.01$; $r = -0.55$, $P = 0.03$) and diastolic ($r = 0.61$, $P = 0.01$; $r = 0.50$, $P = 0.05$) twist. In addition, global T_1 was associated with reduced peak systolic longitudinal velocities ($r = -0.57$, $P = 0.02$) and increased systolic longitudinal dyssynchrony ($r = 0.58$, $P = 0.02$).

Discussion

The findings of this study demonstrate several myocardial structural and functional differences in transplant recipients compared to controls. Global and regional T_2 and T_1 were significantly elevated in transplant recipients, suggesting a higher baseline degree of edema and interstitial expansion, which was not attributable to comorbid conditions like ACAR or CAV. These structural changes may be secondary to myocardial damage sustained by undergoing surgery, immunosuppressive medications, or another transplant-related process affecting the myocardium at the cellular level.

Functionally, transplant recipients displayed impaired systolic longitudinal function compared to healthy controls, with reduced ability of the allograft to shorten following transplant, as well as altered LV coordination of lengthening and shortening. Increased diastolic radial velocities after transplant may be due to increased heart rate in transplant recipients due to denervation, thereby shortening diastole and causing more rapid filling. It is important to note that these subtle functional differences between transplant recipients and controls were found despite no difference in ejection fraction, suggesting that regional MR measures (TPM) may be more sensitive to subclinical LV changes.

Significant associations between structural and functional measures indicate relationships between information obtained through these distinct sequences. T_2 and ECV displayed a significant positive association across all LV segments, demonstrating a possible connection between these two measures of edema and interstitial expansion. Notably, functional measures also correlated with structural measures. Increased myocardial edema, marked by elevated T_2 , was associated with reduced systolic longitudinal function, marked by lower peak myocardial velocities and elevated dyssynchrony. Increased segmental edema and fibrosis, marked by elevated peak T_2 and peak T_1 , were also associated with increased systolic radial dyssynchrony. Among recent transplant recipients, fibrotic and/or edematous change, indicated by elevated T_1 , was associated with impaired systolic longitudinal function and systolic and diastolic twist. Even though the correlations between structural and functional measures were significant, they were only of moderate strength. The lack of a strong association may be due to temporal incongruity of structural and functional change (may see one before the other), threshold-based dependence of one on the other (may only see change with a certain degree of the other), or use of TPM for the assessment of LV velocities (lack of LV strain analysis).

The results of our study expand upon findings from prior studies of heart transplant recipients. T_2 and T_1 were significantly higher in transplant recipients compared to controls, which supports the findings of two studies that have compared MR data between recipients and controls.^{13,26} Another study showed a trend to higher T_2 and T_1 values in transplant recipients, but found no significant difference.¹⁴ In our subgroup analysis comparing transplant recipients with and without a history of ACAR, we found no significant differences across all MR parameters, which was unexpected, given strong prior evidence that ACAR is associated with increased T_2 .^{13–16} Our lack of association between a history of ACAR and T_2 may be secondary to a limited sample size or the fact that prior studies examined only patients during active episodes of ACAR.

With respect to TPM, our results were mixed in comparison to prior studies. We found reduced systolic longitudinal function and increased diastolic radial function in transplant recipients, supporting findings from several smaller prior studies^{13,25,27}; however, other studies also found reduced diastolic longitudinal and radial velocities in transplant recipients.^{13,25} In our subgroup analysis comparing transplant recipients with and without a history of CAV, we found greater diastolic longitudinal dyssynchrony, supporting prior evidence associating CAV with decreased diastolic function.¹⁸

In our cohort of transplant recipients, there was a strong positive relationship between T_2 and ECV; although the relationship between T_2 and ECV had not been examined in transplant recipients, our results are similar to those in other populations, such as postmyocardial infarction.²⁸ Our study also found moderate but significant relationships between structural and functional measures. Similar to another study,¹³ we found a significant inverse relationship between T_2 and systolic longitudinal velocities. Our study also found a positive association between systolic radial dyssynchrony and peak T_2 and peak T_1 , supporting prior evidence that radial dyssynchrony is sensitive to regional functional change in transplant recipients.^{13,27}

Even though assessing relationships between three structural measures (T_2 , T_1 , ECV) and three regional functional measures (peak myocardial velocity, dyssynchrony, twist) was a strength of our study, inclusion of one regional functional sequence (TPM) was a limitation. Use of an additional functional sequence (eg, MR tagging²⁹ or DENSE³⁰ for myocardial displacement or strain analysis) would allow comparison between MR functional measures and determine which ones are most useful at detecting subtle regional change. In addition to including MR-derived strain measures, comparison to structural and functional tools used in other imaging modalities (ie, echocardiography) would be valuable, possibly leading to a more comprehensive multimodal assessment of LV morphology and function.

Another limitation of our study was our sample size. Many of our enrolled patients were not included because they had incomplete MR studies, mostly due to failure to include TPM in the protocol or inability to obtain postcontrast images due to low GFR. Transplant recipients were included throughout their long-term follow-up and with a variety of relevant comorbidities. Recipients with a history of ACAR and CAV, the two primary cardiac comorbidities posttransplant, were well represented, allowing for a range of allograft health (and structure and function) in our cohort. Nevertheless, a larger cohort of diverse transplant recipients, combined with additional functional MR and other noninvasive measures, would allow for more complete study of the best structural and functional tools available to detect changes in transplanted hearts. Additionally, a longitudinal design would allow for more exploration of the association between structural and functional measures. Assessment of their temporal relationship would provide more information regarding which changes occur first, as well as the progression of structural and functional changes.

Heart rate was significantly different between transplant recipients and controls. Higher heart rates predominantly shorten diastole, and the timing of systole and early diastole are largely maintained. For TPM, no major impact of heart rate on the quantification of systolic and that rely on diastolic peak velocities was seen. For T_1 and T_2 mapping, the increase in

heart rate to ~90 bpm in Tx patients resulted in an average R-R interval of 670 msec, which provided adequate time to collect data during the diastolic acquisition window.

In conclusion, multiparametric MR offers comprehensive evaluation of global and regional changes in LV structure and function in a single examination. MR demonstrates many structural and functional changes in transplanted hearts compared to controls and suggests a structure-function relationship of cardiac abnormalities posttransplant. Additional studies are warranted to further evaluate the relationships between these structural and functional changes to determine the progression of cardiac pathology.

Acknowledgements

Grant Support: National Institutes of Health, (NIH); contract grant numbers: NHLBI grant R01 HL117888.

References

1. Lund LH, Edwards LB, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: Thirty-third adult heart transplant report — 2016; Focus theme: Primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016;35:1158–1169. [PubMed: 27772668]
2. From AM, Maleszewski JJ, Rihal CS. Current status of endomyocardial biopsy. *Mayo Clin Proc* 2011;86:1095–1102. [PubMed: 22033254]
3. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005;24:1710–1720. [PubMed: 16297770]
4. Lampert BC, Teuteberg JJ, Shullo MA, Holtz J, Smith KJ. Cost-effectiveness of routine surveillance endomyocardial biopsy after 12 months post-heart transplantation. *Circ Heart Fail* 2014;7:807–813. [PubMed: 25104042]
5. Butler CR, Thompson R, Haykowsky M, Toma M, Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: A review. *J Cardiovasc Magn Reson* 2009;11:7. [PubMed: 19284612]
6. Mena C, Wencker D, Krumholz HM, McNamara RL. Detection of heart transplant rejection in adults by echocardiographic diastolic indices: A systematic review of the literature. *J Am Soc Echocardiogr* 2006;19: 1295–1300. [PubMed: 17000376]
7. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson* 2017;19(18).
8. Giri S, Chung YC, Merchant A, et al. T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson* 2009;11:56. [PubMed: 20042111]
9. Lee DC, Aquino A, Izquierdo-Gomez M, et al. Measurement of extracellular volume fraction by cardiac magnetic resonance imaging detects diffuse myocardial fibrosis in systemic sclerosis. *J Cardiovasc Magn Reson* 2012;14:028.
10. Ferreira VM, Piechnik SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial tissue characterization by magnetic resonance imaging: Novel applications of T1 and T2 mapping. *J Thorac Imaging* 2014;29:147–154. [PubMed: 24576837]
11. Foll D, Jung B, Schilli E, et al. Magnetic resonance tissue phase mapping of myocardial motion: New insight in age and gender. *Circ Cardiovasc Imaging* 2010;3:54–64. [PubMed: 19996380]
12. Jung B, Foll D, Bottler P, Petersen S, Hennig J, Markl M. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution mr tissue phase mapping. *J Magn Reson Imaging* 2006;24:1033–1039. [PubMed: 16947325]

13. Markl M, Rustogi R, Galizia M, et al. Myocardial T2-mapping and velocity mapping: Changes in regional left ventricular structure and function after heart transplantation. *Magn Reson Med* 2012;70:517–526. [PubMed: 23008092]
14. Miller CA, Naish JH, Shaw SM, et al. Multiparametric cardiovascular magnetic resonance surveillance of acute cardiac allograft rejection and characterization of transplantation-associated myocardial injury: A pilot study. *J Cardiovasc Magn Reson* 2014;16:52. [PubMed: 25160654]
15. Marie PY, Angioi M, Carteaux JP, et al. Detection and prediction of acute heart transplant rejection with the myocardial T2 determination provided by a black-blood magnetic resonance imaging sequence. *J Am Coll Cardiol* 2001;37:825–831. [PubMed: 11693758]
16. Butler CR, Thompson R, Haykowsky M, Toma M, Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: A review. *J Cardiovasc Magn Reson* 2009;11:7 [PubMed: 19284612]
17. Miller CA, Sarma J, Naish JH, et al. Multiparametric cardiovascular magnetic resonance assessment of cardiac allograft vasculopathy. *J Am Coll Cardiol* 2014;63:799–808. [PubMed: 24355800]
18. Korosoglou G, Osman NF, Dengler TJ, et al. Strain-encoded cardiac magnetic resonance for the evaluation of chronic allograft vasculopathy in transplant recipients. *Am J Transplant* 2009;9:2587–2596. [PubMed: 19843034]
19. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified looklocker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. *Magn Reson Med* 2004;52: 141–146. [PubMed: 15236377]
20. Markl M, Schneider B, Hennig J. Fast phase contrast cardiac magnetic resonance imaging: Improved assessment and analysis of left ventricular wall motion. *J Magn Reson Imaging* 2002;15:642–653. [PubMed: 12112514]
21. Jung B, Honal M, Ullmann P, Hennig J, Markl M. Highly k-t-space accelerated phase-contrast MRI. *Magn Reson Med* 2008;60:1169–1177. [PubMed: 18958854]
22. Cerqueira MD, Weissman NJ, Dilsizian V, et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; 105:539–542. [PubMed: 11815441]
23. Lin K, Chowdhary V, Benzuly KH, et al. Reproducibility and observer variability of tissue phase mapping for the quantification of regional myocardial velocities. *Int J Cardiovasc Imaging* 2016;32:1227–1234. [PubMed: 27116238]
24. Rosen BD, Fernandes VR, Nasir K, et al. Age, increased left ventricular mass, and lower regional myocardial perfusion are related to greater extent of myocardial dyssynchrony in asymptomatic individuals: The multiethnic study of atherosclerosis. *Circulation* 2009;120:859–866. [PubMed: 19704101]
25. Foell D, Wengenmayer T, Jung B, et al. Analysis of segmental myocardial performance in patients after heart transplantation. In: *Proc 19th Annual Meeting ISMRM, Montreal*; 2011.
26. Wisenberg G, Pflugfelder PW, Kostuk WJ, McKenzie FN, Prato FS. Diagnostic applicability of magnetic resonance imaging in assessing human cardiac allograft rejection. *Am J Cardiol* 1987;60:130–136. [PubMed: 3300244]
27. Foll D, Markl M, Menza M, et al. Cold ischaemic time and time after transplantation alter segmental myocardial velocities after heart transplantation. *Eur J Cardiothorac Surg* 2014;45:502–508. [PubMed: 24026855]
28. Carberry J, Carrick D, Haig C, et al. Remote zone extracellular volume and left ventricular remodeling in survivors of ST-elevation myocardial infarction. *Hypertension* 2016;68:385–391. [PubMed: 27354423]
29. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human heart: Tagging with MR imaging — a method for noninvasive assessment of myocardial motion. *Radiology* 1988;169:59–63. [PubMed: 3420283]
30. Aletras AH, Ding S, Balaban RS, Wen H. DENSE: Displacement encoding with stimulated echoes in cardiac functional MRI. *J Magn Reson* 1999; 137:247–252. [PubMed: 10053155]

FIGURE 1:
Schematic diagram of study design. ECV: extracellular volume fraction.

FIGURE 2:

Comparison of TPM, T₂, T₁, and ECV images between patients in control and transplant groups. Data obtained from the image are shown below the image. The first column contains TPM-derived LV velocity maps, and the remaining columns contain T₂-, T₁-, and ECV-maps color-coded by value. ECV: extracellular volume fraction.

FIGURE 3:

Segmental comparison of structural measures (T₂, T₁, ECV) between controls and transplant recipients. Columns 1, 2: Regional distribution of T₂, native T₁, and ECV in controls and transplant recipients (based on the 16-segment AHA model). Segmental values represent the average T₂, T₁, or ECV values for that segment across each cohort. Right column: Significant segmental differences between controls and Tx recipients are shown in white.

FIGURE 4:

Segmental comparison of peak myocardial velocities between controls and transplant recipients. Columns 1, 2: Regional distribution of TPM-derived peak systolic and diastolic radial and longitudinal myocardial velocities in controls and transplant recipients (based on the 16-segment AHA model). Segmental values represent the average peak velocity for that segment across each cohort. Right column: Significant segmental differences between controls and Tx recipients are shown in white.

FIGURE 5:

Segmental correlation analysis between T_2 and ECV. Top: Regional distribution of T_2 and ECV, representing average values over the cohort of 61 transplant recipients. Bottom: Segmental Pearson coefficient plot between T_2 and ECV indicating significant ($P < 0.05$) positive relationships for all 16 segments.

TABLE 1.

Patient Characteristics

	Controls (N = 14)	Tx recipients (N = 61)	P- value
Age at MRI (years)	47.7 ± 16.7	48.0 ± 16.4	NS
Sex (female)	5 (36%)	24 (39%)	NS
Time Since Tx (yr)		5.5 ± 5.7	
Hx Significant ACAR (#)		14 (23%)	
Hx CAV (#)		14 (23%)	
Heart Rate (1/min)	61.2 ± 6.4	87.6 ± 12.3	<0.01
Cardiac Output (L/min)	5.3 ± 1.5	6.4 ± 1.8	NS
EF (%)	64.5 ± 7.2	64.2 ± 10.2	NS

NS: not significant. Tx: transplant. ACAR: acute cardiac allograft rejection. CAV: cardiac allograft vasculopathy. Hx: history of. EF: ejection fraction.

TABLE 2.
Structural and Functional Parameter Comparisons Between Controls and Tx Recipients

	Controls (N = 14)	Tx recipients (N = 61)	P- value
Myocardial structure			
Global T2 (msec)	45.2 ± 2.3	50.5 ± 3.4	<0.01
Peak T2 (msec)	49.2 ± 2.4	55.7 ± 4.5	<0.01
Global T1 (msec)	993.8 ± 34.1	1037.8 ± 48.0	<0.01
Peak T1 (msec)	1064.2 ± 48.2	1111.8 ± 67.9	0.02
Global ECV (%)	25.9 ± 2.7	27.2 ± 3.7	NS
Peak ECV (%)	29.6 ± 3.4	31.3 ± 4.8	NS
Myocardial function			
PV Rad Sys (cm/s)	2.7 ± 0.4	2.7 ± 0.5	NS
PV Rad Dia (cm/s)	-2.9 ± 0.7	-3.9 ± 0.9	<0.01
PV Long Sys (cm/s)	5.1 ± 1.2	2.9 ± 1.1	<0.01
PV Long Dia (cm/s)	-3.7 ± 1.5	-3.4 ± 1.2	NS
Dsynch Rad Sys (msec)	27.7 ± 8.8	32.5 ± 11.7	NS
Dsynch Rad Dia (msec)	52.0 ± 22.0	36.9 ± 13.5	<0.01
Dsynch Long Sys (msec)	32.1 ± 25.1	60.2 ± 30.2	<0.01
Dsynch Long Dia (msec)	48.7 ± 20.2	54.9 ± 26.4	NS
Twist Sys (cm/s)	2.3 ± 0.9	2.2 ± 0.7	NS
Twist Dia (cm/s)	-2.6 ± 1.0	-2.9 ± 0.9	NS

ECV: extracellular volume fraction. PV: peak myocardial velocity. Dsynch: dyssynchrony. Rad: radial. Long: longitudinal. Sys: systolic. Dia: diastolic. NS: not significant.

TABLE 3.
Pearson Correlation Analysis Results Between Structural and Functional Parameters

Myocardial structure							
	Global T2	Peak T2	Global T1	Peak T1	Global ECV	Peak ECV	
Myocardial function	PV Rad Sys	0.173	0.126	-0.174	-0.138	0.046	-0.106
	PV Rad Dia	-0.137	-0.130	-0.058	-0.040	-0.209	-0.173
	PV Long Sys	-0.285*	-0.263*	-0.149	-0.206	0.013	-0.072
	PV Long Dia	0.064	0.048	-0.030	-0.043	-0.177	-0.178
	Dsynch Rad Sys	0.121	0.261*	0.218	0.270*	0.161	0.231
	Dsynch Rad Dia	-0.085	-0.091	-0.105	-0.027	-0.027	0.023
	Dsynch Long Sys	0.116	0.196	0.100	0.203	-0.084	-0.022
	Dsynch Long Dia	0.011	0.093	0.074	0.155	-0.024	0.026
	Twist Sys	0.115	0.119	-0.077	-0.026	-0.075	-0.162
	Twist Dia	-0.048	-0.051	-0.074	-0.141	0.039	0.114
	Cardiac Output	0.170	0.134	0.129	0.198	0.208	0.113
	EF	0.066	-0.011	-0.151	-0.051	0.007	0.021

Values in the table are Pearson (r) coefficients. Significant correlations ($P < 0.05$) are shown in bold and denoted by *. ECV: extracellular volume fraction. PeakVel: peak myocardial velocity. Dyssynch: dyssynchrony. Rad: radial. Long: longitudinal. Sys: systolic. Dia: diastolic. EF: ejection fraction.