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Diffuse Ventricular Fibrosis in Atrial Fibrillation

Noninvasive Evaluation and Relationships With Aging and Systolic Dysfunction

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Objectives The purpose of this study was to evaluate diffuse myocardial fibrosis of the left ventricle (LV) in patients with atrial fibrillation (AF).

Background Diffuse myocardial fibrosis is a hallmark of cardiomyopathy. Unlike replacement fibrosis, it is not visualized on delayed-enhancement cardiac magnetic resonance (CMR) imaging, but may be quantified with contrast-enhanced T_1 mapping methods. In atrial fibrillation (AF), it may be induced by arrhythmia or reflect pre-existing cardiomyopathy.

Methods Ninety subjects underwent CMR using a clinical 1.5-T scanner: 23 controls, 40 paroxysmal AF patients, and 27 persistent AF patients. Cardiac morphology and function was evaluated from CMR cine imaging. A histologically validated T_1 mapping sequence was used to calculate post-contrast T_1 relaxation time (T_1 time) of the LV myocardium as an index of diffuse myocardial fibrosis.

Results Age was similar across controls, paroxysmal AF patients, and persistent AF patients (54 ± 12 years, 58 ± 9 years, and 56 ± 10 years, p = NS). Persistent AF patients had larger indexed left atrium volume (55 ± 18 ml vs. 41 ± 12 ml and 47 ± 14 ml) and lower ejection fraction (54 ± 10% vs. 65 ± 6% and 61 ± 8%) than controls and paroxysmal AF patients ($p < 0.05$). Post-contrast ventricular T_1 time differed across all groups (controls, 535 ± 86 ms; paroxysmal AF, 427 ± 95 ms; persistent AF, 360 ± 84 ms; $p < 0.001$). Univariate predictors of post-contrast ventricular T_1 time included age, sex, AF category, ejection fraction, LV mass, congestive heart failure, and body mass index. After multivariate analysis, age, AF category, and ejection fraction remained independent predictors.

Conclusions Post-contrast ventricular T_1 mapping identifies diffuse LV fibrosis in patients with AF and provides new insights into the association between AF and adverse ventricular remodeling. (J Am Coll Cardiol 2012;60:2402–8)

Diffuse myocardial fibrosis is a hallmark of normal aging (1), and is also observed in common cardiovascular diseases including hypertensive heart disease (2), diabetic cardiomyopathy (3), and idiopathic dilated cardiomyopathy (4). Characterized by an increase in collagen and other extracellular matrix components in the interstitium and perivascular spaces, it represents a reactive process mediated by cardiac fibroblasts that does not require myocyte necrosis. Functional consequences of diffuse fibrosis are increased myocardial stiffness, diastolic impairment (5,6), and proarrhythmia due to altered electrophysiologic substrate (7,8).

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In contrast to reparative fibrosis, where regional tissue injury induces focal fibrosis and may manifest as macroscopic scar, diffuse interstitial fibrosis cannot be visualized using conventional cardiac magnetic resonance (CMR) delayed-enhancement (DE) imaging. Magnetic resonance

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imaging (MRI) quantitation of global and regional interstitial fibrosis has recently become possible with the development of novel contrast-enhanced T_1 mapping techniques (9–11). The technique of T_1 mapping allows direct myocardial signal quantification, and has been validated against collagen content in animal models (12,13) and in subjects with cardiomyopathy (9).

In the setting of atrial fibrillation (AF), diffuse interstitial fibrosis may occur as a result of tachycardia-mediated cardiomyopathy in conjunction with LV dilation and systolic dysfunction (14). Conversely, it may reflect the presence of a cardiomyopathy that precedes and contributes to the development of AF. The presence of concurrent AF and cardiomyopathy has been associated with an increased risk of heart failure progression and lethal ventricular arrhythmia, independently of ejection fraction (EF) (15–21). However, little has been published on the relationship between diffuse fibrosis of the ventricle and AF in humans. In this present study, we quantified diffuse fibrosis and evaluated its determinants in a population of highly symptomatic patients with AF and in healthy controls.

Methods

Study population. The study was performed at the Alfred Hospital, Victoria, Australia, between October 2009 and October 2011, and was approved by the Alfred Human Research Ethics Committee. Healthy volunteers and patients with AF were recruited for CMR. The AF group included patients with symptomatic AF who were resistant to or intolerant of at least 1 antiarrhythmic agent and were scheduled for catheter ablation of AF. The AF subjects were categorized as "paroxysmal," whose episodes were self-terminating within 7 days, or as "persistent," whose episodes lasted >7 days or required electrical cardioversion. Isolated AF was defined as AF in the absence of structural heart disease, hypertension, and diabetes mellitus. Healthy volunteers who were not receiving any medications and who had no history of cardiac disease, hypertension, diabetes, dyslipidemia, smoking, or any other acute illness were recruited as controls. Subjects with claustrophobia or a history of any metallic prosthetic implant contraindicating CMR were excluded.

CMR protocol. Subjects underwent CMR using a clinical 1.5-T MRI scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, Wisconsin). Sequences were acquired during breath-holds of as long as 15 s. Left ventricular (LV) function was assessed by a steady-state free precession pulse sequence (repetition time 3.8 ms, echo time 1.6 ms, 30 phases, slice thickness 8 mm). Delayed hyperenhancement was obtained 10 min after a bolus (0.2 mmol/kg body weight to a maximum of 20 mmol) of gadolinium-diethylene triamine penta-acetic acid (Magnevist, Schering, Berlin, Germany) to identify regional fibrosis using an inversion-recovery gradient echo technique (repetition time 7.1 ms, echo time 3.1 ms, inversion time individually determined to null the myocardial signal 180 to 250 ms, slice thickness 8 mm, matrix 256 × 192, number of acquisitions 2).

Abbreviations and Acronyms

- **AF** = atrial fibrillation
- **BMI** = body mass index
- **CMR** = cardiac magnetic resonance
- **DE** = delayed enhancement
- **EF** = ejection fraction
- **LA** = left atrial
- **LV** = left ventricular
- **MRI** = magnetic resonance imaging
- **NYHA** = New York Heart Association

For evaluation of diffuse interstitial fibrosis, a T_1 mapping sequence, described previously (9), was used to acquire images in mid-LV short-axis view over a range of inversion times. This consisted of an electrocardiogram-triggered, inversion-recovery prepared, 2-dimensional fast gradient echo sequence employing variable temporal sampling of k-space (Global Applied Science Laboratory, GE Healthcare) (22). Ten images were acquired sequentially at increasing inversion times (75 ms to 750 ms) 15 min post-contrast over a series of 3 to 4 breath-holds using the following imaging parameters: repetition/echo time 3.7 ms/1.2 ms, flip angle 20°, 256 × 128 acquisition matrix, 36 × 27-cm field of view, 8-mm slice thickness, trigger delay 300 ms, and views per segment 24. These images were then processed with a curve fitting technique to generate T_1 maps as described in the following text.

All cine CMR sequences were performed in 3 standard short-axis slices (apical, mid, and basal), kept identical for each sequence throughout the CMR examination (23). From an end-diastolic, 4-chamber, long-axis view, 5 equally spaced slices were planned, so that the 2 outer slices lined up exactly either with the tip of the apex or the mitral annulus. The 2 outer slices were then deleted, leaving 3 slices corresponding to typical basal, mid, and apical short-axis views. Delayed enhancement imaging was performed in both long- and short-axis views. For T_1 mapping, the mid-LV short-axis slice was utilized.

Evaluation of LV function and regional fibrosis. The left ventricle function was evaluated globally using the biplane area-length method using 2- and 4-chamber long-axis views. Regional fibrosis was identified by delayed enhancement within the myocardium, defined quantitatively by myocardial post-contrast signal intensity >5 SD above that within a reference region of remote nonfibrotic myocardium within the same slice.

Evaluation of diffuse fibrosis with T_1 mapping. The T_1 mapping sequences were analyzed using a dedicated research software package (VizPack Version 7.2.0, Global Applied Science Laboratory, GE Healthcare). The software enabled analysis of regions of interest to determine pixel-by-pixel and mean post-contrast ventricular T_1 time by fitting data acquired at various preparation times to the exponential curve $M_z(t = TI) = M_0(A\text{-}Be^{-t/T1})$ relating the sample magnetization M_z observed at time $t = TI$ to the equilibrium magnetization M_0 and sample T_1, where TI denotes inversion time for an inversion recovery experiment. For each image, an regions of interest was drawn around the entire LV myocardium along the endocardial and epicardial borders to calculate post-contrast ventricular T_1 time for each subject. To exclude contrast kinetics as a confounding factor in the analysis of

post-contrast myocardial T_1 time, post-contrast T_1 time was determined for the LV blood pool using regions of interest traced within the LV endocardial border.

Statistics. All data are expressed as mean ± SD unless otherwise indicated. Comparisons between 2 groups were made using unpaired or paired Student's *t* test for continuous variables and the chi-square test for categorical variables. For comparisons across 3 groups, 1-way analysis of variance with Bonferroni correction was used for parametric variables, and Kruskal-Wallis test with Dunn's post-hoc test for nonparametric variables. Simple and multiple linear regressions were used to assess predictors of post-contrast ventricular T_1 time, with categorical values entered into regression analyses using dummy coding. A p value of < 0.05 was considered significant, and all reported p values are 2-tailed. Analyses were conducted using SPSS software (version 17, SPSS, Chicago, Illinois).

Results

Subject characteristics. A total of 90 subjects were evaluated in the study period: 23 healthy controls, 40 subjects with paroxysmal AF, and 27 subjects with persistent AF. General characteristics are presented in Table 1. Mean age was similar across controls and AF subjects. Persistent AF subjects had greater mean CHA_2DS_2-VaSc score (1 point each for congestive heart failure, hypertension, age 65 to <75 years, diabetes, stroke, vascular disease, and female sex category; 2 points each for age ≥75 years and previous stroke) than controls and paroxysmal AF subjects. Both AF groups had worse New York Heart Association (NYHA) functional class than controls. Persistent AF subjects more frequently had a history of congestive heart failure, and were more frequently prescribed angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers), aldosterone antagonists, furosemide, and warfarin than were paroxysmal AF subjects. At the time of CMR, there were no significant differences across controls, paroxysmal AF subjects, and persistent AF subjects in resting heart rate, body mass index (BMI), estimated glomerular filtration rate (24), or cardiovascular comorbidities.

Cardiac morphology, function, and regional fibrosis. Morphological and functional data are presented in Table 2. Persistent AF subjects had significantly lower LV EF compared with controls and paroxysmal AF subjects. Left ventricular end-diastolic volume and LV mass were higher in persistent AF subjects compared with controls, but not after correction for body surface area. Left atrial (LA) volume and indexed LA volume were greater in persistent

Table 1 Subject Characteristics

Characteristics	Control (n = 23)	Paroxysmal AF (n = 40)	Persistent AF (n = 27)	p Value
General characteristics				
Age, yrs	54 ± 12	58 ± 9	56 ± 10	0.23
Male	12 (52)	27 (68)	22 (81)	0.09
CHA_2DS_2-VaSc score	0.7 ± 0.8	1.4 ± 1.2	1.5 ± 1.0*	<0.05
NYHA class II to IV	0 (0)	22 (55)*	18 (67)*	<0.0001
NYHA class III or IV	0 (0)	6 (15)	4 (15)	0.15
NYHA class IV	0 (0)	1 (3)	1 (4)	0.67
Resting heart rate, beats/min	58 ± 25	61 ± 29	61 ± 26	0.85
Estimated GFR, ml/min	84 ± 32	86 ± 24	89 ± 27	0.76
Body mass index, kg/m^2	25 ± 7	28 ± 5	28 ± 5	0.15
Comorbidities				
Congestive heart failure	—	4 (10)	14 (52)†	<0.001
Coronary artery disease	—	6 (15)	5 (19)	0.73
Diabetes mellitus	—	2 (5)	1 (4)	1.00
Hypertension	—	17 (42)	9 (33)	0.60
Smoking	—	3 (8)	2 (7)	1.00
Medications				
ACE inhibitor or ARB	—	14 (35)	20 (74)†	<0.01
Aldosterone antagonist	—	1 (3)	5 (19)†	<0.05
Beta-blocker	—	24 (60)	21 (78)	0.19
Calcium-channel blocker	—	3 (8)	7 (26)	0.08
Digoxin	—	7 (18)	7 (26)	0.54
Furosemide	—	1 (3)	5 (19)†	<0.05
Statin	—	9 (23)	3 (11)	0.33
Warfarin	—	10 (25)	18 (67)†	<0.001
Antiarrhythmics tried	—	1.5 ± 0.6	1.1 ± 0.4†	<0.05

Values are mean ± SD or n (%). *Significant difference compared to the control group. †Significant difference compared to the paroxysmal atrial fibrillation (AF) group.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHA_2DS_2-VaSc = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65 to <75 years, sex category (female) (1 point each; 2 points for age ≥75 years and previous stroke); GFR = glomerular filtration rate; NYHA = New York Heart Association.

Table 2 Cardiac Morphology, Function, and Regional Fibrosis

	Control (n = 23)	Paroxysmal AF (n = 40)	Persistent AF (n = 27)	p Value
LV ejection fraction, %	65 ± 6	61 ± 8	54 ± 10*†	<0.001
LV end-diastolic volume, ml	145 ± 35	160 ± 41	179 ± 33*	<0.01
LV end-diastolic volume index, ml/m^2	76 ± 14	79 ± 17	86 ± 17	0.08
LV mass, g	103 ± 29	111 ± 25	128 ± 38*	<0.05
LV mass index, g/m^2	54 ± 11	55 ± 11	61 ± 19	0.12
LA volume, ml	80 ± 22	100 ± 32	114 ± 41*	<0.01
LA volume index, ml/m^2	41 ± 12	47 ± 14	55 ± 18*	<0.05
Delayed enhancement	0 (0)	2 (5)	3 (11)	0.22

Values are mean ± SD or n (%). *Significant difference compared to the control group. †Significant difference compared to the paroxysmal atrial fibrillation (AF) group.
LA = left atrial; LV = left ventricular.

AF subjects versus controls. There was no significant difference between the paroxysmal and persistent AF groups in the proportion of subjects with delayed enhancement. Of the 5 patients with delayed enhancement, 3 had prior myocardial infarcts each involving DE in 1 of 16 segments; 1 subject had a small region of DE in the basal inferolateral wall of uncertain significance; and 1 subject had extensive DE in 5 segments involving the inferior, septal, and anterior walls that was consistent with hypertrophic cardiomyopathy. No other patients had a diagnosis of hypertrophic cardiomyopathy.

Post-contrast ventricular T_1 time in controls and AF subjects. Post-contrast ventricular T_1 time was shortened in subjects with paroxysmal AF and persistent AF compared to controls (Fig. 1). Paroxysmal AF subjects also had shorter mean post-contrast ventricular T_1 time than persistent AF subjects did. All differences in post-contrast ventricular T_1 time across controls, paroxysmal AF subjects, and persistent AF subjects remained significant after exclusion of the 5 scans of subjects with delayed enhancement from the comparison. Mean post-contrast T_1 time of the LV blood pool did not vary significantly across the 3 groups, excluding potential differences in contrast kinetics across the 3 groups as a confounder to the measurement of post-contrast myocardial T_1 time. Among controls, there was a significant inverse relationship between advancing age and post-contrast ventricular T_1 time (Fig. 2). After univariate analysis, age and resting heart rate ($p < 0.1$) were entered into a multivariate model, which yielded only age as a significant independent predictor of post-contrast ventricular T_1 time among controls (Table 3).

Univariate and multivariate correlations with post-contrast ventricular T_1 time. Relationships with post-contrast ventricular T_1 time were evaluated for the entire study cohort using simple and multiple linear regressions (Table 4). After univariate regression, diagnosis of AF of any class, persistent AF class, LV EF, congestive heart failure, and BMI ($p < 0.1$) were entered into a multivariate model together with

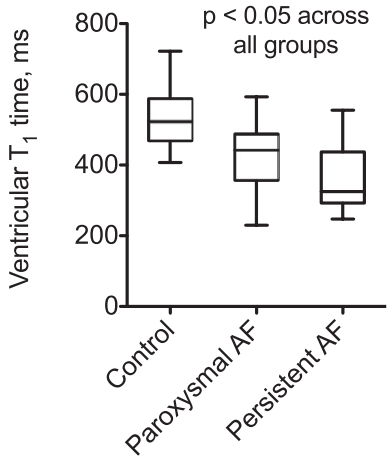

Figure 1 Post-Contrast Ventricular T_1 Time in Control and AF Subjects

Post-contrast ventricular T_1 time was different across all 3 groups: healthy controls (535 ± 86 ms, n = 23), paroxysmal atrial fibrillation (AF) subjects (427 ± 95 ms, n = 40), and persistent AF subjects (360 ± 84 ms, n = 27). Differences remained significant subjects with delayed enhancement (5) were excluded from the analysis (535 ± 86 ms vs. 425 ± 98 ms vs. 356 ± 86 ms, $p < 0.001$). Post-contrast T_1 time of the left ventricular blood pool did not vary significantly across the 3 groups (262 ± 28 ms vs. 252 ± 35 ms vs. 239 ± 43 ms, p = NS).

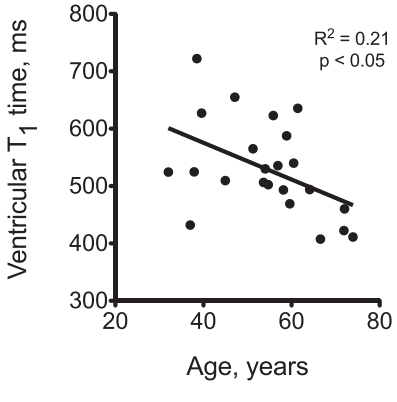

Figure 2 Relationship Between Post-Contrast Ventricular T_1 Time and Age Among Healthy Control Subjects

In control subjects (n = 23), post-contrast ventricular T_1 time decreased with advancing age ($R^2 = 0.21$, $p < 0.001$).

Table 3 Relationship Between Post-Contrast Ventricular T_1 Time and Subject Characteristics Among Controls

	Univariate Model			Multivariate Model			
	F	R^2	p Value	B	SE B	β	p Value
Age†	5.66	0.21	<0.05	−2.9	1.3	−0.42	<0.05
Male*	0.04	0.00	0.83	—	—	—	—
Body mass index	0.97	0.04	0.33	—	—	—	—
Resting heart rate†	3.29	0.15	0.09	2.8	1.7	0.31	0.12
Estimated GFR	1.31	0.06	0.27	—	—	—	—

*Categorical variables were entered into analyses using dummy coding. †Univariate predictors with p values < 0.1 were entered into the multivariate model.
GFR = glomerular filtration rate.

age, which yielded only age, AF class, and LV EF as independent correlates of post-contrast ventricular T_1 time.

Post-contrast ventricular T_1 time and characteristics of subjects with isolated AF. Characteristics of subjects with isolated AF (n = 12) and age- and sex-matched controls (n = 12) are summarized in Table 5. Paired comparisons showed no significant differences in CHA_2DS_2-VaSc score, resting heart rate at the time of CMR, BMI, or estimated glomerular filtration rate across the 2 groups. Subjects with isolated AF had worse NYHA functional class, and greater indexed LV end-diastolic volume and indexed LA volume. There were no significant differences in LV EF or LV mass index across the 2 groups, and no subject had delayed enhancement. Post-contrast ventricular T_1 time was shortened in subjects with isolated AF compared with age- and sex-matched controls, whereas post-contrast T_1 time of the LV blood pool was similar across the 2 groups (Fig. 3).

Discussion

In this study, a previously histologically validated contrast-enhanced magnetic resonance T_1 mapping sequence was used to quantify diffuse interstitial myocardial fibrosis of the left ventricle in a cohort of highly symptomatic AF patients and healthy controls. The major finding of this study is that AF category, along with advancing age, and declining LV EF, is independently associated with increasing diffuse fibrosis. Furthermore, a subset of patients with isolated AF demonstrated diffuse fibrosis suggesting that AF itself may play an independent role in adverse cardiac remodeling.

Ventricular fibrosis is a key pathologic feature of many heart diseases. It may occur in a focal distribution due to regional tissue injury and reparative fibrosis, or in a diffuse interstitial distribution in the absence of significant myocyte loss. Whereas cardiac biopsy was previously the only means available to detect interstitial fibrosis, contrast-enhanced T_1 mapping methods now permit its noninvasive quantitation and play a complementary role to conventional DE-MRI in the comprehensive assessment of myocardial fibrosis. Post-contrast myocardial T_1 time has been shown to correlate inversely with histologic assessment of myocardial fibrosis, and is shortened in patients with heart failure and diabetic cardiomyopathy where it is associated with diastolic dysfunction (9,25,26). Importantly, in our study, there were no significant differences between study groups in the post-contrast T_1 times of the blood pool, which confirms that the observed differences in post-contrast myocardial T_1 time were not due to differences

Table 4 Relationships With Post-Contrast Ventricular T_1 Time

	Univariate Model			Multivariate Model			
	F	R^2	p Value	B	SE B	β	p Value
Age†	2.28	0.03	0.13	−1.9	0.9	−0.18	<0.05
Male*	2.41	0.02	0.12	—	—	—	—
Any AF*†	34.91	0.28	<0.001	−75.2	22.8	−0.31	<0.001
Persistent AF*†	24.73	0.22	<0.001	−49.2	24.6	−0.21	<0.05
LV EF†	22.62	0.20	<0.001	2.6	1.1	0.22	<0.05
LV EDV index	1.26	0.01	0.26	—	—	—	—
LV mass index	0.36	0.00	0.55	—	—	—	—
LA volume index	1.09	0.02	0.30	—	—	—	—
Hypertension*	0.06	0.00	0.81	—	—	—	—
Diabetes mellitus*	0.16	0.00	0.69	—	—	—	—
CAD*	0.74	0.01	0.39	—	—	—	—
CHF*†	12.11	0.12	<0.001	−24.5	27.8	−0.09	0.38
Body mass index†	6.00	0.06	<0.05	−2.4	1.7	−0.12	0.16
Resting heart rate	0.84	0.01	0.36	—	—	—	—
Estimated GFR	0.27	0.00	0.61	—	—	—	—

*Categorical variables were entered into analyses using dummy coding. †Age and univariate predictors with p values < 0.1 were entered into the multivariate model together with age.
CAD = coronary artery disease; CHF = congestive heart failure; EDV = end-diastolic volume; EF = ejection fraction; other abbreviations as in Tables 1 and 2.

Table 5 Characteristics of Subjects With Isolated AF Versus Age- and Sex-Matched Controls

Characteristics	Controls (n = 12)	Isolated AF (n = 12)	p Value
General characteristics			
Age, yrs	54 ± 9	54 ± 10	0.9
Male	9 (75)	9 (75)	1.0
CHA_2DS_2-Vasc score	0.4 ± 0.7	0.4 ± 0.6	0.5
NYHA class II to IV	0 (0)	6 (50)	<0.05
NYHA class III or IV	0 (0)	3 (25)	0.22
NYHA class IV	0 (0)	0 (0)	—
Resting heart rate, beats/min	63 ± 10	66 ± 18	0.8
Body mass index, kg/m^2	26 ± 3	26 ± 4	1.0
Estimated GFR, ml/min	90 ± 18	93 ± 12	0.7
Magnetic resonance imaging findings			
LV ejection fraction, %	66 ± 6	64 ± 6	0.2
LV end-diastolic volume, ml	143 ± 36	166 ± 22	<0.05
LV end-diastolic volume index, ml/m^2	73 ± 15	82 ± 8	<0.05
LV mass, g	100 ± 23	104 ± 15	0.7
LV mass index, g/m^2	51 ± 10	51 ± 5	0.8
LA volume, ml	68 ± 26	99 ± 25	<0.01
LA volume index, ml/m^2	34 ± 11	49 ± 13	<0.01
Delayed enhancement	0 (0)	0 (0)	1.0

Values are mean ± SD or n (%).
Abbreviations as in Tables 1 and 2.

in contrast kinetics among the 3 groups. Given the limited clinical scenarios in which myocardial tissue sampling is appropriate, little has been published on ventricular fibrosis in human AF. Frustaci et al. (27) described endomyocardial LV biopsy findings in 14 patients with lone AF and normal hemodynamics. Findings were abnormal in all subjects, 6 having myocarditis or cardiomyopathic changes, and notably, 8 having nonspecific interstitial fibrosis. Similarly, in a series of patients with various supraventricular tachycardias, Kobayashi et al. (28) demonstrated ventricular fibrosis in 4 of 9 AF subjects.

In ovine and canine models of cardiac disease, hypertension and heart failure (conditions associated with diffuse fibrosis) promote AF through the induction of atrial remodeling (29,30). Conversely, AF induces systolic heart failure and ventricular fibrosis through the mechanism of tachycardia-mediated cardiomyopathy (14). Relevant to the frequently paroxysmal course of AF is the finding that interstitial fibrosis may increase during the recovery phase of tachycardia-mediated cardiomyopathy after normalization of EF (31). Taken together, these studies suggest that patients with AF may harbor ventricular fibrosis as a cause or consequence of the arrhythmia, even when cardiomyopathy is not clinically apparent.

In this study, post-contrast ventricular T_1 time shortened with increasing age, consistent with prior human and animal studies describing progressive fibrosis of the senescent heart (1,32). Gazoti Debessa et al. (1) showed collagen content to increase in the human LV by almost 50% between the third and seventh decades of life. In the present analysis, healthy controls and AF patients were of similar age, yet substantial shortening of post-contrast ventricular T_1 time in AF patients was observed, indicating the presence of diffuse fibrosis. The LV EF was also an independent predictor, in line with previous results (9). However, LV hypertrophy, although an established cause of ventricular fibrosis and identified as univariate predictor in the analysis, was not an independent predictor in the present study.

Examination of subjects with isolated AF revealed LV dilation and diffuse fibrosis compared with age- and sex-matched healthy persons. Although causal relationships cannot be established in a cross-sectional study, it is less likely that AF resulted from occult cardiomyopathy in this group, given the preservation of LV function and absence of LV hypertrophy and established causes of diastolic heart failure. A more plausible explanation is that these patients fall in the spectrum of AF-mediated cardiomyopathy. Large-animal models demonstrate that tachycardia-mediated cardiomyopathy induces LV systolic dysfunction, dilation, and interstitial fibrosis (14), while its recovery phase is associated with persistent dilation for as long as 12 weeks after resolution of tachycardia (33) and progression of interstitial fibrosis (6,31) despite normalization of EF. Spinale et al. (6) characterized this fibrosis in a canine model, describing a diffuse increase in hydroxyproline content, increased collagen type III alpha expression, confluence of interstitial collagen weave, and thickening of collagen struts and fibrils. In humans, persistence of adverse LV remodeling has been demonstrated as long as 14 months after successful tachycardia ablation (34). Thus, structural LV remodeling in isolated AF may result from accumulated insults effected by bouts of tachycardia.

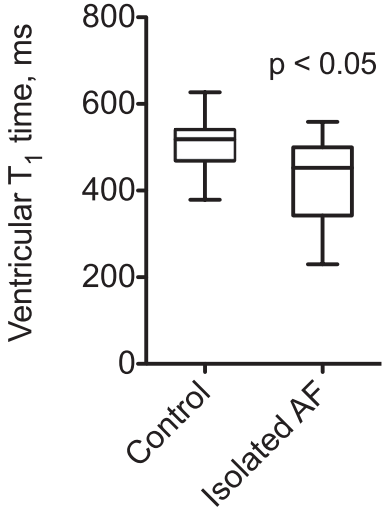

Figure 3 Post-Contrast Ventricular T_1 Time in Subjects With Isolated AF and Age- and Sex-Matched Controls

Post-contrast ventricular T_1 time was shortened in subjects with isolated atrial fibrillation (AF) compared with age- and sex-matched controls (430 ± 96 ms vs. 518 ± 92 ms, $p < 0.01$), whereas post-contrast T_1 time of the left ventricular blood pool was similar across the 2 groups (260 ± 28 ms vs. 261 ± 29 ms, p = nonsignificant).

Study limitations. Depending on the T_1 mapping technique employed, estimation of myocardial T_1 time may be affected by subject parameters such as heart rate and renal function (35). However, no differences in these potential confounders were noted across the 3 study groups, nor did they correlate with post-contrast ventricular T_1 time on regression analysis. The higher rate of angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) therapy in patients with persistent AF may have reduced the extent of diffuse fibrosis in this patient group. Nonetheless, patients with persistent AF demonstrated a greater degree of diffuse fibrosis compared to those with paroxysmal AF.

Conclusions

Post-contrast T_1 mapping identifies diffuse interstitial fibrosis of the LV in patients with AF. Ventricular fibrosis may either be a cause or consequence of the arrhythmia. This study provides new insights into the association between AF and adverse ventricular remodeling.

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Key Words: atrial fibrillation ■ cardiac magnetic resonance ■ T_1 mapping ■ ventricular fibrosis.