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Diagnostic Value of Native T₁ Mapping in Arrhythmogenic Right Ventricular Cardiomyopathy

Correct identification of arrhythmogenic right ventricular cardiomyopathy (ARVC) is pertinent because ventricular arrhythmias can occur early in the disease (1). Ventricular arrhythmias in ARVC typically have a re-entrant mechanism caused by diffuse fibrosis. Although late gadolinium enhancement (LGE) cardiac magnetic resonance cannot quantitatively assess diffuse changes (2), native T₁ mapping is a promising technique to detect diffuse fibrosis. In this proof-of-concept study, we aimed to analyze the value of native T₁ mapping in ARVC.

We included subjects who underwent cardiac magnetic resonance (1.5-T, Achieva, Philips Medical Systems, Best, the Netherlands) with T₁ mapping (Philips’ modification of the 3D Modified Look-Locker Imaging [MOLLI] sequence) (2). Included subjects (n = 43) were divided into 3 groups: 1) genotype-positive patients with ARVC as per 2010 diagnostic task force criteria (n = 13); 2) genotype-positive at-risk relatives not fulfilling task force criteria (n = 17); and 3) control subjects who were evaluated for ARVC but were eventually diagnosed with right ventricular outflow tract ventricular tachycardia (n = 13). Native T₁ mapping was measured in the short-axis view according to the American Heart Association 16-segment model using cvi42 (Circle Cardiovascular Imaging version 5.6.6, Calgary, Canada). Global T₁ values were calculated as mean native T₁ times of all segments. T₁ dispersion was calculated as the SD of native T₁ times in all segments within a given patient. Intraobserver and interobserver variability were evaluated by remeasuring T₁ times in 15 randomly selected subjects. We analyzed only left ventricular (LV) T₁ mapping results because the thin right ventricular wall rendered T₁ mapping susceptible to partial volume effects (overt patients [1,460 ± 211 ms] vs. relatives [1,336 ± 131 ms] vs. control subjects [1,360 ± 116 ms]).

Mean age was 37 ± 17 years, and 51% of the patients were female. There were no differences in age (p = 0.10) or sex (p = 0.53) between the groups. By design, all patients with overt ARVC and at-risk relatives carried a pathogenic mutation (piakophilin-2 [70%], phospholamban [27%], or desmoplakin [3%]). LV LGE was seen in 9 of 13 (69%) overt patients, in 7 of 17 (41%) relatives, and in no control subjects.

Mean LV T₁ times were significantly higher in overt patients (1,067 ± 41 ms) compared with control subjects (1,038 ± 27 ms; p = 0.04), but no statistically significant difference was noted between relatives (1,055 ± 38 ms) and control subjects (p = 0.17). Additionally, T₁ dispersion was significantly greater in both overt patients (93 ± 33 ms; p = 0.02) and relatives (79 ± 15 ms; p = 0.03) compared with control subjects (67 ± 12 ms). This was driven by elevated T₁ times in the LV posterolateral (p ≪ 0.02) and inferior (p = 0.01) regions for both overt patients and relatives and in the anterior (p = 0.01) region for overt patients (Figures 1A to 1C). Using receiver-operating characteristic analysis (overt vs. control), the optimal threshold for abnormal T₁ dispersion was >73 ms (sensitivity, 73%; specificity, 77%; area under the curve: 0.80). Interestingly, 11 of 17 (65%) at-risk relatives had abnormal T₁ dispersion, and 64% (n = 7 of 11) of this group had no LGE or other signs of structural or electrical disease. The intraobserver and interobserver correlation of mean native T₁ times was excellent (intraclass correlation coefficient 0.94).

This study is the first to compare T₁ mapping between patients with ARVC and control subjects. Mean native T₁ time was significantly higher in overt patients compared with control subjects, thus suggesting that the changes in cardiac microstructure are dominated by fibrosis rather than fatty replacement (decreases native T₁ time). In addition, both genotype-positive patients with ARVC and at-risk relatives have a greater dispersion of native T₁ times compared with control subjects, a finding that predominantly reflected changes in posterolateral and inferior regions. A previous study in patients with ARVC with a desmosomal or phospholamban mutation already showed that regional LV changes typically affect the posterolateral wall (3). Our results confirm and extend these findings by revealing that these changes can already be observed in asymptomatic mutation carriers before the development of an overt clinical phenotype. Moreover, a large proportion of at-risk relatives with elevated T₁ dispersion had no LGE, a finding suggesting greater sensitivity for subtle ventricular changes.

We believe that the findings of this study may fuel future studies in a hypothesis-generating manner. Because our results were obtained in a small group of patients, these findings require larger prospective
studies to determine the incremental diagnostic and prognostic value of T1 mapping over established tests for ARVC. Before clinical application, interstudy variability testing including assessment of post-processing methods and determination of reference values for native T1 times and dispersion will be essential. We did not evaluate extracellular volume because reliable hematocrit data were unavailable in most patients. Future studies should preferably include this measure in an evaluation of ARVC.

In conclusion, native T1 mapping helps differentiate patients with overt ARVC and at-risk relatives from control subjects, and it may have the potential to detect early ARVC.

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mid-left anterior descending artery using a transcatheter balloon angioplasty technique (2). The animal stress cardiac magnetic resonance (CMR) protocol included the following: 1) pre-ferumoxytol cine and T₁ mapping at rest and peak stress (4-min adenosine infusion [200 to 400 mg/kg/min]); 2) ferumoxytol (4 mg/kg) infusion; and 3) rest and stress ferumoxytol-enhanced (FE) T₁ mapping. Five patients with positive (n = 3) or equivocal (n = 2) rubidium-82 positron emission tomography stress test results underwent regadenoson FE CMR. The FE CMR protocol included the following: 1) ferumoxytol (4 mg/kg infusion); and 2) multislice FE T₁ mapping at rest and stress (regadenoson 0.4 mg intravenously). We acquired T₁ maps in animal and human subjects using 5(3)3 balanced steady-state free precession (bSSFP) Modified Look-Locker Imaging (MOLLI) and used an in-house T₁ fitting algorithm to account for heart rate variation. Groups were compared using paired Student’s t-tests. Values are reported as mean ± SD.

There were no ferumoxytol-related or vasodilator-related adverse events. Mean post-ferumoxytol blood pool T₁ values at baseline and at peak vasodilation were similar (p = 0.5). Compared with native T₁ reactivity (Figure 1A), ferumoxytol amplified the T₁ reactivity by 12.8-fold in normal myocardium (native T₁ reactivity: 0.8 ± 0.2%; FE T₁ reactivity: –10.2 ± 5.4%; p < 0.01), 7.5-fold in remote myocardium (2.1 ± 0.8% vs. –15.7±1.7%; p < 0.01), and 18-fold in vasodilator-induced hyperperfused myocardium (0.4 ± 0.3% vs. –7.2 ± 0.7%; p < 0.01). The effect size for FE T₁ reactivity was larger than native T₁ reactivity (6.5 [SDpooled = 1.3] vs. 2.8 [SDpooled = 0.6]). Compared with remote myocardium of patients with IHD, the FE T₁ reactivity values in hyperperfused segments were significantly blunted (–8.8 ± 1.9% vs. –3.2 ± 15.9%; p < 0.01). Figure 1B illustrates the qualitative and quantitative potential of FE T₁ maps to depict hypoperfusion at rest and coronary steal physiology at peak vasodilation.

Our findings are hypothesis generating and support the early feasibility of FE CMR T₁ vasodilator testing for detection of IHD. The higher amplitude and dynamic range achieved with ferumoxytol increased the effect size of FE T₁ reactivity and improved its ability to differentiate between remote and hypoperfused myocardium. There are limitations, including the possibility of a blunted T₁ response from capillary leakage in the setting of ischemia. The use of ferumoxytol is also not without risks and needs to be weighed against the benefits. To date, however, ferumoxytol has demonstrated a positive safety profile for off-label diagnostic use.

Ferumoxytol-Enhanced CMR for Vasodilator Stress Testing: A Feasibility Study

Researchers recently proposed using native myocardial T₁ mapping with vasodilator stress testing for evaluation of ischemic heart disease (IHD) (1). A change of 1.5% in native T₁ between rest and peak stress was able to detect significant epicardial coronary stenosis (1). Although this approach is promising, the modest amplitude and narrow dynamic range for native T₁ reactivity (percentage of change in T₁ at peak vasodilation relative to baseline) may pose challenges in daily clinical practice. We propose to increase the amplitude and dynamic range of T₁ reactivity through the off-label use of ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, Massachusetts). Ferumoxytol is used for intravenous treatment of iron deficiency anemia, but it has superparamagnetic properties with high r₁ relaxivity and a long intravascular half-life. We posited that ferumoxytol would sensitize the myocardial T₁ to the vasodilator-induced dynamic differences between rest and peak stress and significantly boost the T₁ reactivity. Because ferumoxytol shortens the T₁, we expected the myocardial T₁ to decrease during vasodilator stress because of the increased distribution space of ferumoxytol.

We studied Yorkshire swine (33 to 52 kg; n = 4 normal, n = 3 coronary stenosis [80% to 90%]) and patients with IHD (n = 5; age 38 to 71 years). For animal studies, we created partial stenosis of the mid-left anterior descending artery using a transcatheter balloon angioplasty technique (2). The animal stress cardiac magnetic resonance (CMR) protocol included the following: 1) pre-ferumoxytol cine and T₁ mapping at rest and peak stress (4-min adenosine infusion [200 to 400 mg/kg/min]); 2) ferumoxytol (4 mg/kg) infusion; and 3) rest and stress ferumoxytol-enhanced (FE) T₁ mapping. Five patients with positive (n = 3) or equivocal (n = 2) rubidium-82 positron emission tomography stress test results underwent regadenoson FE CMR. The FE CMR protocol included the following: 1) ferumoxytol (4 mg/kg infusion); and 2) multislice FE T₁ mapping at rest and stress (regadenoson 0.4 mg intravenously). We acquired T₁ maps in animal and human subjects using 5(3)3 balanced steady-state free precession (bSSFP) Modified Look-Locker Imaging (MOLLI) and used an in-house T₁ fitting algorithm to account for heart rate variation. Groups were compared using paired Student’s t-tests. Values are reported as mean ± SD.

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**REFERENCES**