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Original Article

Measurement of diffuse ventricular fibrosis with myocardial T1 in patients with atrial fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) is associated with cardiac fibrosis, which can now be measured noninvasively using T1-mapping with cardiac magnetic resonance imaging (CMRI). This study aimed to assess the impact of AF on ventricular T1 at the time of CMRI.

Methods: Subjects with AF scheduled for AF ablation underwent CMRI with standard electrocardiography gating and breath-hold protocols on a 1.5 T scanner with post-contrast ventricular T1 recorded from 6 regions of interest at the mid-ventricle. Baseline demographic, clinical, and imaging characteristics were examined using univariate and multivariable linear regression modeling for an association with myocardial T1.

Results: One hundred fifty-seven patients were studied (32% women; median age, 61 years [interquartile range {IQR}, 55–67], 50% persistent AF [episodes > 7 days or requiring electrical or pharmacologic cardioversion], 30% in AF at the time of the CMRI). The median global T1 was 404 ms (IQR, 381–428). AF at the time of CMRI was associated with a 4.4% shorter T1 ($p=0.000$) compared to sinus rhythm when adjusted for age, sex, persistent AF, body mass index, congestive heart failure, and renal dysfunction (estimated glomerular filtration rate < 60). A post-hoc multivariate model adjusted for heart rate suggested that heart rate elevation ($p=0.009$) contributes to the reduction in T1 observed in patients with AF at the time of CMRI. No association between ventricular T1 and AF recurrence after ablation was demonstrated.

Conclusion: AF at the time of CMRI was associated with lower post-contrast ventricular T1 compared with sinus rhythm. This effect was at least partly due to elevated heart rate. T1 was not associated with the recurrence of AF after ablation.

1. Introduction

Atrial fibrillation (AF) is a common disease that has been identified as both a cause and consequence of adverse cardiac electrical and structural remodeling [1,2]. Structural remodeling in the form of cardiac fibrosis occurs in both the atria and ventricles, and it is known to contribute to the development of AF [3–5]. Diffuse myocardial fibrosis can now be measured using cardiac magnetic resonance imaging (CMRI) post-contrast T1 relaxation (T1) time. Gadolinium-based contrast accumulates in areas of increased extracellular space, resulting in a shorter T1. The degree to which contrast shortens T1 is, therefore, a reflection of the extent of diffuse myocardial fibrosis. A shorter T1 in both the atria and ventricles predicts AF presence and severity, and it may predict the clinical response to AF therapies such as catheter-based AF ablation [5,6].

Given the increasing interest in exploring the potential clinical applications of T1, it is important to understand the factors that influence its measurement. Experimental evidence shows that at

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the time of CMRI, cardiac rhythm abnormalities such as tachycardia or irregularity may lead to an underestimation of T1 [7,8]. Tachycardia and irregularity are characteristic of AF; however, the effect of AF on myocardial T1 in humans has not been previously investigated. Accordingly, the primary goal of this study was to test the hypothesis that AF at the time of CMRI is an independent predictor of shortened ventricular T1 in patients with AF referred for catheter-based ablation. As a secondary goal, given previous reports of ventricular T1 predicting AF recurrence after ablation [6], we sought to provide independent validation of that finding.

2. Material and methods

2.1. Study population

Subjects were enrolled in the Vanderbilt AF Ablation Registry and provided written informed consent. The study protocol was approved by the Vanderbilt Institutional Review Board. Patients with data that met the following eligibility criteria were included in our analysis: age $>$ 18 years, AF ablation after 1/1/2008, a pre-ablation CMRI performed at Vanderbilt University, and no prior history of catheter-based or surgical ablation for AF. To explore the association with AF recurrence, only subjects with at least 6 months of clinical follow-up after AF ablation were included.

2.2. CMRI protocol

As part of routine clinical care, a CMRI study was performed prior to AF ablation to provide detailed assessment of cardiac and PV anatomy and to generate a three-dimensional (3D) electroanatomic map. Imaging was performed using a 1.5-T Siemens Avanto (Siemens Healthcare, Erlangen, Germany) with an 8-channel cardiac coil. Ventricular function was assessed using breath-hold, electrocardiogram-gated, serial short-axis steady-state free precession cine images as previously described [9]. Intravenous Gd-DTPA contrast (gadopentate dimeglumine, Magnevist®, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) was administered at a dose of 0.2 mmol/kg. The size of the left atrium was measured in the anterior–posterior orientation on axial half-Fourier acquisition turbo spin-echo images. A Look-Locker sequence was obtained in a short-axis plane at the level of the papillary muscles 10 min after contrast administration with these imaging parameters: field of view, 275–400 $\times$ 340–400 mm; matrix, 66–96 $\times$ 192; slice thickness, 8 mm; flip angle, 30°; and no parallel imaging. Standard Look-Locker imaging included 15–35 images acquired every other R-R interval with phase intervals of approximately 30 ms. The images were electrocardiography gated and acquired using a segmented k-space during breath-holds. For the left ventricular (LV) volumes, ejection fraction, and mass measurements, epicardial and endocardial contours were drawn in end-diastole and end-systole on a Leonardo Workstation (Siemens Healthcare, Erlangen, Germany).

2.3. Quantification of myocardial T1

The Look-Locker images were analyzed utilizing an open source software program (MRMap version 1.3 [http://mrmap.sourceforge.net]) [10,11]. The T1 map generated was saved as a Digital Imaging and Communications in Medicine image and imported into MatLab (MathWorks, Natick, MA, USA). Six regions of interest were manually drawn in the midventricular segment corresponding to the anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral walls in short-axis orientation. The myocardial T1 values for each voxel in each of the 6 regions of interest were then exported for averaging and analysis. A global T1 value was calculated by averaging the T1 from the 6 regions of interest.

2.4. Catheter ablation

In brief, AF ablation was performed with the patient under general anesthesia with continuous invasive monitoring of blood pressure and oxygen saturation. A 3D mapping system (Carto, Biosense-Webser, Inc., Diamond Bar, CA, USA) was used for non-fluoroscopic catheter navigation, computed tomographic, or magnetic resonance image integration as well as tagging of ablation sites. Trans-septal access was obtained using fluoroscopy and intracardiac or transesophageal echocardiographic guidance. An irrigated-tip ablation catheter was used. Circumferential left atrial (LA) ablation lines were placed around the antrum of the ipsilateral pulmonary veins, and the demonstration of pulmonary vein (PV) isolation was the major procedural endpoint. PV potentials were recorded using a circular mapping catheter placed in each PV to test for the absence of signals conducting into the PV during LA pacing (entrance block) or into the LA from the PVs during PV pacing (exit block). Additional ablation was performed until PV isolation was achieved. Empiric linear lesions to the LA roof, basal posterior wall, and mitral isthmus and/or ablation of complex fractionated electrograms were placed based on operator discretion. Anticoagulation with heparin was used in an attempt to maintain an activated clotting time $>$ 300 s during LA access.

2.5. Follow-up

Patients were seen in clinical follow-up at 1, 3, 6, and 12 months. Ambulatory 48-h Holter (3-month) or 7-day auto-triggered event monitoring (6- and 12-month) was performed to assess for asymptomatic AF recurrence. Recurrence was defined as $>$ 30 s of AF, atrial tachycardia, or atrial flutter (AF/AT/AFL). As is standard for AF ablation reporting, a 3-month blanking period was used such that recurrences during that period were not counted toward the arrhythmia recurrence endpoint [12].

2.6. Statistical analysis

Baseline patient characteristics are reported as the frequency and percentage for categorical variables and as the median and interquartile range (IQR) for continuous variables. Groups were compared using a Wilcoxon sum rank test for continuous variables and a Chi-square test or Fisher's exact test for categorical variables. The analysis for predictors of global T1 was performed using multivariable linear regression. To avoid over-fitting our multivariable linear regression model, we calculated the number of covariates based on a ratio of $>$ 15 subjects per degree of freedom. Age and sex were pre-specified covariates for our final model, and additional covariates were selected if the p value on univariate analysis was $<$ 0.10. Covariates in the regression models were evaluated for multicollinearity by calculation of the variance inflation factor (VIF), and covariates were excluded when VIF values were $>$ 2.5. Continuous variables were graphically assessed for normality and log-transformed to improve the residuals. A complete case analysis was performed, and records with a missing value were excluded from the final analysis. As a secondary analysis, a Cox proportional hazards model was used to test the ability of T1 to predict time to first occurrence of any atrial tachyarrhythmia after ablation. A 10:1 ratio of degrees of freedom to events was used for the Cox proportional hazards model. The assumptions of the Cox proportional hazards model were met including: (1) censoring was non-informative; and (2) the assumption of proportional hazards was examined using log–log plots that demonstrated parallel curves with proportional