Cardiac magnetic resonance imaging with T2 mapping for the monitoring of acute heart transplant rejection in patients with problematic endomyocardial biopsy: in anticipation of new recommendations

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Introduction Acute cardiac allograft rejection (ACAR) in heart transplant (HTx) recipients is a cell-mediated and/or antibody-mediated reaction against a donor heart.[1] It affects about 44% of patients after HTx within the first 5 years posttransplantation and represents a major cause of morbidity and mortality in this patient population.[2] Endomyocardial biopsy (EMB) remains the gold standard for the diagnosis of ACAR (Supplementary material, *Section S1*).[1] However, given the low cost-effectiveness, nonnegligible risk of complications,[3,4] and the well-known potential for false negatives due to sampling error ascribed to EMB, an effective alternative has long been searched for. Cardiac magnetic resonance (CMR) with its recent advancements could be helpful in this regard.[5-8] In anticipation of new guidelines for the diagnosis and management of ACAR in patients after HTx, we present preliminary CMR data of patients followed at the University Clinical Centre in Gdańsk, Poland and discuss contemporary MR techniques, illustrated by serial assessment of a complex HTx case.

Methods The current role of CMR techniques including parametric mapping (Supplementary material, *Section S2*), special considerations regarding reference values, and possible transplant surveillance strategies are briefly discussed, based on preliminary data from 17 consecutive CMR scans in HTx patients followed in our institution, including 5 scans in EMB-confirmed ACAR (+) patients and 12 scans in clinically stable, ACAR (–) patients aged 21 to 75 years (mean [SD], 53 [6] years; 4 female patients [24%]) at 5 to 22 years (median [IQR], 11 [8–14] years) posttransplantation. Parametric mapping data of the ACAR-negative patients were then compared with 22 healthy controls.

The utility of CMR is exemplified in detail by serial CMR findings in a 33-year-old male patient at 4 years after HTx, whose index ACAR was previously described[5] and whose subsequent 5-year follow-up is outlined here. The study was approved by the institutional ethics committee and the patients provided written informed consent to participate in the study.

Statistical analysis The *t* test and the Mann–Whitney test were used depending on data distribution and subgroup sizes. A *P* value of less than 0.05 was considered statistically significant (Supplementary material, *Section S3*).

ACAR treatment (2015) ↓ ACAR treatment (2016) ↓

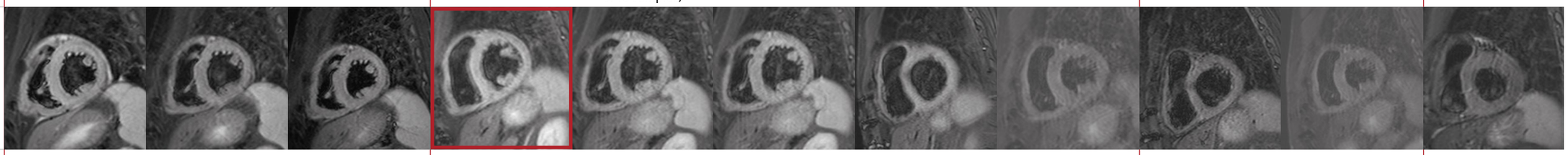
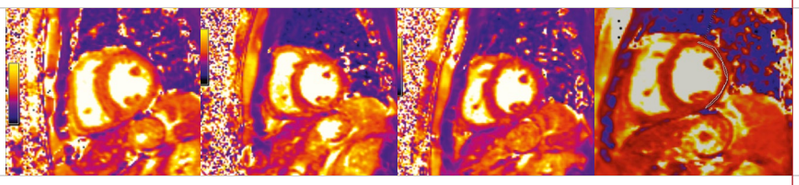
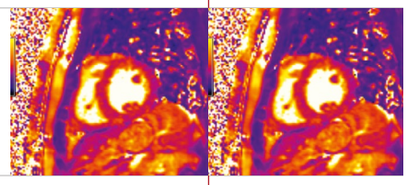
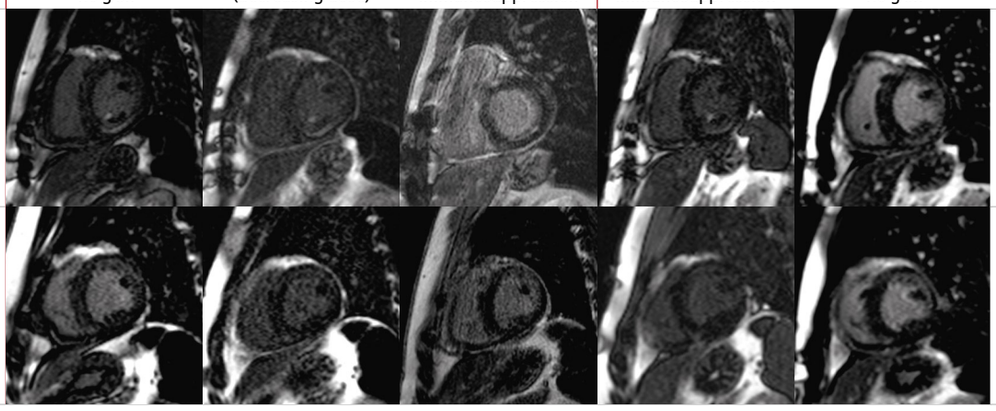
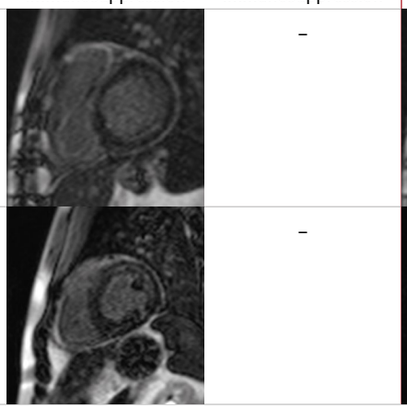
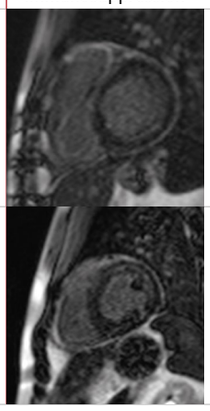
	2015			2016			2016		2017		2019
Study, date	3.03	18.03	20.05	13.01	6.04	20.04	10.05	16.11	6.03	15.11	22.03
LVEF	42%	52%	61%	59%	48%	53%	55%	55%	55%	61%	56%
EDV, m	184	155	142	201	225	179	156	145	173	187	142
ESV, ml	107	75	56	83	120	81	70	66	79	73	63
EMB	1R	–	–	–	2R (no myocardium in 9/10 samples)	–	–	–	–	–	–
Edema imaging (T2STIR)											
T2STIR ratio LV/ skeletal muscle	2.5	2.4	2.1	2.5	2.6	2.5	2.5	1.9	2.1	1.9	2.1
T2 mapping	–	–	–	–					–		
T2 time (global myocardial)	–	–	–	–	68	58	56	53	–	53	54
Treatment	Methylprednisolone 1.0 g 3x	Prednisone (decreasing dose)	Maintenance immunosuppression	Maintenance immunosuppression	Methylprednisolone 1.0 g 3x	Prednisone (decreasing dose)	Maintenance immunosuppression	Maintenance immunosuppression	Maintenance immunosuppression	Maintenance immunosuppression	Maintenance immunosuppression
Fibrosis / scar (LGE) basal						–		–		–	–
Fibrosis / scar (LGE) mid						–		–		–	–

FIGURE 1 Summary of findings in the consecutive cardiac magnetic resonance scans of the 33-year-old patient (described previously[5]) with reference to acute cardiac allograft rejection (ACAR) treatment. Black arrows show ACAR treatment. Red arrow shows the follow-up scan at which the patient was clinically stable, physically active (10 km bike riding every day), with stable left ventricular (LV) function parameters, but a marked increase in short-tau inversion recovery T2-weighted sequence (T2STIR) signal intensity (SI) of the myocardium as compared to SI of the skeletal muscle (SI ratio of 2.5; red frame) was readily apparent. This, in the context of the subsequent follow-up visit 2 months later (reduced exercise tolerance, LV enlargement, LV ejection fraction [LVEF] deterioration, and again high T2STIR SI ratio) could have been interpreted as an early feature of acute myocardial injury (hence, the next follow-up visit was scheduled early). Features of acute myocardial injury consistent with a new ACAR confirmed by endomyocardial biopsy (EMB) can be noted, with an improvement apparent on subsequent scans. Note that not all the scans were done with contrast, as late gadolinium enhancement (LGE) images were largely stable, the patient poorly tolerated multiple breathholds, and the relevant information (ie, features suggestive of acute injury or function decline) in subsequent follow-up scans could be acquired without contrast. Maintenance immunosuppression included everolimus and mycophenolate mofetil.
Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume

Results and discussion To illustrate the utility of CMR, we summarize serial findings in a 33-year-old male at 4 years post HTx due to nonischemic cardiomyopathy (FIGURE 1; Supplementary material, *Section S4* and *Figure S1*). This patient sustained 4 prior ACAR episodes and recent left anterior descending (LAD) coronary artery stenting due to graft vasculopathy. Prior to the index admission, the patient underwent 13 EMB procedures.

The left ventricular volumes and ejection fraction as well as measures of myocardial injury from consecutive CMR examinations are summarized in FIGURE 1, with reference to ACAR treatment. Due to temporary contraindications to EMB and fibrosis found in multiple EMB samples, the management decisions over the following years were driven largely by serial CMR findings, with elective approach to EMB, which became more challenging with every attempt. Until August 2020, the patient remained clinically stable, and subsequent CMR scans showed stable LV volumes and no features of acute myocardial injury.

With the advent of quantitative parametric techniques, per-pixel measurement ("mapping") of the basic magnetic properties of the myocardium became possible (Supplementary material,

Section S2).[6] Thus, tissue characterization with CMR evolved from a predominantly qualitative to a predominantly quantitative exam. In our patients, parametric mapping was used as of 2016.

The complex myocardial status in stable HTx recipients likely precludes the use of the T1 and T2 values from healthy controls as reference values. Therefore, we decided to prospectively acquire T1 and T2 values in our consecutive stable HTx patients (irrespective of their past ACAR history) at their regular follow-up. Patients were considered stable when asymptomatic, and when no alterations suggestive of subclinical ACAR were found on ECG, 24-h Holter monitoring, echocardiography, and routine blood tests. These values could subsequently serve as self-reference in the event of future suspected ACAR. On the other hand, these values could also serve as an internal HTx-specific reference range of "normal" myocardial T2 if CMR was called for due to insufficient, unavailable or clinically discordant EMB data. Of note, the T2 values in stable HTx recipients were clearly above our reference range from the healthy age-matched individuals (median [IQR], 50 [48–52] ms vs 46 [44–47] ms; P <0.001; Supplementary material, *Table S1*). However, they were also markedly lower than the T2 in patients with ongoing ACAR confirmed by biopsy (median [IQR], 50 [48–52] ms vs 58 [53–62] ms; P <0.009; Supplementary material, *Table S2*).

In recent years, several studies addressed the use of parametric CMR as a noninvasive tool for ACAR surveillance. Bonnemains et al[7] found that in all HTx patients with positive (grade ≥2R) EMB, T2 values exceeded 60 ms. However, no reference values in healthy volunteers were reported. As confirmed by our preliminary data, T2 values (measured as an average T2 value of a global region of interest in a mid-ventricular short axis slice) in healthy volunteers are significantly lower than in nonrejecting patients (Supplementary material, *Table S1*). In 2015, a large multicenter trial (French acronym, DRAGET) was designed to test the hypothesis that advanced CMR can replace invasive rejection monitoring with EMB.[8] In 2015, a 3-dimensional T2 mapping sequence was developed[9] and subsequently evaluated for the detection of the focal hotspots of myocardial injury, specifically those related to ACAR.[10] While the results of the DRAGET trial are pending, a number of studies on multiparametric CMR in HTx were published recently.[11-13] Vermes et al[11] reported that using a combination of a T2 (>57.7 ms) and extracellular volume (ECV; >32%) cutoff values for ACAR detection could have prevented 63% of routine biopsies. Our preliminary data seem to be in line with these findings, as both the T2 and ECV values are markedly higher in the nonrejecting group. It should be noted, however, that in our group, the same holds true for the relative, nonparametric edema assessment by short-tau inversion recovery T2-weighted sequence (T2STIR) signal intensity (SI) ratio of the myocardium and of the skeletal muscle, which can be useful if parametric mapping is unavailable (Supplementary material, *Table S2*). Recently, a large study on T1 mapping validated by histopathology demonstrated that the myocardial T1 values above 1029 ms could discern between acute rejection and past rejection or no rejection[12] (Supplementary material, *Section S5*). Our preliminary findings also show marked T1 difference between rejecting and nonrejecting HTx patients, as well as between healthy controls and nonrejecting HTx patients (mean [SD], 1123 [64] ms vs 1019 [38] ms and 993 [21] vs 1019 [38] ms; P = 0.001 and P = 0.004, respectively; Supplementary material, *Tables S1* and *S2*). However, it should be kept in mind that higher T1 and/or ECV values may result from variable extent of interstitial fibrosis (ie, chronic irreversible changes) rather than from edema (acute potentially reversible changes). This naturally draws more attention to an increased T2 as probably more specific to acute, potentially reversible, injury related to ACAR.

The limitations of the present study include small sample size and the possible effect of gender on the results (further discussed in Supplementary material, *Section S1*).

Conclusions In the presented case, the role of routine EMB for future ACAR monitoring would most likely be limited due to extensive fibrosis of the interventricular septum. Edema detected and measured by CMR, with or without LV enlargement, can be an early sign of imminent ACAR. Thus, it can prompt early management decisions including closer surveillance, lifestyle advice and/or early pharmacological intervention. Multiparametric CMR, with all due considerations, can potentially provide a noninvasive alternative for the longitudinal assessment of the heart graft. Whether it can be recommended as EMB replacement in certain clinical scenarios remains to be confirmed by prospective multicenter studies and positioned by the much anticipated International Society for Heart and Lung Transplantation guidelines.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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