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Three-Dimensional Self-Navigated T_2 Mapping for the Detection of Acute Cellular Rejection After Orthotopic Heart Transplantation

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Background. T_2 mapping is a magnetic resonance imaging technique measuring T_2 relaxation time, which increases with the myocardial tissue water content. Myocardial edema is a component of acute cellular rejection (ACR) after heart transplantation. This pilot study compares in heart transplantation recipients a novel high resolution 3-dimensional (3D) T_2-mapping technique with standard 2-dimensional (2D) T_2-mapping for ACR detection. **Methods.** Consecutive asymptomatic patients (n = 26) underwent both 3D T_2 mapping and reference 2D T_2 mapping magnetic resonance imaging on the day of endomyocardial biopsy (EMB). 3D T_2 maps were obtained at an isotropic spatial resolution of 1.72 mm (voxel volume 5.1 mm^3). 2D and 3D maps were matched anatomically, and maximum segmental T_2 values were compared blinded to EMB results. In addition, all 3D T_2 maps were rendered as 3D images and inspected for foci of T_2 elevation. **Results.** T_2 values of segments from 2D and reformatted 3D T_2 maps agreed ($p > 0.5$). The highest 2D segmental T_2 values were 49.9 ± 4.0 ms (no ACR = 0R, n = 18), 48.9 ± 0.8 ms (mild ACR = 1R, n = 3), and 65.0 ms (moderate ACR = 2R). Rendered 3D T_2 maps of cases with 1R showed foci with significantly elevated T_2 signal (T_2 = 58.2 ± 3.6 ms); 5 cases (28%) in the 0R group showed foci with increased T_2 values (>2 SD above adjacent tissue) that were not visible on the 2D T_2 maps. **Conclusions.** This pilot study in a small cohort suggests equivalency of standard segmental analysis between 3D and 2D T_2-mapping. 3D T_2 mapping provides a spatial resolution that permits detection of foci with elevated T_2 in patients with mild ACR.

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The International Society of Heart and Lung Transplantation registry indicates that 25% of adult heart transplant (HTx) recipients have 1 or more episodes of acute cellular rejection (ACR) within the first postoperative year.[1] ACR accounts directly for 4% of posttransplant mortality and may also play a causal role for primary graft failure, which entails 22% of deaths after HTx.[1] Histological grading of endomyocardial biopsies (EMB) remains the standard surveillance for detection of ACR. However, the sensitivity of EMB for detection of ACR is limited to 70%, as indicated by

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series comparing results from histological grading of EMBs with autopsy findings.[2-4] Furthermore, there is a specificity concern, because concordance of histological grading by different pathologists was only 71% in the 937 EMBs obtained by the cardiac allograft rejection gene expression observational study II trial.[5]

In an animal model of heart transplant rejection, the T_2 relaxation time, a physiological property of a given tissue in a magnetic field, increased with the severity of rejection and in linear relationship with the myocardial tissue water content.[6] Compatible with these observations, the International Society of Heart and Lung Transplantation ACR grading recommendations require the presence of edema for diagnosing severe rejection (3R), but not in mild (1R) or moderate (2R) ACR.[7] This does not exclude the presence of edema in human low-grade ACR but acknowledges that standard processing of EMB for histological reading does not permit reliable detection of minor quantities of interstitial edema.

At present, ACR detection in HTx recipients on the basis of fast breath-held 2-dimensional (2D) T_2 mapping at a magnetic field strength of 1.5 T permits analysis of 3 slices of 10-mm thickness with a spatial resolution of $1.9 \times 2.5 \times 8 = 37$ mm^3 or greater. This technique can be used to very accurately detect 2R or greater ACR, which histologically presents with multifocal or diffuse infiltration of the whole heart.[8] Mild rejection with its patchy nature, however, requires whole-heart screening with high spatial resolution for reproducible discrimination of edematous from adjacent nonedematous tissue.[9] Though the clinical relevance of 1R may be argued,[1] its high incidence and the risk for progression to more severe ACR[10] provide a strong argument for its noninvasive detection. Furthermore, absence of ACR when using a technique that is able to detect 1R will impact on the guidance of immunosuppression. This pilot study therefore aimed to validate a novel 3-dimensional (3D) self-navigated cardiac T_2-mapping technique with high spatial resolution ($1.72 \times 1.72 \times 1.72 = 5.1$ mm^3) at 3 T throughout the whole heart[11] by direct comparison with 2D T_2-mapping at high resolution ($1.25 \times 1.25 \times 5 = 7.8$ mm^3)[12] and EMB-based ACR detection.

MATERIALS AND METHODS

Approval from the local ethics committee was obtained (protocol 250/2013). All participants provided written informed consent. A total of 26 consecutive asymptomatic HTx recipients in stable phase after HTx (55–4275 days) were included (mean age, 52 ± 9 years; 3 women; mean donor age, 42 ± 12 years; time after HTx, 699 ± 674 days). Immunosuppression was always guided by EMB histology; coronary angiograms showed no relevant coronary vasculopathy.

Magnetic resonance imaging (MRI) was performed on the day of EMB procurement using a clinical magnetic resonance scanner with a magnetic field strength of 3 T (Magnetom Trio, Siemens Healthcare) and with a 32-channel radiofrequency coil. High-resolution navigator-gated radial 2D T_2 maps[12] were acquired in 3 short-axis slices as a reference (see Table 1 for magnetic resonance pulse sequence details). The self-navigated isotropic 3D radial whole-heart T_2 map[11] (voxel size $1.72 \times 1.72 \times 1.72 = 5.1$ mm^3) was obtained during free breathing. Acquisition, processing and reading of the MRI results was performed with the observer blinded to EMB results.

Segments of 2D and 3D T_2 maps were manually drawn in accordance with current AHA guidelines[13] after reformatting and slice-thickness matching of the latter. Equivalency of 3D with reference 2D T_2 mapping was tested comparing the highest segmental 2D and 3D T_2 values in groups of HTx recipients without (0R), mild (1R), or moderate/severe ACR (≥2R). In addition, all 3D T_2 maps were rendered as 3D images (Figure 1) and inspected for foci of T_2 elevation.

All values are represented as mean ± SD T_2 values were compared with a 2-sided paired Student's t-test with Bonferroni correction for multiple comparisons, with P less than 0.05 considered significant. In case of a single value in a group, standard deviation or P value was not calculated.

RESULTS

Mild ACR was present in 3 patients, 1 patient had 2R; no EMB showed immunohistological signs of acute humoral rejection. Four 3D T_2 maps were discarded due to insufficient image quality. Mean T_2 values of segments from 2D and reformatted 3D T_2 maps agreed well: the highest 2D and 3D segmental T_2 values of the 3 ACR groups were 49.9 ± 4.0 ms versus 49.1 ± 3.8 ms (0R), 48.9 ± 0.8 ms versus 49.2 ± 1.3 ms (1R), and 65.0 ms versus 66.1 ms (2R) ($P > 0.51$ for all comparisons). However, rendered 3D T_2 maps of the 3 cases with 1R showed foci with significantly elevated T_2 (T_2 = 58.2 ± 3.6 ms) that were not visible on

TABLE 1.

An overview of the used MRI parameters

Parameter	2D T_2 maps	3D T_2 maps
No. maps per scan	3	1
Pulse sequence basis	Radial GRE	Radial bSSFP
Echo time TE, ms	1.9	1.33
Repetition time TR, ms	4.3	2.6
Total radial readouts per image (–)	310	5696
T_2 preparation durations, ms	0/30/60	0/30/60
Flip angle, degrees	15	35/70
Spatial resolution, mm^3	$1.2 \times 1.2 \times 5 = 6.9$	$1.72 \times 1.72 \times 1.72 = 5.1$
Respiratory motion compensation	Lung-liver navigator	Self-navigation
readouts per heartbeat (–)	21	32
Total acquisition duration	~3 × 5 min (depending on the respiration pattern and heart rate)	Fixed 178 heartbeat; ~18 min

GRE, gradient echo; bSSFP, balanced steady-state free precession.

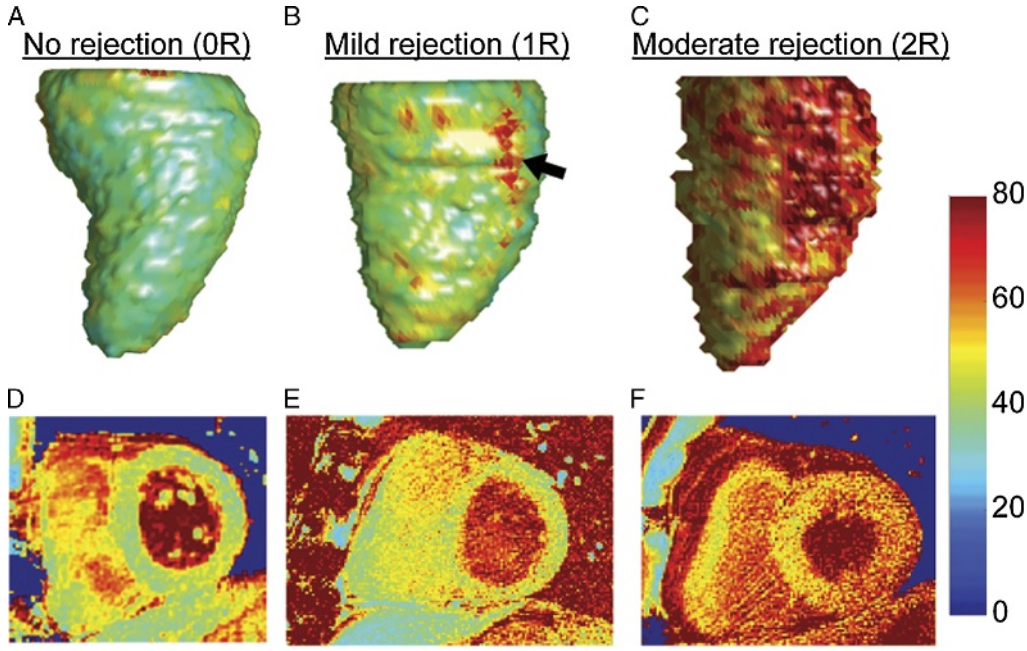

FIGURE 1. 3D and 2D T_2 maps of patients with ACR 0R, 1R, and 2R. A-C, Examples of volume-rendered 3D T_2 maps that were segmented along the center of the endocardium of the LV. D-F, Corresponding basal 2D T_2 maps. The 3D T_2 maps of patients with 1R show patches with significantly elevated T_2 values (black arrow). The color bar indicates T_2 values in ms.

respective 2D T_2 maps (Figures 1B, E). In addition, rendered T_2 maps from 5/18 patients (28%) without ACR in the EMB showed foci with increased T_2 values with greater than 2 standard deviations of difference when compared with adjacent tissue and similar to foci detected in patients with 1R ACR (Figure 1B, black arrow). The 3D T_2 map of the single 2R case showed elevated T_2 values throughout the left ventricle (LV) in a relatively heterogeneous pattern (Figure 1C).

DISCUSSION

This pilot study with 26 consecutive asymptomatic HTx recipients presenting for a scheduled control biopsy demonstrates corresponding segmental T_2 values in 2D and 3D T_2 maps of patients with 0R and 1R, indicating equivalency of the novel 3D T_2 mapping algorithm with the actual T_2 mapping standard. Furthermore, rendered 3D T_2 map showed foci with significantly increased T_2 values compatible with local ACR in all patients with EMB-proven ACR suggesting that this novel algorithm has the potential to detect ACR with a sensitivity that is noninferior to the criterion standard of ACR detection. Consistent with previous studies,[8] the 2R case demonstrated throughout the whole LV elevated T_2 values that were several standard deviations above the 0R value.

Retrospective analysis of the 4 discarded maps showed that the main cause of insufficient image quality was most likely insufficient communication with the performing technologist, because in 3 of the 4 patients, only routine shimming was performed, whereas cardiac shimming is essential for balanced steady-state free precession–based cardiac pulse sequences at 3 T.[14] This resulted in several dark-band artifacts (banded signal voids) through the heart, which in turn caused the self- navigation to perform suboptimally. In addition, in 2 of the 4 patients, the timing was most likely not set to the correct phase of the heart, resulting in too noisy and blurred data.

In this pilot study, rendered 3D T_2 maps showed foci with significantly elevated T_2 values in 28% of patients without histological signs of ACR in the EMB. Moreover, the respective 2D T_2 mapping segments in these study patients did not show elevated T_2 values compared to adjacent segments. This observation may suggest superior sensitivity of 3D T_2 mapping when compared with histological grading of EMBs or 2D T_2 mapping. In fact, both techniques have inherent major methodological limitations that decrease their sensitivity for mild ACR detection: in particular, sampling error related to EMB procurement and dilution of the T_2 values of increased intensity in a larger voxel volume. The results of this pilot study therefore encourage the investigation of the hypothesis that 3D T_2 mapping may allow for noninvasive detection of mild ACR. However, this hypothesis needs validation in a larger patient cohort and should use concomitant intragraft gene expression analysis to prove the presence of ACR in patients with foci of increased T_2 values but negative histology in the EMB.

The guidelines for the care of heart transplant patients recommend adjustments of maintenance immunosuppressive therapy only in HTx recipients with moderate or severe ACR,[5] which may argue the prognostic benefit associated with the detection of mild ACR. However, intragraft gene expression analysis indicates that the gene expression profile of histological grade 1R ACR is close to the profile of 2R ACR in almost half of all cases.[10] Because ACR $\geq$2R is associated with a decrease in survival after HTx,[15,16] adjustment of the strength of ongoing maintenance immunosuppressive therapy in patients with 1R ACR might be beneficial, and 3D T_2 mapping might be a useful tool for noninvasive detection of mild ACR. However, before HTx recipients are exposed to the risks associated with increased strength of immunosuppression, a critical appraisal of the prognostic

relevance of focally increased T_2 values is mandatory in a longitudinal follow-up study of HTx patients with EMB-guided immunosuppression.

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