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Left Ventricular Native T_1 time and the Risk of Arial fibrillation Recurrence after Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation

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Abstract

Background—Native T_1 mapping has emerged as a noninvasive non-contrast magnetic resonance imaging (MRI) method to assess for diffuse myocardial fibrosis. However, LV native T_1 time in AF patients and its clinical relevance are unclear.

Methods—Fifty paroxysmal AF patients referred for PVI (60±8 years, 37 male) and 11 healthy control subjects (57±8 years, 10 male) were studied. All patients were in sinus rhythm during the MRI scan. Native T_1 mapping images were acquired using a Modified Look-Locker imaging (MOLLI) sequence in 3 short-axis planes (basal, mid and apical slices) using an electrocardiogram triggered single-shot acquisition with a balanced steady-state free precession readout. Late gadolinium enhanced (LGE) MRI was acquired to evaluate for LV myocardial scar.

Results—LV ejection fraction was similar between groups (AF: 61±6%; controls: 60±6%, p=0.75). No LV myocardial scar was observed in any patient on LGE. Myocardial native T_1 time was greater in AF patients (1099±52 vs 1042±20 msec, p<0.001). During a median follow-up period of 326 days, 18 of 50 (36%) patients experienced recurrence of AF. Multivariate Cox proportional hazard analysis identified elevated native T_1 time as an independent predictor of recurrence of AF (HR: 6.53, 95% CI: 1.25–34.3, p=0.026).

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Conclusions—There are differences in the native LV myocardial T_1 time between AF patients with preserved LV function referred for PVI and normal controls. Native T_1 time is an independent predictor of recurrence of AF after PVI in patients with paroxysmal AF.

Keywords

T_1 mapping; magnetic resonance imaging; fibrosis; atrial fibrillation; cardiomyopathy; recurrence of atrial fibrillation

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting 2% for those <65 years and 9% of those ≥65 years in the United States[1]. The symptoms of AF vary greatly, ranging from minimal to severe disability. AF is associated with a 5-fold increased risk of stroke[2] and a 3-fold increased risk of heart failure[3–5]. In AF patients, diffuse myocardial interstitial fibrosis may occur due to tachycardia induced cardiomyopathy[6]. Previous studies demonstrated that tachycardia induced cardiomyopathy may progress to heart failure and lethal ventricular arrhythmia in AF patients[7–9]. Therefore, detection of underlying LV myocardial abnormalities in AF patients is essential for clinical management.

Native T_1 mapping has been introduced as a robust magnetic resonance imaging (MRI) technique for the assessment of diffuse myocardial fibrosis in various cardiovascular disease. Recent studies has demonstrated that native T_1 mapping detects left ventricular (LV) myocardial abnormalities in patients with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM)[10], cardiac amyloidosis[11] and Anderson-Fabry disease[11, 12]. Native T_1 mapping could be useful to assess the extent of myocardial injury by acute myocardial infarction[13]. To the best of our knowledge, no data are available regarding LV native T_1 time in AF patients. We hypothesized that native T_1 mapping could detect the subclinical LV myocardial abnormality in AF patients.

Therefore, we sought to compare native myocardial T_1 time by using a modified Look-Locker inversion recovery (MOLLI) sequence in patients with AF and healthy control subjects; and to investigate whether native T_1 time can predict the recurrence of AF after their first pulmonary vein isolation (PVI) in patients with paroxysmal AF.

Materials and Methods

Study subjects

Inclusion criteria of this prospective study included a history of paroxysmal AF patients referred for their first PVI. Exclusion criteria included patients in AF during MRI scan, reduced LV systolic function (LVEF<50%)[14], cardiomyopathy (HCM, DCM[15]), cardiac sarcoidosis and amyloidosis, severe valvular heart disease, prior myocardial infarction and contraindication to MRI examination (claustrophobia, pacemaker implantation etc.). According to this criteria, we enrolled 50 paroxysmal AF patients. Eleven subjects without any history of cardiovascular diseases including AF were recruited as healthy controls.

Acquisition of MRI

All MRI data were acquired using a 1.5-T MRI system and a 32-channel cardiac phased array receiver coil (Achieva, Philips Healthcare, Best, The Netherlands). The study protocol was approved by our institutional review board, and written informed consent was obtained from all study subjects. Cine MRI, T_1 mapping and 3 dimensional late gadolinium enhancement (LGE) MRI were imaged in all participants. T_1 mapping of LV myocardium was performed using a MOLLI sequence[16].

Cine MRI acquisition—Electrocardiogram (ECG) monitoring leads were positioned on supine patients. Vertical and horizontal long-axis cine MRI images of the LV were acquired using a steady-state free precession (SSFP) sequence. LV volumes and mass were calculated from an LV short-axis stack of cine images extending from the apex to the base (repetition time (TR), 3.3 ms; echo time (TE), 1.6 ms; flip angle (FA), 60°; field-of-view (FOV), 320×320 mm; acquisition matrix, 128×128; slice thickness, 8 mm; gap, 2 mm).

Native T_1 mapping by MOLLI—T_1 mapping images of LV myocardium were acquired in 3 short-axis planes (basal, mid and apical). Images were acquired during an end-expiration breath-hold using an ECG-triggered single-shot acquisition with a balanced SSFP readout (TR, 3.1 ms; TE, 1.5 ms; FA, 35°; FOV, 360×337 mm^2; acquisition matrix, 188×135; voxel size, 1.9×2.5 mm^2; slice thickness, 8 mm).

Late gadolinium enhancement—Fifteen minutes after the injection of 0.2 mmol/kg gadobenate dimeglumine (MultiHance; Bracco, Rome, Italy), LGE images were acquired using a 3 dimensional sequence[17] (TR, 5.3 ms; TE, 2.1 ms; FA, 70°; FOV, 320×320×125 mm^3; acquisition matrix, 224×224×23; spatial resolution,1.4×1.4×4 to 5mm; reconstruction resolution, 0.6×0.6×2 to 2.5mm).

Image analysis

Data were analyzed using a commercial workstation (Extend MR WorkSpace, version 2.3.6.3, Philips Healthcare). To determine LV mass, end-diastolic epi- and endocardial LV borders were manually traced on the short axis dataset. LV mass was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/mL) of myocardial tissue[18]. Left atrial transverse dimensions were measured in the end-systolic phases using 4 chamber view. Short-axis slices of native T_1 mapping images were analyzed using custom software (MediaCare, Boston, Massachusetts). After manually contouring endocardial and epicardial LV borders, the LV was divided into 6 segments for base and mid slices, 4 segments for apical slice using the anterior right ventricular-LV insertion point as reference. The 16 segment model was used to compare the native T_1 time in each segment. Motion correction was performed using the Adaptive Registration of varying Contrast-weighted images for improved Tissue Characterization (ARCTIC) approach for both T_1 mapping[19]. To evaluate inter-observer reproducibility, measurements of native T_1 time from 10 AF patients and 10 normal subjects were independently taken by two observers. One of the two observers measured native T_1 time twice to assess intra-observer reproducibility. Visual assessment was performed to evaluate presence or absence of LV myocardial scar on LGE MRI by two independent observers.

Procedure of PVI

The electrophysiology procedure was performed by a femoral venous approach. A decapolar catheter was positioned in the coronary sinus and a second catheter was placed in the right atrium. Transseptal punctures were performed to obtain left atrial access. Following transseptal puncture, patients received intravenous heparin to maintain a serum activated clotting time >250msec. Three-dimensional electroanatomic mapping of the left atrium and PV was performed using a non-irrigated 4 or 8 mm tip NaviStar™ catheter (Biosense Webster) and CARTO™ (Biosense Webster) and/or EnSite NavX™ (Endocardial Solutions) recording systems. Ablation was performed for 20–60 sec with a target temperature of 52°C. All PV were routinely isolated for all patients.

Clinical follow up

Follow up information was obtained from online medical record. Early AF recurrence was defined as AF occurring within 3 months after PVI. Late AF recurrence was defined as AF occurring between 3 months and 12 months after PVI[20–22]. AF recurrence was confirmed by either ECG or cardiac monitoring (remote implanted loop recorder). Complete follow-up was obtained from all patients.

Statistical analysis

Data were analyzed using SPSS software (version 17.0, SPSS, Inc., Chicago, IL, USA) and MedCalc for Windows (version 14.8.1, MedCalc Software, Ostend, Belgium). Continuous values are presented as means ± standard deviation (SD). Categorical values are expressed as number (%). Normality was determined by the Shapiro-Wilk test. Differences between AF patients and control subjects were evaluated using an unpaired *t*-test for normally distributed variables, and the Mann-Whitney U test for skewed variables. Bland and Altman plot[23], coefficient of variation, intraclass correlation coefficient (ICC) were used to assess intra- and inter-observer reproducibility for measuring native T_1 time. Repeatability coefficients were calculated as 1.96 times the SD of the differences on the Bland-Altman plots. The differences of native T_1 time between 3 slices (base, mid and apex) were assessed using one way analysis of variance with Tukey's correction. Elevated myocardial T_1 time was defined as >1082msec, which was 2SD of native T_1 time in healthy control subjects. We calculated the cumulative incidence of AF recurrence after PVI using the Kaplan-Meier method and compare the two groups with a Log-rank test (elevated LV T_1 time group (n=31) vs non-elevated LV T_1 time group (n=19)). Multivariate Cox proportional hazards model was used to estimate the hazard ratio (HR) for recurrence of AF and reported with 95% confidence interval (CI). A P value <0.05 was considered statistically significant.

Results

Patients' characteristics

Table 1 summarizes the clinical characteristics of the AF patients and control subjects. AF patients were heavier (p=0.009) and with greater CHA2DS2-VASc score (p=0.011). Incidence of hypertension (p=0.046) and dyslipidemia (p=0.028) were higher in AF patients. There was no difference in age, gender, systolic blood pressure, diastolic blood pressure,

heart rate or the incidence of diabetes mellitus or current smoking. The duration of AF was defined as the time between initial AF confirmed by an electrocardiogram and MRI acquisition date.

Cardiac MRI findings

Table 2 summarizes cardiac MRI anatomic measures for the two groups. There were no significant difference in LV ejection fraction, end-diastolic volume, end-systolic volume or mass. Left atrial dimension was significantly higher in AF patients (p=0.018). No LV LGE was observed in any subjects.

Native T_1 time in AF patient and controls

Example native T_1 mapping images are shown in Figure 1. Figure 2 demonstrated comparison of individual native T_1 time between AF patients and controls. Myocardial native T_1 time was significantly elevated in patients with AF (1099±52 msec vs 1042±20 msec, p=0.003). Significant difference of LV native T_1 time was found between healthy control and AF patients with recurrence (1042±20 msec vs 1126±53 msec, p<0.001), between AF patients with recurrence and AF patients without recurrence (1126±53 msec vs 1084±45 msec, p=0.023). However, no difference was found between healthy controls and AF without recurrence (1042±20 msec vs 1084±45 msec, p=0.055). Table 3 summarizes myocardial native T_1 time for each slice. Native T_1 time was elevated in all 3 slices in AF patients compared to normal subjects.

Clinical follow-up

During a median follow-up duration of 326 days (range: 4–691 days), 18 of 50 (36%) AF patients experienced recurrence of AF after PVI (16 recurrences for patients with elevated LV T_1 (>1082msec), 2 recurrences for patients with non-elevated LV T_1 (≤1082msec)). Figure 3 illustrated Kaplan Meier event free survival curve for AF recurrence after PVI. Significant difference was observed between AF patients with elevated LV native T_1 time and AF patients with non-elevated LV native T_1 time both in late AF recurrence (p=0.030 by Log-rank test) and in early and late AF recurrence (p=0.006 by Log-rank test). Table 4 shows the results of multivariate Cox proportional hazard analysis for AF recurrence after PVI. Multivariate analysis demonstrated that native LV T_1 time >1082msec is an independent and significant predictor of AF recurrence (hazard ratio: 6.53, 95%CI: 1.25–34.3, p=0.009)

Reproducibility for measurement of native T_1 time

The results of reproducibility for native T_1 time measurements were summarized in Table 5. Both in AF patients and control subjects, high reproducibility of native T_1 time measurements were observed for intra-observer reproducibility and inter-observer reproducibility.

Discussion

In this prospective study of consecutive AF patients referred for MRI prior to PVI, we identified elevated native T_1 time in AF patients as compared with control subjects. To the

best of our knowledge, this is the first investigation to examine native T_1 time in AF patients by using the MOLLI sequence. Furthermore, we found the significant difference of AF recurrence after PVI between patients with elevated LV T_1 time and patients with non-elevated LV T_1 time, suggesting that native LV T_1 time might be useful for the risk stratification for AF recurrence after PVI in paroxysmal AF patients.

Diffuse left ventricular myocardial abnormality in AF patients detected by *post-contrast* and *native* T_1 mapping

Several studies have demonstrated the clinical utility of post-contrast T_1 mapping for the detection of diffuse myocardial abnormality in AF patients. Ling et al. showed that post-contrast T_1 mapping can identify diffuse LV fibrosis in AF patients[24]. This report provided new insight into association between AF and adverse LV remodeling. Neilan et al. revealed that extra cellular volume quantification of LV myocardium is an independent predictor of AF recurrence in hypertensive AF patients who underwent PVI[20]. McLellan et al. demonstrated a shorter post-contrast T_1 time of LV myocardium in patients with recurrent AF as compared to those without AF recurrence; post-contrast T_1 time is an independent predictor of AF recurrence[25]. These reports showed the pathophysiological link between LV myocardial fibrosis detected by post contrast T_1 mapping and atrial fibrillation. In the current study, we measured the LV native (non-contrast) myocardial T_1 time in AF patients undergoing PVI and found a significant difference between AF patients and control subjects. Although the difference of native T_1 time between AF patients and healthy controls was statistically significant, comparison of individual native T_1 time showed substantial overlap between AF patients and healthy controls (13 of 50 (26%) AF patients were less than native T_1 time of 1062msec, which is maximum native T_1 time of healthy subjects), suggesting that native T_1 time might not be able to differentiate AF patients from healthy controls in about one fourth of the AF population. However, overlap of native T_1 time was small between healthy control and AF patients with recurrence (only 2 of 18 patients, Figure 2). Important finding of this study was that the elevated native T_1 time was an independent and significant predictor of AF recurrence after PVI. These results indicated that LV native T_1 time might be useful as a possible surrogate marker to detect high-risk AF patients who are going to develop AF recurrence after PVI in near future, rather than an isolated marker to differentiate abnormal LV myocardium of AF patient and healthy LV myocardium of normal subjects.

Possible mechanism of elevated native T_1 time in AF patients

AF is known to be associated with various pathophysiologic disorders of cardiovascular system, including endothelial dysfunction[26–30], inflammation and oxidative stress[31–33], and atherosclerosis[34–36]. Freestone et al. demonstrated that endothelial dysfunction evaluated by flow-mediated dilatation is present in AF patients[26]. Lim et al. showed that catheter ablation and successful maintenance of sinus rhythm leads to a decrease in platelet activation and an improvement in endothelial function[30]. In addition, Li et al. revealed that inflammatory biomarkers such as Interleukin (IL)-6, IL-8, IL-10, tumor necrosis factors-alpha, monocyte chemoattractant protein 1, vascular endothelial growth factor, and N-terminal pro-brain natriuretic peptide were elevated in AF patients[31]. Another possible mechanism for elevated T_1 time is myocardial edema. Previous studies showed that T_1 time is substantially increased

in acute myocardial edema in animal[37] and human studies[38]. Ferreira et al. showed that native T_1 mapping has a higher sensitivity compared with T_2 weighted image and LGE image for detecting acute myocarditis[38–40]. Elevated native T_1 time might be explained by myocardial edema, which could be related to high inflammatory activity in AF patients[41]. Although the evidence which clearly explains a mechanism of diffuse LV myocardial abnormality in AF patients is lacking, these cardiovascular pathophysiologic abnormalities may be associated with elevation of native T_1 time observed in the current study.

Clinical Implication

Our AF population did not have LV systolic dysfunction on cine MRI and myocardial enhancement on LGE MRI in any study subjects. However, native T_1 time was significantly elevated in AF patients and elevated native T_1 time could predict future AF recurrence after PVI. This result was similar to the results of previous studies using post contrast T1 mapping images. However, the strong point of this study was that non-contrast (native) T_1 mapping could assess myocardial T_1 time even for AF patients with renal dysfunction at a high risk of nephrogenic systemic fibrosis[42]. Recent studies demonstrated the clinical utility of cardiac MRI and CT for AF ablation. Ang R. et al showed that pulmonary vein measurements on pre-procedural CT/MR imaging can predict difficult PVI and phrenic nerve injury during cryoballoon ablation[43]. Kim et al. reported that pericardial fat volume is associated with clinical recurrence after catheter ablation for persistent atrial fibrillation, but not paroxysmal atrial fibrillation[44]. Another study by Costa FM et al. revealed that left atrial volume is more important than the type of atrial fibrillation in predicting the long-term success of catheter ablation[45]. In the current study, the follow up duration for AF recurrence was relatively short, therefore, further study is necessary to investigate whether LV native T_1 time is useful to predict AF occurrence in long term follow up period after PVI.

Study limitation

Our study has several limitations. First, this is single center study of a relatively small population of AF patients all referred for PVI. Second, we did not performed endomyocardial biopsy to confirm the presence of myocardial fibrosis. Third, although LGE MRI showed no myocardial infarction, we did not perform X-ray coronary angiography or computed tomography angiography to exclude coronary artery disease, which is common in this population. Forth, not all the AF patients and healthy control had implantable loop recorders. Therefore, asymptomatic AF recurrence might be missed.

Conclusion

Native LV myocardial T_1 time is increased in AF patients with preserved LV function referred for PVI. Native T_1 time is an independent predictor of recurrence of AF after PVI in patients with paroxysmal AF. These result suggested that LV native T_1 time might be useful for the risk stratification to detect high risk AF patients for AF recurrence after PVI.

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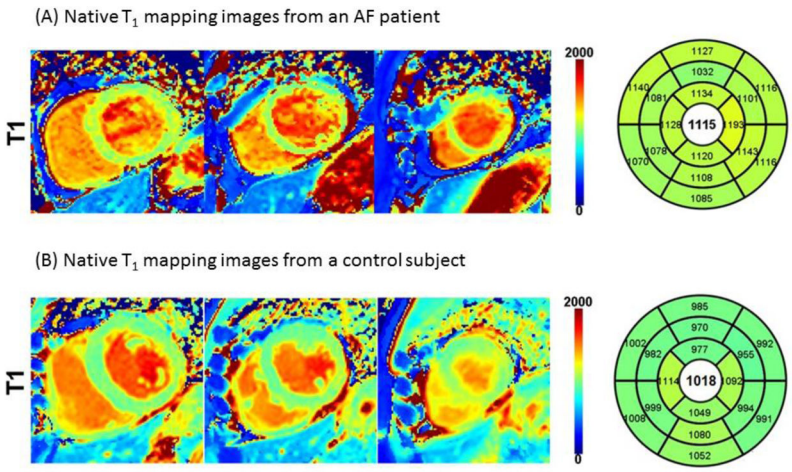

Figure 1. Native T_1 mapping images from a 62 year-old male atrial fibrillation (AF) patient and a 64 year-old male control subject

(A) AF patient. Native T_1 time was elevated at 1115 msec. (B) Healthy control subject. Mean native T_1 time was 1018 msec, and is within normal range.

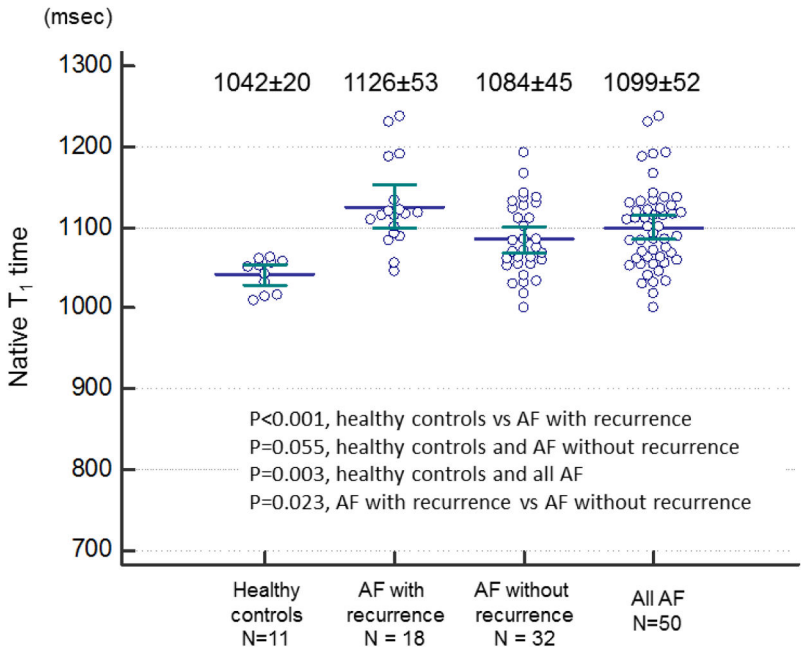

Figure 2. Comparison of individual native T_1 time in AF patients and healthy controls

Significant difference of LV native T_1 time was found between healthy control and AF patients with recurrence, between healthy controls and all AF patients, between AF patients with recurrence and AF patients without recurrence. However, no difference was found between healthy controls and AF without recurrence.

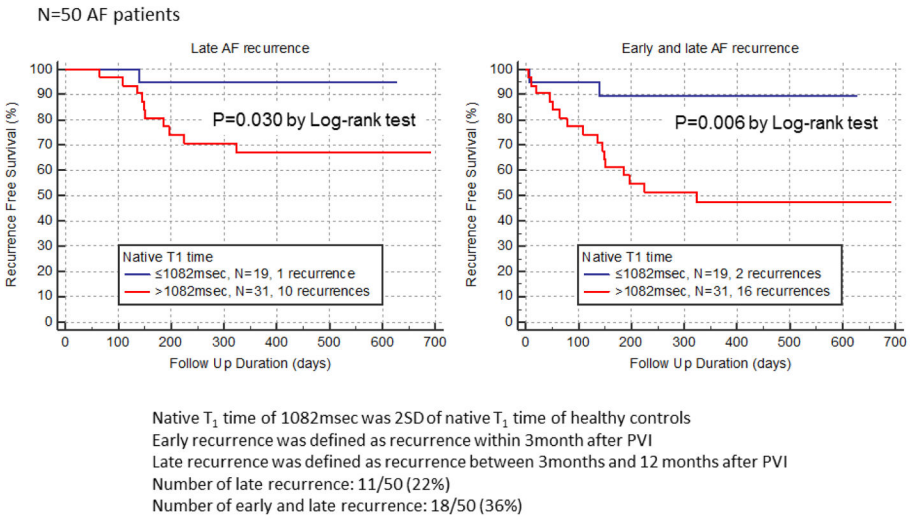

Figure 3. Kaplan Meier event free survival curve for AF recurrence after pulmonary vein isolation

AF recurrence rate was significantly higher in AF patients with native T_1 time >1082msec than those with ≤1082msec both in late recurrence (p=0.030 by Log rank test) and in early and late recurrence (p=0.006).

Table 1

Characteristics of study subjects

	AF patients, N=50	*Controls, N=11*	*P-value*
Male	37 (74%)	10 (77%)	0.83
Age, years	60 ± 8	57 ± 8	0.080
BMI, kg/m^2	27.9 ± 4.0	24.4 ± 3.0	0.009
SBP, mmHg	120 ± 15	108 ± 33	0.057
DBP, mmHg	75 ± 13	75 ± 14	0.84
HR, beats per minutes	63 ± 10	63 ± 9	0.70
CAD risk factors			
Hypertension	14 (28%)	0 (0%)	0.046
Dyslipidemia	16 (32%)	0 (0%)	0.028
Diabetes mellitus	3 (6%)	0 (0%)	0.40
Current smoker	1 (2%)	0 (0%)	0.64
Family history of CAD	9 (18%)	1 (8%)	0.47
Medication			
Calcium channel blocker	9 (18%)	0 (0%)	0.13
ACE/ARB	9 (18%)	0 (0%)	0.13
Beta blocker	23 (46%)	0 (0%)	0.004
Anti-arrhythmic agent	23 (46%)	0 (0%)	0.004
Anticoagulant	41 (82%)	0 (0%)	< 0.001
Statin	18 (36%)	0 (0%)	0.017
CHA2DS2-VASc score	1.0 ± 1.1	0.1 ± 0.3	0.011
Duration of AF, years	3.9 ± 4.9	-	-

ACE; angiotensin converting enzyme inhibitors, AF; atrial fibrillation, ARB; angiotensin receptor blockers, BMI; body mass index, CAD; coronary artery disease, DBP; diastolic blood pressure, HR; heart rate, SBP; systolic blood pressure

Table 2

Cardiac MRI measures

	AF patients, N=50	*Controls, N=11*	*P-value*
Cine MRI parameters			
LVEDV, mL	158 ± 40	152 ± 39	0.64
LVEDVI, mL/m^2	77 ± 16	79 ± 14	0.79
LVESV, mL	63 ± 22	62 ± 19	0.75
LVESVI, mL/m^2	30 ± 9	32 ± 8	0.80
LVSV, mL	96 ± 24	90 ± 24	0.64
LVSVI, mL/m^2	47 ± 10	47 ± 8	0.83
LVEF, %	61 ± 6	60 ± 6	0.75
LV mass, g	97 ± 31	107 ± 41	0.36
LV mass index, g/m^2	47 ± 12	56 ± 16	0.59
LA dimension, mm	42 ± 11	34 ± 9	0.018
LGE findings			
Presence of LV LGE	0	0	-

AF, atrial fibrillation; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; ESV, end-systolic volume; ESVI, end-systolic volume index; HR, heart rate; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; RV, right ventricle; SV, stroke volume; SVI, stroke volume index

Table 3

Native myocardial T_1 time in each slice levels

	Base	***Mid***	***Apex***	***+P value between slices***
AF patients, n=50	1093 ± 72	1100 ± 65	1109 ± 66	0.51
Control subjects, n=11	1035 ± 25	1037 ± 32	1060 ± 25	0.075
****P value (AF vs controls)***	0.010	0.003	0.018	

Values are presented as mean ± SD.

+P-values represent significance of difference between 3 slices (base, mid and apex) both in AF patients and controls (one way analysis of variance with Tukey's correction).

*P-values represent significance of difference between AF patients and controls in base, mid and apex.

AF, atrial fibrillation

Table 4

Multivariate Cox proportional hazard analysis for AF recurrence after pulmonary vein isolation

	HR	*95% CI*	*P value*
Age, per years	0.97	0.85 – 1.10	0.65
Gender, male	1.97	0.29 – 13.7	0.49
Hypertension, yes	0.23	0.033 – 1.64	0.14
Dyslipidemia, yes	1.67	0.29 – 9.57	0.57
Obesity (BMI>25 kg/m^2)	0.79	0.16 – 3.81	0.76
Family history of CAD, yes	0.43	0.062 – 2.95	0.39
LVEDVI, per mL/m^2	1.12	0.77 – 1.64	0.56
LVESVI, per mL/m^2	0.89	0.52 – 1.51	0.66
LVSVI, per ml/m^2	0.89	0.60 – 1.30	0.54
LVEF, per %	1.06	0.75 – 1.49	0.76
LV mass index, per g/m^2	1.02	0.96 – 1.09	0.48
LA dimension, per mm	1.01	0.95 – 1.07	0.83
CHA2DS2-VASc score, per 1 score	1.67	0.87 – 3.19	0.12
AF duration, per year	1.04	0.91 – 1.18	0.58
Native T_1 time, >1082msec	6.53	1.25 – 34.3	0.026

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HR, hazard ratio; LA, left atrial; LV, left ventricle; OR, odds ratio

Table 5

Reproducibility of native T_1 measurement in AF patients and healthy controls

	10 healthy controls		10 AF subjects	
	Intra-observer reproducibility	**Inter-observer reproducibility**	**Intra-observer reproducibility**	**Inter-observer reproducibility**
Repeatability coefficient	25msec	27msec	40msec	46msec
Intra class correlation coefficient	0.96 (95%CI: 0.85–0.99, p<0.05)	0.95 (95%CI: 0.80–0.99, p<0.05)	0.92 (95%CI: 0.87–0.95, p<0.05)	0.91 (95%CI: 0.86–0.94, p<0.05)
Coefficient of Variation	0.8%	1.1%	1.4%	1.6%

AF, atrial fibrillation; CI, confidence interval

Repeatability coefficients were calculated as 1.96 times the standard deviation of the differences on the Bland-Altman plots.