

Diagnostic value of native T1 mapping in Arrhythmogenic Right Ventricular Cardiomyopathy

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Short title: Native T1 mapping in ARVC patients

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Correct identification of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is pertinent as ventricular arrhythmias (VA) can occur early in the disease(1). VAs in ARVC typically have a re-entrant mechanism caused by diffuse fibrosis. While late gadolinium-enhancement cardiac magnetic resonance imaging (LGE-CMR) 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 CMR (1.5T, Achieva [Philips Medical Systems] with T1 mapping (Philips' modification of the 5(3)3 Modified Look-Locker Imaging [MOLLI] sequence)(2). Included subjects (n=43) were divided into three groups: 1) genotype-positive ARVC patients as per 2010 diagnostic Task Force Criteria (TFC) (n=13); 2) genotype-positive at-risk relatives not fulfilling TFC (n=17) and 3) controls who were evaluated for ARVC but were eventually diagnosed with right ventricular outflow-tract ventricular tachycardia (RVOT-VT) (n=13). Native T1 mapping was measured in short-axis view according to the American Heart Association 16-segment model using cvi42 (Circle Cardiovascular Imaging[version 5.6.6]). Global T1 values were calculated as mean native T1 times of all segments. T1 dispersion was calculated as the standard deviation of native T1 times in all segments within a given patient. Intra- and inter-observer variability were evaluated by re-measuring T1 times in 15 randomly selected subjects. We only analyzed left ventricular (LV) T1 mapping results because the thin RV wall rendered T1 mapping susceptible to partial volume effects (overt patients[1460±211ms] vs. relatives[1336±131ms] vs. controls[1360±116ms]).

Mean age was 37±17years and 51% were female. There were no differences in age (p=0.10) or sex (p=0.53) between the groups. By design, all overt ARVC patients and relatives

carried a pathogenic mutation (Plakophilin-2[70%], Phospholamban[27%] and Desmoplakin [3%]). LV LGE was seen in 9/13 (69%) overt patients, 7/17 (41%) relatives and no controls.

Mean LV T1 times were significantly higher in overt patients ($1067\pm 41\text{ms}$) compared to controls ($1038\pm 27\text{ms}$, $p=0.04$) but no statistically significant difference was noted between relatives ($1055\pm 38\text{ms}$) and controls ($p=0.17$). Additionally, T1 dispersion was significantly greater in both overt patients ($93\pm 33\text{ms}$, $p=0.02$) and relatives ($79\pm 15\text{ms}$, $p=0.03$) compared to controls ($67\pm 12\text{ms}$). This was driven by elevated T1 times in the LV posterolateral ($p\leq 0.02$) and inferior ($p=0.01$) regions for both overt patients and relatives; and in the anterior ($p=0.01$) region for overt patients (**Figure 1**). Using ROC analysis (overt vs. control), the optimal threshold for abnormal T1 dispersion was $>73\text{ms}$ (sensitivity 73%, specificity 77%, $\text{AUC}=0.80$). Interestingly, 11/17 (65%) at-risk relatives had abnormal T1 dispersion of whom 64% ($n=7/11$) had no LGE or other signs of structural/electrical disease. The intra- and inter-observer correlation of mean native T1 times was excellent ($\text{ICC}\geq 0.94$).

This study is the first to compare T1 mapping between ARVC patients and controls. Mean native T1 time was significantly higher in overt patients compared to controls, suggesting that the changes in cardiac microstructure are dominated by fibrosis rather than fatty replacement (decreases native T1 time). In addition, both genotype-positive ARVC patients and relatives have a greater dispersion of native T1 times compared to controls, which predominantly reflected changes in posterolateral and inferior regions. A previous study in ARVC patients 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 prior to the

development of an overt clinical phenotype. Moreover, a large proportion of at-risk relatives with elevated T1 dispersion had no LGE, suggesting greater sensitivity for subtle ventricular changes.

We believe that the findings of this study may fuel future studies in a hypothesis-generating manner. As our results were obtained in a small population, 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 postprocessing methods and determination of reference values for native T1 times/dispersion will be essential. We did not evaluate extracellular volume, since reliable hematocrit data was unavailable in most patients. Future studies should preferably include this measure in evaluation of ARVC.

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

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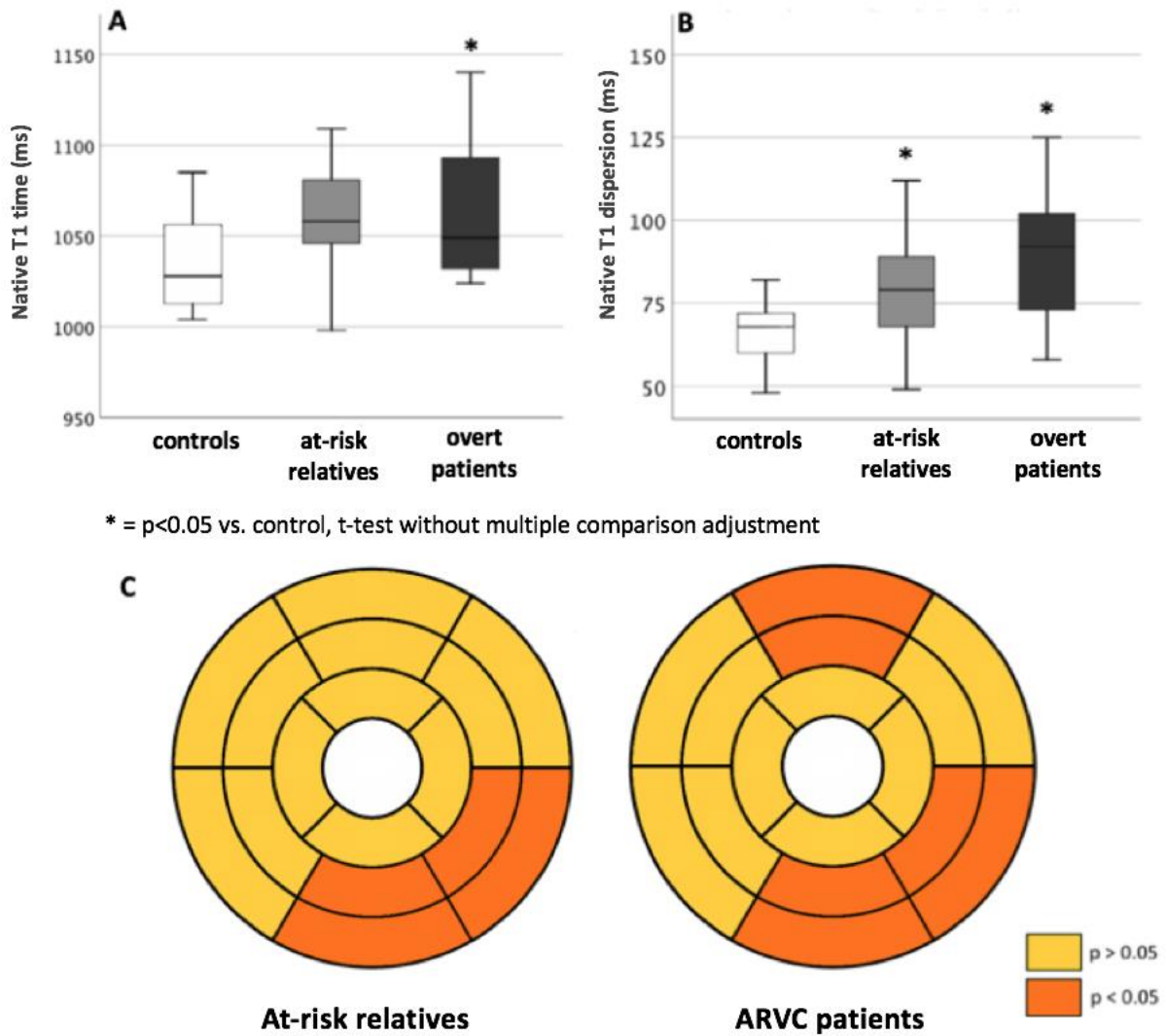


Figure 1: Native T1 times and dispersion

A) Mean T1 times; B) T1 dispersion; C) Bullseyes of native T1 times of relatives vs. controls and patients vs. controls.