

Prospective Study

Magnetic resonance imaging of the transplanted pediatric heart as a potential predictor of rejection

Steven C Greenway, Frederic Dallaire, Paul F Kantor, Anne I Dipchand, Rajiv R Chaturvedi, Monali Warade, Eugenie Riesenkauff, Shi-Joon Yoo, Lars Grosse-Wortmann

Steven C Greenway, Department of Paediatrics, University of Calgary, Calgary, AB T2N 1N4, Canada

Steven C Greenway, Frederic Dallaire, Paul F Kantor, Anne I Dipchand, Rajiv R Chaturvedi, Eugenie Riesenkauff, Shi-Joon Yoo, Lars Grosse-Wortmann, Labatt Family Heart Centre, the Hospital for Sick Children, Department of Paediatrics, University of Toronto, Toronto, ON M5G 1X8, Canada

Frederic Dallaire, Division of Pediatric Cardiology, University of Sherbrooke and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC J1H 5N4, Canada

Paul F Kantor, Department of Pediatric Cardiology, Stollery Children's Hospital, Edmonton, AB T6G 2B7, Canada

Monali Warade, Shi-Joon Yoo, Lars Grosse-Wortmann, Department of Diagnostic Imaging, the Hospital for Sick Children, University of Toronto, Toronto, ON M5G 1X8, Canada

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Correspondence to: Lars Grosse-Wortmann, MD, Labatt Family Heart Centre, the Hospital for Sick Children, Department of Paediatrics, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada. lars.grosse-wortmann@sickkids.ca
Telephone: +1-416-8137326
Fax: +1-416-8137591

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Abstract

AIM

To evaluate cardiac magnetic resonance imaging (CMR) as a non-invasive tool to detect acute cellular rejection (ACR) in children after heart transplant (HT).

METHODS

Thirty pediatric HT recipients underwent CMR at the time of surveillance endomyocardial biopsy (EMB) and results were compared to 14 non-transplant controls. Biventricular volumes, ejection fractions (EFs), T2-weighted signal intensities, native T1 times, extracellular volumes (ECVs) and presence of late gadolinium enhancement (LGE) were compared between patients and controls and between

patients with International Society of Heart and Lung Transplantation (ISHLT) grade \geq 2R rejection and those with grade 0/1R. Heart rate (HR) and brain natriuretic peptide (BNP) were assessed as potential biomarkers.

RESULTS

Significant ACR (ISHLT grade \geq 2R) was an infrequent event in our population (5/30, 17%). Ventricular volumes, EFs, LGE prevalence, ECVs, native T1 times, T2 signal intensity ratios, HR and BNP were not associated with the presence of \geq 2R ACR.

CONCLUSION

In this pilot study CMR did not reliably identify ACR-related changes in pediatric HT patients.

Key words: Heart; Pediatric; Transplantation; Magnetic resonance imaging; Rejection

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Core tip: After heart transplantation the diagnosis of significant acute cellular rejection (ACR) changes management and is associated with adverse outcome. Endomyocardial biopsy is the gold standard for the detection of ACR but has important limitations. This prospective trial examined the use of cardiac magnetic resonance imaging (CMR) for the diagnosis of ACR in pediatric heart transplant recipients. Significant rejection was a rare event in our cohort and was not associated with changes in CMR parameters in this pilot study.

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INTRODUCTION

Acute cellular rejection (ACR) is an immune-mediated process leading to allograft damage and decreased graft survival. It is a serious and potentially lethal complication after heart transplant (HT). The gold standard for the detection of rejection is an endomyocardial biopsy (EMB). However, EMB is an invasive procedure, exposes the patient to ionizing radiation and carries a small but important risk of serious complications^[1-4].

Cardiac magnetic resonance imaging (CMR) has been proposed as a non-invasive method for the detection of rejection in adults after HT. However, CMR measurements used in adults for the detection of rejection or myocardial inflammation, including T2-weighted imaging^[5,6], native T1 times and extracellular volume fractions (ECVs) derived from T1 mapping^[7], myocardial thickness,

ventricular volumes and ejection fraction (EF)^[8,9] have not been systematically evaluated in pediatric HT recipients with EMB-proven ACR.

In this pilot study we sought to assess the utility of parameters of ventricular function and myocardial tissue characterization for the non-invasive detection of ACR in children and adolescents after HT.

MATERIALS AND METHODS

Patients and study design

This single center, prospective, cross-sectional study was approved by the institutional research ethics board and included pediatric (age < 18 years) HT patients who were scheduled for a clinically-indicated EMB between April 2010 and March 2011. All consecutive and eligible patients without contraindications to contrast-enhanced CMR during the study period were invited to participate. In patients who underwent more than one CMR/EMB procedure during the study period only the first set of investigations was analyzed for this study. Following written informed consent, CMR was performed immediately prior to cardiac catheterization and EMB. Control subjects were asymptomatic relatives of patients diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC) who had normal echocardiograms, electrocardiograms (ECGs), signal-averaged ECGs as well as CMR scans and who were negative for ARVC-associated mutations if testing had been performed. Control subjects did not receive gadolinium as part of their CMR study. Heart rate (HR) was obtained from the average HR during the short axis CMR cine acquisition for ventricular volumetry.

Standardized immunosuppression post-transplantation for all patients included the use of thymoglobulin for induction (1-5 doses depending on risk factors), tacrolimus and mycophenolate mofetil. Perioperative steroids were discontinued 6 mo post-HT until 2007 and thereafter were discontinued at 5 d post-HT. Routine surveillance for rejection included serial echocardiograms, ECGs and cardiac catheterization with decreasing frequency over time post-transplantation.

EMB

At the authors' institution right ventricular EMBs are obtained at 1, 6 and 12 mo and then annually up to 5 years post-HT; thereafter only if there is clinical or echocardiographic suspicion for rejection. During the EMB five or six tissue samples were obtained from the right ventricular surface of the interventricular septum, stained with hematoxylin and eosin and evaluated using light microscopy. Samples were graded by a hospital pathologist who was blinded to the CMR and biochemistry results (below) and reported according to the International Society of Heart and Lung Transplantation (ISHLT) Standardized Cardiac Biopsy Grading Criteria^[10]. Congruent with clinical practice grades 2R and 3R were classified as significant ACR and grades 0R and 1R as

non-significant ACR. Tissue samples were also evaluated for the presence of antibody-mediated rejection (AMR) by C4d immunohistochemical staining.

CMR

CMR was performed using a 1.5 Tesla scanner (Magnetom Avanto, Siemens AG Healthcare Sector, Erlangen, Germany) and a phased-array multi-channel surface receiver coil.

Ventricular volumetry and late gadolinium enhancement

A stack of multiphase short axis slices was acquired using the steady state free precession technique for left and right ventricular volumes, as described previously^[11,12]. Ventricular volumes were extracted from the cine short axis stack in end-diastole and end-systole in the routine clinical fashion using commercially available software (QMass, version 7.2, Medis, Leiden, The Netherlands). Ventricular volumes were reported as indexed to recipient body surface area. EFs for both ventricles were calculated using end-diastolic and end-systolic volumes. The presence of late gadolinium enhancement (LGE) was determined qualitatively on standard long-axis (4-chamber, 2-chamber and 3-chamber) and short-axis slices using phase-sensitive inversion-recovery acquisitions > 10 min after the administration of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist®, Bayer, Leverkusen, Germany).

T1 mapping and extracellular volumes

We previously described our T1 mapping approach for these patients in detail^[13]. In short, a modified Look-Locker inversion recovery sequence (MOLLI) with inversion pulses of 100 msec and 150 msec, respectively, as well as 3 and 5 single-shot images after these inversion pulses was used to measure native and post-contrast longitudinal relaxation T1 times of myocardium and blood. Images were acquired in diastole at a single mid-ventricular short axis slice orientation before and > 10 min after administration of contrast (same injection as described above for LGE). Breathholds were used in cooperative patients and all other patients were scanned during free breathing. Longitudinal relaxation times (T1 times) were measured using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, AB, Canada). Contours were drawn in the interventricular septum, the left ventricular (LV) free wall and in a region encompassing the entire LV myocardium. T1 times in the blood pool were measured in the LV cavity. The ECV was calculated using pre- and post-gadolinium T1 times of blood and myocardium as well as the patient's hematocrit, obtained at the time of the scan^[14].

T2-weighted imaging

An ECG-gated turbo spin-echo readout sequence without fat saturation pulse preceded by a double inversion recovery dark-blood preparation and the following parameters was obtained in a single midventricular short axis slice^[15]: Inplane spatial resolution 1.6 mm, slice

thickness 6-10 mm, TE 59 ms. Imaging was performed in diastole during every other or every third heartbeat, depending on the HR, to achieve a TR of at least 1000 ms. The scanner's body coil was used for a homogeneous signal reception within the field of view. Myocardial signal intensity was measured around the circumference of the short axis slice and normalized to that of skeletal muscle using a dedicated module within the CVI42 software^[16].

Brain natriuretic peptide levels

A blood sample was drawn upon insertion of the peripheral intravenous cannula needed for the CMR and analyzed for brain natriuretic peptide (BNP) levels (Modular Analytics, Roche Diagnostics, Laval, QC, Canada).

Statistical analysis

CMR data from transplant patients were stratified according to the presence (grade \geq 2R) or absence (grade 0R or 1R) of significant ACR. Most variables were not normally distributed and results are thus presented as medians, 10th and 90th percentiles. Medians between groups were compared using a non-parametric Wilcoxon two-sample test or the Kruskal-Wallis test where appropriate. A *P*-value < 0.05 was considered statistically significant. All analyses were performed using SAS for Windows 9.4 (SAS Institute Inc., Cary, NC, United States). Statistical review of the study was performed by a biomedical statistician (FD).

RESULTS

Patient demographics and non-imaging biomarkers of rejection

The CMR studies from 14 non-transplant pediatric controls and 30 pediatric HT recipients were included in this study. The EMBs from 25 HT patients (83%) showed no significant ACR (ISHLT grades 0R or 1R) while 5 (17%) demonstrated significant rejection (ISHLT 2R). No patient had ISHLT grade 3R ACR. None of our HT patients were identified as having AMR. There were no statistically significant differences between the transplant groups with < 2R and \geq 2R ISHLT rejection with respect to age at CMR or for time since transplant (Table 1). Patients with grade 2R rejection were younger than the controls and "no rejection" groups at the time of CMR but this difference was not statistically significant. HR and BNP were significantly increased in both groups of HT patients compared to controls but there were no statistically significant differences between the "no rejection" and "rejection" HT groups.

Ventricular function, volumes and mass

Biventricular end-diastolic volumes were decreased in the rejection group compared to the controls but not in the group without rejection (Figure 1). LVEF was decreased and LV mass increased only in the "no rejection" group compared to controls (Table 2). However, no significant

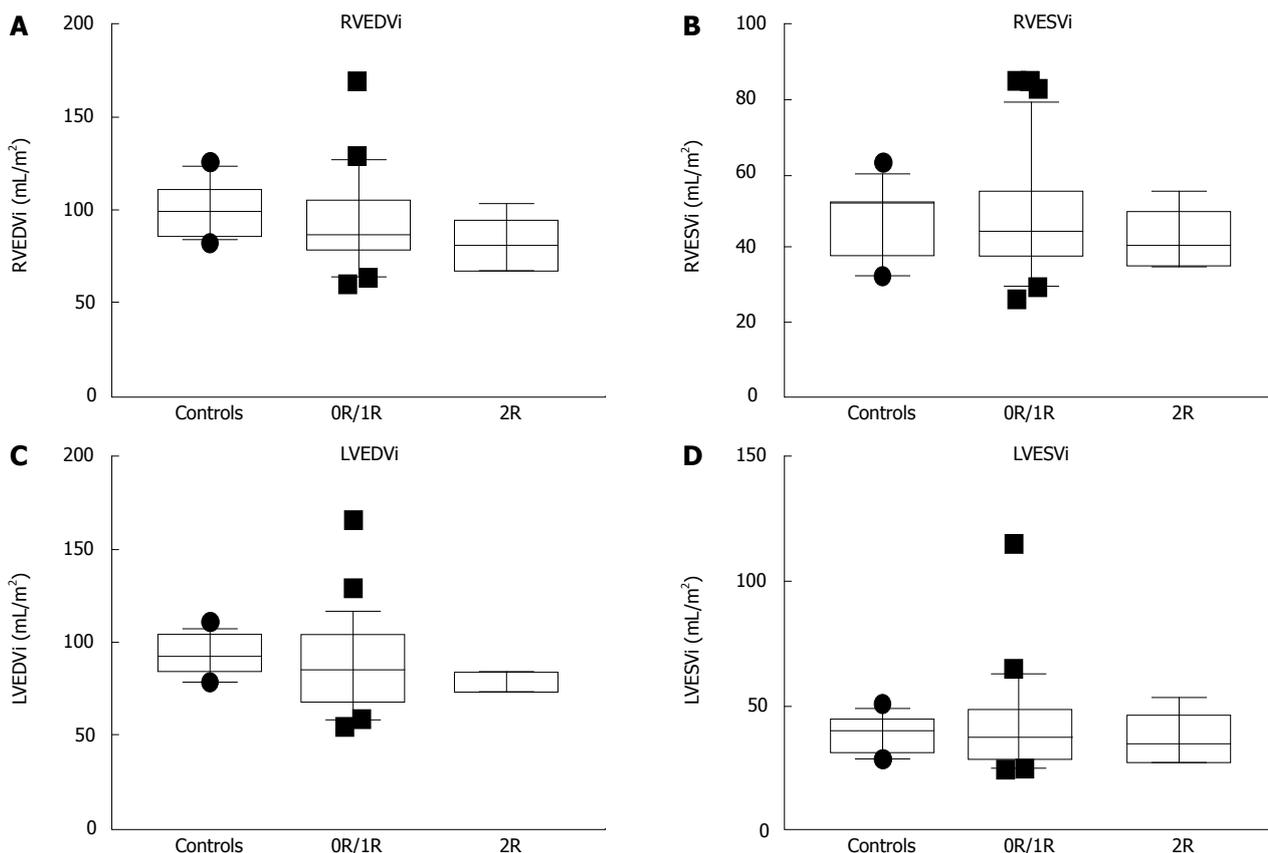


Figure 1 Box and whiskers plots for end-diastolic and end-systolic ventricular volumes of controls and transplant patients without (OR/1R) and with (2R) significant rejection. A: Right ventricular end-diastolic volume indexed to body surface area (RVEDVi); B: Right ventricular end-systolic volume indexed to body surface area (RVESVi); C: Left ventricular end-diastolic volume indexed to body surface area (LVEDVi); D: Left ventricular end-systolic volume indexed to body surface area (LVESVi).

| Table 1 Patient characteristics | | | |
|---------------------------------|------------------|-----------------------------|-------------------------------|
| | Controls | No rejection (OR/1R) | Rejection (2R) |
| Number | 14 | 25 | 5 |
| Female (%) | 8 (57) | 10 (40) | 1 (20) |
| Days post-transplant | - | 702 (78, 1797) | 160 (12, 800) |
| Age at CMR (yr) | 12.8 (9.2, 15.3) | 13.6 (2.2, 17) | 7.7 (1.6, 17.5) |
| HR | 71 (57, 84) | 96 ^b (82, 126) | 108 ^d (101, 130) |
| BNP | 9.2 (5, 12.9) | 38.7 ^f (5, 81.6) | 59.9 ^e (14.9, 202) |

Data shown as number (percentage) or median (10th, 90th percentiles). Significantly different compared to controls, ^b*P* = 5.76E-05, ^d*P* = 0.005, ^f*P* = 0.005, ^e*P* = 0.03. There were no significant differences between the transplanted rejection groups. HR: Heart rate in beats per minute; BNP: Brain natriuretic peptide in ng/L; CMR: Cardiac magnetic resonance imaging.

differences between HT patients with and without clinically important rejection were observed with regards to ventricular volumes, ejection fractions, LV mass or LV mass/volume ratio. The absence of a significant change in ventricular volumes with rejection may be confounded by the increase in ventricular size with age (Figure 2). There was no significant association between BNP and CMR parameters.

Native T1 times, myocardial extracellular volume fraction and LGE

The MOLLI sequence for T1 mapping became available to us after study enrollment had begun and therefore this data was available only in a subgroup of patients (Table 3). With regards to patient demographics there were no significant differences between this patient subset and the entire cohort. There were no significant differences in native T1 times and ECV fraction between patients with < 2R and ≥ 2R ISHLT rejection. LGE was not observed in any of the HT patients. Native T1 times and ECV were not quantified and LGE imaging was not obtained in controls who did not receive contrast.

Myocardial T2-weighted imaging

The global ratios of myocardial:skeletal muscle T2 signal intensities on a mid-ventricular short axis slice were similar between groups and did not differ between controls (median 1.37, 10th percentile 1.29, 90th percentile 1.67) and transplant patients with no rejection (median 1.3, 10th percentile 1.02, 90th percentile 1.6) or with rejection (median 1.3, 10th percentile 1.12, 90th percentile 1.47). There were no significant differences between transplant patients with < 2R and ≥ 2R ACR rejection.

Table 2 Ventricular volumes, function and mass

| | Controls | No rejection (OR/1R) | Rejection (2R) |
|-----------------------------|--------------------|------------------------------|---------------------------------|
| Number | 14 | 25 | 5 |
| RVEDVi (mL/m ²) | 98.5 (85.7, 120.4) | 86.6 (64.1, 124.4) | 80.6 ^a (68.1, 102.7) |
| RVESVi (mL/m ²) | 50.5 (33.9, 56.1) | 44.1 (30.7, 77) | 41 (34.9, 55.4) |
| RVEF (%) | 53.4 (48, 60) | 50 (41, 57) | 47.4 (40, 56) |
| LVEDVi (mL/m ²) | 93 (79.2, 104) | 85.2 (58.9, 112) | 74.1 ^c (73.7, 85) |
| LVESVi (mL/m ²) | 40.3 (29.8, 45) | 37.5 (24.6, 60.9) | 33.8 (27.2, 52) |
| LVEF (%) | 58.8 (53.2, 63) | 54 ^a (46, 64) | 56 (36, 63) |
| LV mass (g/m ²) | 53.5 (45.8, 61) | 61.5 ^b (50, 84.6) | 66.1 (48, 80) |

Data shown as median (10th, 90th percentiles) except for number. Significantly different compared to controls, ^a*P* = 0.03, ^c*P* = 0.02, ^a*P* = 0.05, ^b*P* = 0.003. There were no significant differences between the transplant rejection groups. RVEDVi: Right ventricular end-diastolic volume indexed to recipient body surface area; RVESVi: Right ventricular end-systolic volume indexed to recipient body surface area; RVEF: Right ventricular ejection fraction; LVEDVi: Left ventricular end-diastolic volume indexed to recipient body surface area; LVESVi: Left ventricular end-systolic volume indexed to recipient body surface area; LVEF: Left ventricular ejection fraction; LV mass: Left ventricular mass indexed to recipient body surface area; CMR: Cardiac magnetic resonance imaging.

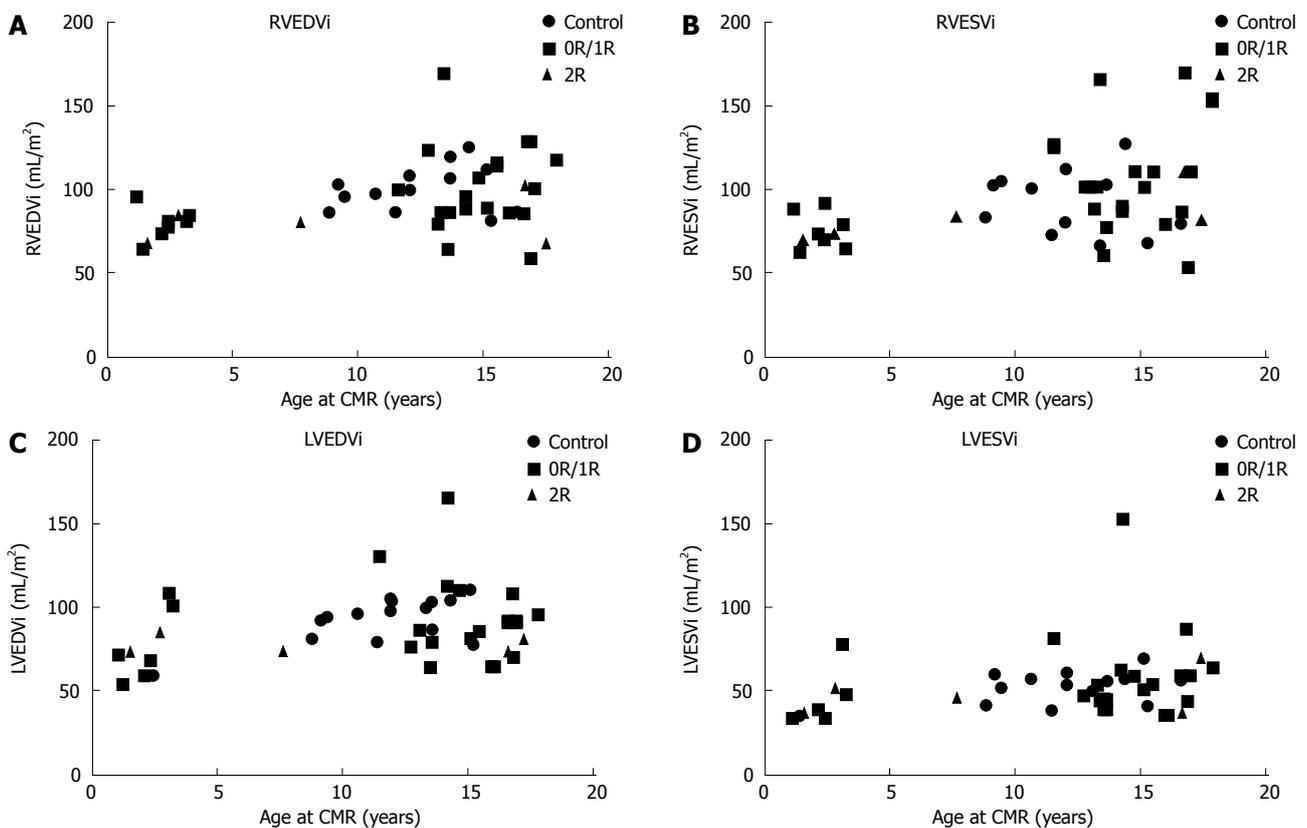


Figure 2 Ventricular volumes plotted as a function of age for controls and transplant patients without (OR/1R) and with (2R) significant rejection. A: Right ventricular end-diastolic volume indexed to body surface area (RVEDVi); B: Right ventricular end-systolic volume indexed to body surface area (RVESVi); C: Left ventricular end-diastolic volume indexed to body surface area (LVEDVi); D: Left ventricular end-systolic volume indexed to body surface area (LVESVi).

DISCUSSION

Despite a growing body of evidence in adult HT patients and important information from animal experiments the role of CMR for the detection of ACR in children has not been explored^[17-19]. CMR tissue characterization overcomes important limitations of EMB such as the potential of containing scar from a previous EMB in the

histological sample and the fact that specimens are collected from the RV surface of the interventricular septum and may not be representative of the remainder of the myocardium^[17]. The current study compared descriptors of myocardial edema, expansion of the myocardial extracellular space, presence of patchy myocardial scarring as well as ventricular size and function between controls and HT recipients as well

Table 3 T1 and extracellular volume data for heart transplant patients

| | No rejection (0R/1R) | Rejection (2R) |
|----------------------|----------------------|-------------------|
| Number | 18 | 4 |
| Female (%) | 8 (44) | 1 (25) |
| Days post-transplant | 485 (13, 1818) | 142 (12, 800) |
| Age at CMR (yr) | 13.2 (1.4, 16.9) | 5.3 (1.6, 16.8) |
| Native T1 (ms) | | |
| IVS | 1008 (963, 1067) | 976 (967, 1026) |
| LV free wall | 988 (903, 1018) | 978 (924, 1016) |
| Entire LV | 991 (930, 1031) | 978 (944, 1020) |
| Hematocrit | 0.37 (0.26, 0.44) | 0.35 (0.29, 0.38) |
| ECV | | |
| IVS | 0.3 (0.26, 0.34) | 0.29 (0.26, 0.33) |
| LV free wall | 0.27 (0.24, 0.34) | 0.28 (0.25, 0.31) |
| Entire LV | 0.29 (0.26, 0.33) | 0.29 (0.27, 0.32) |

Data shown as number (percentage) or median (10th, 90th percentiles). There were no significant differences between the groups. ECV: Extracellular volume; IVS: Interventricular septum; LV: Left ventricle.

as between HT patients with < 2R and \geq 2R ISHLT rejection. However, in contrast to the experience in adult HT populations for several of these parameters, we were unable to demonstrate an association of any of them with ACR in pediatric HT recipients^[17,19].

None of the 30 patients in our study displayed patchy myocardial scarring as evidenced by LGE. This finding is in contrast to studies in adult HT recipients which found myocardial scarring on LGE imaging in a sizeable proportion (although this was not correlated with rejection)^[19,20]. The reason for this discrepancy remains unclear, but may be related to the younger age of the donor hearts used for pediatric HT^[21,22]. While LGE reflects patchy myocardial scarring of a certain size native T1 and ECV are regarded as measures of expansion of the extracellular matrix. Both are elevated in states of increased myocardial fibrosis or edema. Acute rejection is characterized histologically by inflammation of the myocardium while chronic or repeated episodes of rejection have been associated with fibrotic remodeling^[7,23,24]. Native T1 and ECV have been explored as markers of ACR in a pilot study in adults after HT but an association with rejection has yet to be demonstrated^[8]. In the current study, albeit in a limited number of patients, ECV and native T1 times did not distinguish between < 2R and \geq 2R ISHLT rejection. T2-weighted imaging is an established approach to detect tissue edema in inflammatory conditions and in the heart it is used as a marker for myocardial edema in myocarditis^[6]. Studies that employed T2 signal intensity for the non-invasive detection of rejection have yielded mixed results in adult HT patients^[5,9,25]. Our early results did not reveal increased signal intensity on T2-weighted imaging in patients with ACR. T2 mapping is another approach to myocardial edema which has yielded promising results in adult ACR^[19,26-28], but this technique was not available to us at the time of the study. When discussing the lack of agreement between CMR markers and histological

indicators of ACR, important shortcomings of EMB as the gold standard for the detection of ACR must be considered. Marie *et al*^[26] found T2 mapping CMR to be "positive" for significant rejection several weeks before a follow-up EMB confirmed it suggesting a lack of sensitivity for EMB.

Ventricular size, LV myocardial mass, and function did not distinguish between patients with < 2R and \geq 2R ISHLT rejection in our study. An increase in indexed right ventricular end-diastolic volume has emerged as a potential predictor of rejection in adults^[19], but the trend in our patients was in the opposite direction for both right and left ventricular end-diastolic volumes. The use of ventricular volumes as a biological marker is potentially problematic for two reasons: Firstly, there is often a size mismatch between the donor and the recipient which can be up to two-fold in children. This mismatch is fairly random and quite possibly obscures any association between ventricular size and the presence of rejection. Secondly, indexing to body surface area, although standard practice, is a crude strategy for normalizing ventricular volumes in children. Z-scores are more reliable in ensuring comparability across a spectrum of ages, body sizes and genders, but universally accepted Z-scores for CMR volumes are missing.

Another potential sign of inflammation is myocardial swelling as evidenced by increased LV "mass". Studies in adults have shown an increase in LV wall thickness during episodes of rejection^[28,29]. However, an increase in LV mass in HT patients also occurs unrelated to rejection due to myocardial hypertrophy either as an adverse effect of medications^[30], myocardial TNF- α expression^[31] or hypertension. In our study there was no significant difference between HT patients with and without \geq 2R ACR with regards to LV mass.

With regards to non-CMR parameters, higher HRs were noted in the HT recipients as compared to controls due to denervation during the transplant operation. However, in our small cohort HR did not differ significantly between patients with and without significant rejection. An elevated BNP has also been proposed as a marker for rejection in pediatric cardiac transplant patients^[32] and, although elevated in the transplant patients, there was no significant difference between the transplant rejection groups.

The most important limitation of this pilot study is the small number of patients with \geq 2R rejection which may have obscured associations of EMB with CMR parameters. The number of patients with available T1 mapping data, in particular, was very small. The small numbers may have also augmented the effects of potential confounders, for example donor:recipient size mismatch in HT patients, and thereby affected the comparability of ventricular volumes. The relatively low prevalence of ACR in the current era is related to improved immunosuppression regimes and, consistent with contemporary outcomes^[33], none of the patients in our study had severe grade 3R rejection. The incidence of moderate (grade 2R) ACR (17%) was similar

to the 13%-23% found by others^[8,19,20]. T1 relaxometry and T2-weighted imaging were based exclusively on measurements in a single mid-ventricular short axis slice. Many experts now recommend a wider representation of all regions of the LV in tissue characterization. Since many of the measures we assessed are associated with intramyocardial edema, which is rare in 2R rejection, it is perhaps unsurprising that the studied CMR parameters were unchanged. It is possible that, rather than detecting acute rejection, CMR may have a greater role in identifying long-term changes in the myocardium perhaps associated with cardiac allograft vasculopathy.

Studies in adults have produced mixed results with regards to the use of CMR as a screening tool for rejection and our pilot study did not identify CMR parameters altered by the presence of 2R rejection. However, myocardial tissue characterization by CMR is undergoing continuous refinement. Given the conceptual association between ACR and myocardial inflammation and the multiple disadvantages of EMB, CMR should continue to be evaluated for its ability to non-invasively detect rejection. Larger trials producing sizable cohorts of patients with clinically-significant rejection episodes and including T2 relaxometry are recommended.

COMMENTS

Background

Cardiac magnetic resonance imaging (CMR) has been proposed as a non-invasive method for the detection of rejection in adults after heart transplant (HT). However, CMR measurements used in adults for the detection of rejection or myocardial inflammation have not been systematically evaluated in pediatric HT recipients with biopsy-proven acute cellular rejection (ACR). In this pilot study, the authors sought to assess the utility of parameters of ventricular function and myocardial tissue characterization for the non-invasive detection of ACR in children and adolescents after HT.

Research frontiers

CMR tissue characterization overcomes important limitations of endomyocardial biopsy (EMB) such as the potential of containing scar from a previous EMB in the histological sample and the fact that specimens are collected from the RV surface of the interventricular septum and may not be representative of the remainder of the myocardium.

Innovations and breakthroughs

CMR has shown potential utility in adult heart transplant recipients. However, in this pilot study CMR did not reliably identify ACR-related changes in pediatric heart transplant patients.

Applications

Given the multiple disadvantages of EMB, CMR should continue to be evaluated for its ability to non-invasively detect rejection. Larger trials producing sizable cohorts of patients with clinically-significant rejection episodes and including T2 imaging are recommended.

Terminology

EMB: Invasive procedure used to sample the endomyocardium of the right ventricle to diagnose rejection; ACR: Damage created by T-cell mediated immune response directed by the recipient against the transplanted organ; T1- and T2-weighted imaging: MRI sequences that are used to differentiate tissues based mainly on their composition of fat and water.

Peer-review

The authors have produced an interesting study evaluating the use of CMR scanning as a means to diagnose acute cellular rejection in paediatric HT recipients.

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